Necrotising pneumonia, *Staphylococcus aureus* and Panton-Valentine leukocidin

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The Panton-Valentin leukocidin (PVL) strain of meticillin-resistant *Staphylococcus aureus* (MRSA) is producing a new pattern of MRSA-related disease in the UK and world-wide. PVL is one of several extracellular cytotoxins produced by *Staphylococcus aureus*, and is usually associated with skin and soft tissue infections. PVL MRSA is uncommon in hospitals, but in the US, and now in the UK, there have been reports of severe, rapidly progressive, community-acquired haemorrhagic, necrotising pneumonia occurring in previously healthy young adults, and associated with a mortality rate of up to 75%. We review features of the pathophysiology, diagnosis and treatment of this condition, whose incidence appears to be increasing in the UK.

Keywords: *meticillin-resistant Staphylococcus aureus; Panton-Valentine leukocidin; necrotising pneumonia*

Introduction

Meticillin-resistant *Staphylococcus aureus* is a bacterium which is well known to intensivists. It has evolved multiple features which enhance its resistance to beta-lactam antibiotics, and has the ability to produce toxins. MRSA can be classified as community-aquired or healthcare-associated. *S. aureus* is a relatively uncommon cause of community-acquired pneumonia (CAP), with only 0.2% of cases of community-aquired pneumonia being attributed to *S. aureus*. However the prevalence rises with increasing disease severity, with 7.6% of cases treated in intensive care units being attributed to infection with *S. aureus*.[1]

The PVL-toxin producing strain

Panton-Valentine leukocidin is one of several extracellular cytotoxins produced by *S. aureus*. The toxin was first described in 1932,[2] and is both dermo-necrotic and leukocidal, destroying leukocytes by creating lytic pores in the cell membrane.[3] The PVL toxin comprises two subunits. When these are combined with haemolysin from the bacterium, toxin molecules with varying cellular affinities and various destructive capability are produced.[4] This occurs even when the staphylococci are sensitive to bactericidal antibiotics such as meticillin. In a UK study of *S. aureus* isolates from 2002-2003, 1.6% were found to carry PVL genes, the majority of which were meticillin-sensitive. Of those causing clinical infection, 65% were associated with skin and soft tissue infections and 17% with pneumonia.[5] More recently, the PVL toxin has been described as an important promoter of virulence, and it features most prominently in community-acquired MRSA.[6] Now, a major new problem is emerging due to PVL-associated MRSA, particularly in the US. PVL-producing MRSA remains uncommon in hospitals in the UK however, and the Health Protection Agency reported only seven deaths related to PVL MRSA in 2005-2006. Despite attempts to collate data on PVL *S. aureus* infections, there are currently no routine cultures taken of post-mortem specimens, and the disease is not notifiable, so the true incidence remains unknown.[4]

The PVL strain was initially implicated in necrotising soft tissue infections or recurrent furunculosis or abscesses. The conditions were rarely life threatening. Three new and more virulent staphylococcal syndromes associated with PVL have become apparent, however. Purpura fulminans due to PVL *S. aureus* may be caused by meticillin-resistant or sensitive organisms and has a mortality of up to 60%.[7] Skin sepsis due to community-acquired MRSA occurs in patients without recent contact with healthcare facilities or known risk factors for such infection.[4] Transmission has been linked to physical contact with outbreaks described in prisoners, military personnel, homosexual men, schoolchildren and athletes.[5,8]

Necrotising pneumonia

The third syndrome associated with PVL MRSA is necrotising pneumonia, which has a mortality of up to 75%.[3] The first British case was reported in 2003, in a 30-year-old woman who developed rapidly fatal necrotising pneumonia following a flu-like illness.[9] Whereas conventionally, *S. aureus* pneumonia affects the elderly with co-morbidities, PVL MRSA affects immuno-competent children and young adults (median age 15 years) and is usually community-acquired, in people with no previous healthcare contact.[3] The syndrome has since been described globally, with over 100 reported cases in continents including North America, Australia, Europe and the Far East.[4]

PVL-producing strains of *S. aureus* have a particular affinity for the exposed basement membrane in the ciliary epithelium of the lung, which is present after viral respiratory illness. The staphylococcal cells rapidly establish themselves on the

membrane, producing toxin which destroys polymorphs locally and liberates inflammatory mediators.[10] Necrotising vasculitis then ensues, causing destruction of lung tissue with large areas of pulmonary infarction and haemorrhage.

