Under the Microscope

Community MRSA and Panton-Valentine leukocidin (PVL): the perfect storm, or a storm in a tea-cup?

Staphylococcus aureus is well known for its propensity to encode and express a formidable range of virulence determinants that can cause considerable morbidity and mortality in its host. Amongst these determinants is Panton-Valentine leukocidin (PVL), a cytolytic exotoxin first described in the late 19th century. This toxin is found in many S. aureus clones; however, of particular concern is the fact that community-acquired methicillin-resistant S. aureus (CA-MRSA) clones that contain the PVL determinant have been associated with severe necrotising cutaneous and pulmonary infections in previously well individuals. These reports raise the spectre of a true ‘superbug’ – one that is readily transmissible, resistant to front-line antimicrobial agents, and potentially more virulent that other S. aureus strains. Specific therapeutic approaches directed towards the expression and/or activity of PVL, or the elimination of carriage and transmission of S. aureus that contains PVL determinants, are being considered; however, the effectiveness of such approaches has yet to be determined.

Pathobiology

PVL is a two-component polymeric pore-forming exotoxin belonging to the syngogehmenotrophic toxin family which includes gamma-haemolysin and other secreted proteins which can combine with each other to form related, but less potent, exotoxins.

PVL binds to and damages the cell membranes of neutrophils, monocytes and macrophages resulting either in cell lysis or neutrophil apoptosis. Neutrophil lysis results in local release of active oxygen species, cytotoxic lysosomal granule contents and proinflammatory mediators, whereas neutrophil apoptosis has been postulated as the mechanism behind the neutropaenia which can be observed during the course of severe ‘PVL-positive’ staphylococcal infection. When injected into the dermis of rabbits, purified PVL causes inflammation and skin necrosis. In a recent study, PVL caused necrotising pneumonia in mice and, in addition, PVL also altered the expression of several genes encoding cell-wall anchored proteins that are important in the pathogenesis of staphylococcal infection, including staphylococcal protein A, clumping factor, and microbial surface components recognising adhesion matrix molecules (MSCRAMMS). However, another study of a murine model of S. aureus sepsis and cutaneous abscess/dermonecrosis did not demonstrate a significant difference in virulence between PVL positive and negative S. aureus strains, suggesting that factors...
other than PVL expression may be more significant in these forms of infection 4.

The genes encoding the components of PVL (LukS-PV and LukF-PV) are located on a prophage. Experimentally, this prophage can be mobilised from the S. aureus chromosome into a lysogenic bacteriophage and inserted into PVL-negative strains by transduction; it is postulated that this is the mechanism for the dissemination of this genetic determinant in nature 2.

**Clinical and molecular epidemiology**

PVL was previously considered uncommon in clinical isolates of methicillin-susceptible S. aureus (MSSA) 9. More recently, it has been recognised that S. aureus isolates responsible for necrotic infections (e.g. cutaneous furuncles and necrotising community-acquired pneumonia) harbour the PVL genes more frequently than strains causing other forms of staphylococcal infection (e.g. infective endocarditis, impetigo, cellulitis and cutaneous abscesses) 10,11.

As described elsewhere in this publication, community-acquired MRSA (CA-MRSA) infection has rapidly emerged worldwide, and is now a common cause of infection in Australia and elsewhere. A number of recent reports have described an association between severe CA-MRSA infection and the presence of genes encoding PVL in the infecting strain. These infections include necrotising pneumonia 12,13 (Figure 2), necrotising fasciitis and myositis 14 as well as disseminated infection and severe sepsis 15.

Several commonly encountered CA-MRSA clones – such as ST30-MRSA-IV (Oceania clone), ST93-MRSA-IV (Queensland clone), ST8-MRSA-IV (USA300 clone), ST1-MRSA-IV (USA400 clone), ST80-MRSA-IV (European CA-MRSA clone) and ST59-MRSA-IV (Taiwan CA-MRSA clone) – predictably contain PVL genes, whereas other strains usually do not. In Western Australia, where over 20 different clones of CA-MRSA co-circulate, PVL is not found, or is uncommon, in most of these clones. However, the proportion of all CA-MRSA isolated in Western Australia that contain PVL genes has increased from 1.1% in 2003 to 8% in 2006, which is likely to be due to importation of the above ‘exotic’ PVL-containing CA-MRSA clones via their human hosts 16.