Diagnosis

As the syndrome commonly affects young, previously healthy people, diagnosing necrotising pneumonia can be very difficult. Community-acquired pneumonia caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes* may present with a similar picture, and pulmonary embolism or vasculitis may also need to be considered as part of the differential diagnosis. Typically, a patient presents in the community, with a recent flu-like illness and possibly with a history of diarrhoea and vomiting. Although the subsequent pneumonia is thought to occur from blood-borne spread from a soft tissue infection, there is commonly no obvious lesion. Initial signs of systemic inflammation, with high fever and tachycardia, can rapidly progress to signs of septic shock.[11] Haemoptysis and leucopaenia are often dramatic, and there is usually a grossly elevated C-reactive protein concentration (>300mg/L). Chest imaging reveals multilobular alveolar infiltrates which rapidly progress to cavitating lung lesions, unlike the clinical picture seen in hospital-acquired MRSA pneumonia.[3,7] Gram staining of sputum demonstrates sheets of gram positive-cocci. The CURB score may be misleadingly low in young adults and should not be used in this context.[12] These patients are often severely hypoxic and have the propensity to deteriorate very rapidly; thus, early involvement of the critical care team is advised. Additional questions should be asked to elicit whether any family members have a history of skin sepsis, any contact with healthcare facilities or are known MRSA carriers.[12]

Treatment

Early diagnosis is essential as typical antimicrobial therapy for community-acquired pneumonia will not affect the PVL toxin-producing strains. There is some evidence that bactericidal antibiotics, such as the beta-lactams, can actually increase toxin formation. Conversely, the protein-inhibiting agents clindamycin and linezolid may reduce toxin formation.[13] Vancomycin should not be used in isolation as adequate lung concentrations are unlikely to be achieved, and toxin formation will not be suppressed. In addition, approximately 47% of PVL-positive clinical isolates of *S.aureus* causing pneumonia are meticillin-resistant[5] so empirical therapy must cover MRSA. The microbiology laboratory must be involved early as specific investigations are required to guide therapy. For example, *S. aureus* that appears resistant to erythromycin, but sensitive to clindamycin, should be checked ("D tested") to exclude inducible resistance to clindamycin.[4] *S. aureus* recovered from suspected cases should be referred to the Health Protection Agency Staphylococcus Reference Laboratory for toxin gene profiling including PVL testing. This is a PCR-based assay that can be completed within a working day. The Department of Health (DH) has recently produced guidance on initial treatment[12] and recommends linezolid 600 mg 12-hourly and high dose clindamycin 1.2-1.8 g 6-hourly in combination, which may be synergistic. There have been many different regimes described, with the addition of rifampicin 600 mg twice daily to linezolid and clindamycin, probably being the most beneficial. There may be a role for adding flucloxacillin or co-trimoxazole empirically,[10,14] whereas the roles of ceftobiprole (a cephalosporin with anti-MRSA properties) and tigecycline in this setting have yet to be determined.[12]

As the toxin continues to be active even if the bacteria can be successfully killed, adjunctive therapy can be used to attempt to inactivate the toxin. Intravenous immunoglobulin should be considered as it may be partly effective in neutralising super-antigens and toxins.[15-17] A dose of 2 g/kg is recommended in DH guidance, repeated if there are no signs of clinical improvement. Anecdotal reports indicate a possible role for activated protein-C, although this is not