A large prospective study from Queensland that compared the clinical and laboratory features of non-multiple resistant MRSA infection to that caused by multi-resistant MRSA and MSSA showed that non-multiple resistant MRSA isolates were significantly more likely to contain PVL genes (55%) compared to multi-resistant MRSA (2%) and MSSA (16%). However, both all-cause and attributable mortality were significantly lower in patients with infection caused by S. aureus (either MSSA or MRSA) that contained PVL genes 17. We have made similar observations in an ongoing prospective study of invasive CA-MRSA infection in Western Australia, where patients with invasive PVL positive S. aureus infection had less morbidity and similar mortality compared to those with invasive PVL negative S. aureus infection.

**Management of PVL positive S. aureus infection**

Antimicrobial agents that inhibit protein synthesis in S. aureus at the ribosomal level (e.g. clindamycin and linezolid) reduce the translation of PVL genes in vitro 18, suggesting that these agents could potentially play a specific ‘antitoxin’ role in the treatment of PVL-positive S. aureus infection. Animal model and clinical data to support this approach are awaited.

Immunisation with purified PVL components (LukF-PV and LukS-PV) partially attenuated the pathologic effects of the toxin in the rabbit model 4, and commercially available human intravenous immune globulin preparations contain antibodies to LukF-PV and LukS-PV, which neutralise PVL activity in vitro 19. Studies that evaluate the efficacy of passive or active immunisation to prevent PVL-induced disease may provide insight into the potential usefulness of these strategies.

The Western Australian Communicable Disease Control Directorate (CDCD) and the WA Gram-positive Bacteria Typing and Research Unit (GPBTRU) have recently developed and implemented a ‘search and destroy’ policy for ‘exotic’ PVL-containing CA-MRSA clones in Western Australia 20. This approach is based on the highly successful approach to the identification and eradication of epidemic MRSA in Western Australian hospitals. Patients with colonisation or infection caused by these MRSA clones are identified by the GPBTRU. This information is communicated to the Healthcare Associated Infection Unit at the CDCD (in accordance with notifiable disease legislation), who coordinate the assessment and management of the index case and the contacts of the case via public health units (further details regarding surveillance and decolonisation methodologies are available 20). It remains to be seen whether this approach can contain the spread of these MRSA strains in the community.
References

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Endemic MRSA management: is screening useful?

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Endemic hospital methicillin-resistant Staphylococcus aureus (MRSA) remains a cause of significant morbidity and mortality. However, there is no universal consensus on optimal control measures. MRSA screening has been reported as a successful intervention but generally in association with a raft of other measures. Improved hand hygiene, antibiotic stewardship and the availability of isolation facilities are considered to be basic components in MRSA control. Targeted screening of high risk patients is likely to be useful for MRSA control but only if results are available in a timely manner and with resources that allow appropriate response to positive results.

Much of the MRSA control literature describes interventions in the outbreak setting. This experience may not be able to be directly generalised to the more common MRSA endemic setting. The main arguments for screening patients are to inform hospital epidemiology and to direct infection prevention strategies. Such screening is often used as a part of a ‘search and isolate’ or ‘search and destroy’ strategy with contact precautions and attempted decolonisation used for patients found to be MRSA positive. Contact isolation of MRSA patients is considered important – one study, although in an outbreak rather than an endemic setting, reported that the rate of MRSA transmission was 16 times higher for a carrier not in contact isolation compared with those in contact isolation. However, although there are reports of MRSA control resulting from a series of co-interventions which included MRSA screening, there are also reports of MRSA control without MRSA screening.

Within Australian hospitals there is wide variation in screening practices. Screening may be passive or active, targeted or universal. Passive surveillance using results of clinical specimens will only identify a minority of MRSA colonised and infected patients – 17.8% in one study. Active screening with patients considered at high risk, e.g. intensive care patients, has been associated with decrease in MRSA disease.