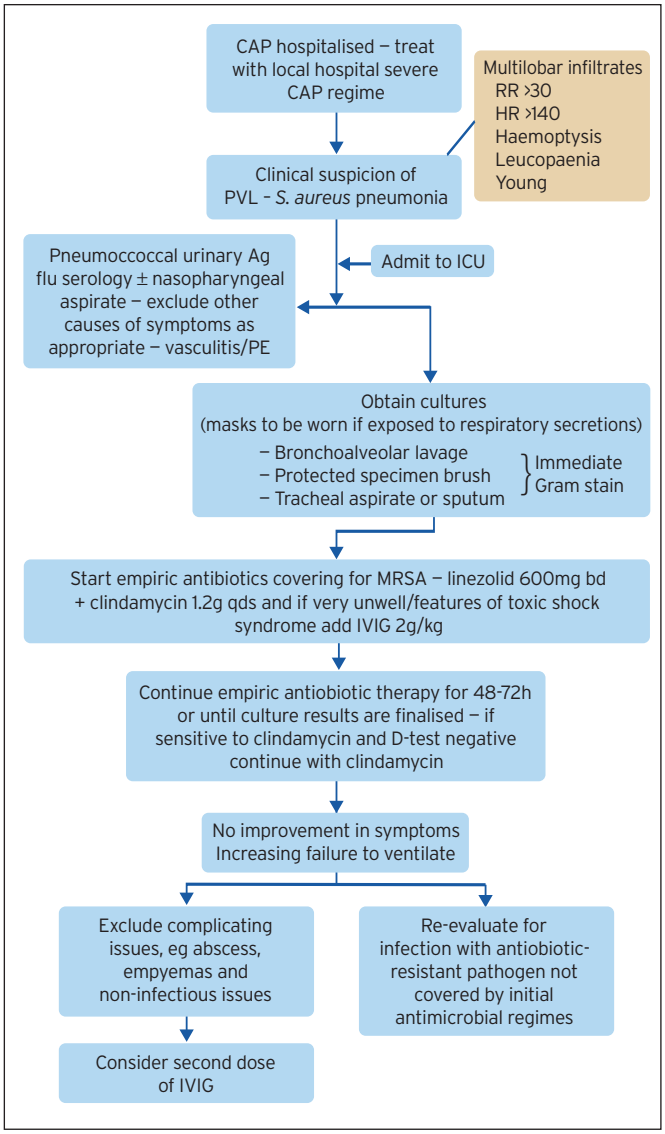

Figure 1 Management of patient with suspected staphylococcal pneumonia in the healthcare setting. IVIG – intravenous immunoglobulin. Adapted from Nathwani D *et al*. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. *J Antimicrobial Chemotherapy* 2008;61:976-94. Figure 2, page 987; by permission of Oxford University Press.

recommended by the DH because of the risk of precipitating further haemorrhage.

Infection control by barrier nursing is critical, and the DH now recommends using face-masks when performing airway manoeuvres, physiotherapy and suction, because infection among close contacts has been reported.[12,14] Closed suction should be used. Screening (nose, throat, perineum, axilla and skin lesions) of close contacts is recommended by the DH and decolonisation may be indicated.[18]

Mortality in the unrecognised case approaches 75%, and even with prompt, appropriate antimicrobial therapy, mortality still ranges from 30-80%.[16,19] Gillet and co-workers[3] quoted a mortality of 32% with PVL *S. aureus* pneumonia, versus 6% mortality in PVL-negative *S. aureus* pneumonia, in a case-matched series of 16 patients, despite the PVL cohort being much younger and fitter than the more elderly cohort who had significant co-morbidities. Patients usually require multi-organ support from an early stage in their admission, and ventilation can be difficult. Ongoing pulmonary haemorrhage and lung tissue destruction causes profound hypoxia, and strategies such as prone ventilation, the use of nitric oxide or extra-corporeal membrane oxygenation may be required (all three, in one recent case at our institution). Occult pneumothoraces can be a feature, although not described in all case series. The chest radiograph can be difficult to interpret in the face of widespread lung destruction, and early CT of the lungs may assist with diagnosing pneumothoraces and empyemas and may even guide clinicians to a diagnosis, especially if lung destruction with pneumatocoeles and cavitation is seen.

Conclusion

Physicians managing patients with community-acquired pneumonia must retain a high degree of suspicion for community-acquired PVL *S. aureus* infection, particularly if presenting following a viral illness. PVL MRSA provides additional difficulty, because of its resistance to the antibiotics commonly used for CAP. Any young patient presenting with bilateral pneumonia, especially if they have a tachycardia of greater than 140 bpm, leucopaenia, cavitation or haemoptysis, should trigger a consideration of antibiotics with anti-toxin activity, barrier nursing, immunoglobulins and rapid microbiological diagnosis. The CAP guidelines may need urgent revision in response to this new challenge.

Further information

The Reference and Diagnostic Testing Services Epidemiological Typing Unit (ETU) is part of the Health Protection Agency's Centre For Infections, Colindale, UK, www.hpa.org.uk.

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