Clinical Outcome for PVL+ *Staphylococcus Aureus* Associated Necrotising Pneumonia may be Optimised Through Combination of Prompt Antimicrobial and Anti-Toxin Treatment

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**Abstract**

Necrotising pneumonia caused by Panton-Valentine Leukocidin *Staphylococcus aureus* confers a high mortality. We describe a child presenting with sepsis and necrotising pneumonia. Septicaemia caused by Panton-Valentine Leukocidin *Staphylococcus* may not be adequately treated with antibiotics to which it appears sensitive through standard culture techniques. Some evidence suggests that early anti-toxin therapy may better optimise clinical outcomes.

**Keywords:** Panton-valentine; PVL; Staphylococcus; Sepsis; Anti-toxin

**Introduction**

Necrotising pneumonia has a mortality rate of 56-61% and is associated with necrotic ulcerations of the tracheal and bronchial mucosa, with massive haemorrhagic necrosis of interalveolar septa [1]. Commonly, young immune-competent individuals present with a history of progressive skin - soft tissue infection and associated sepsis, before succumbing to respiratory involvement through likely haematogenous spread and resultant multi-organ disease [2]. We present a typical such case to demonstrate the challenges of making an early diagnosis, and review the evidence for anti-toxin therapy.

**Case**

A previously well 12 year old Somali boy presented to our Accident and Emergency department with a single day history of peri-orbital oedema, vomiting and fever to 39°C which was treated at home with ibuprofen. He had no preceding atopic history and his only preceding episode was that of *tinea capitis* at 5 years of age. He had not previously been admitted to hospital or been abroad in the last five years, although his mother worked as a nurse on an in-patient adult ward and his grandmother had been admitted with recurrent exacerbations of *Streptococcus pneumoniae* associated with *Neisseria meningitides*.

He had no preceding atopic history and his only preceding episode was that of *tinea capitis* at 5 years of age. He had not previously been admitted to hospital or been abroad in the last five years, although his mother worked as a nurse on an in-patient adult ward and his grandmother had been admitted with recurrent exacerbations of *Streptococcus pneumoniae* associated with *Neisseria meningitides*.

His right leg rested flexed at the knee and externally rotated. His right knee was extubated seven days subsequently. Ultrasound demonstrated soft tissue infection of right knee, left ankle and septic arthritis of left ankle and required a single dose of Vitamin K (7.5 mg) and 1.4 g (50 mg/kg) of Flucloumacillin (GSK). Shortly after his initial assessment, he became flushed, febrile and demonstrated profound respiratory distress, his saturations dropping from 95 to 80% in air and subsequently suffered circulatory collapse. 600 ml (20 ml/kg) of 0.9% NaCl Saline, one 300 ml (10 ml/kg) pack of fresh frozen plasma and 200 mg (7 mg/kg) of Gentamycin (Roche) were administered, according to his estimated weight. He passed dark brown urine which tested positive for myoglobin.

His blood culture grew *Staphylococcus aureus* at 16 hours, sensitive to methicillin, resistant to penicillin and ciprofloxacin, which on toxin typing revealed PVL and enterotoxins G and I.

On intensive care, he was treated for PVL sepsis with complicating cardiogenic shock requiring inotropic support (15 mcg/kg/min of Dopamine and 0.5 mcg/kg/min of Noradrenaline which was weaned within 48 hours), necrotising pneumonia, disseminated intravascular coagulation, and required a single dose of Vitamin K (7.5 mg) and 320 mg (10 mg/kg) intravenous Clindamycin (Pharmacia) four times daily and 320 mg (10 mg/kg) naso-gastric Rifampicin (Aventis Pharma) on his fifth day of admission, while his inflammatory markers were peaking. Little progress was evident, until he received two days of anti-toxin treatment, 30 g (1 mg/kg) of intravenous immunoglobulin (Flebogamma 5%) infusions. He thereafter demonstrated clinical improvement and was extubated seven days subsequently. Ultrasound demonstrated soft tissue infection of right knee, left ankle and septic arthritis of left ankle.

**Table 1**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Description</th>
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<tr>
<td>Event</td>
<td>Details</td>
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<tr>
<td>1. White cell count dropped to 1500 leukocytes per millilitre and his antibiotic regime was changed to 600 mg (maximum dose) intravenous Linezolid (Pharmacia) twice daily, 320 mg (10 mg/kg) intravenous Clindamycin (Pharmacia) four times daily and 320 mg (10 mg/kg) naso-gastric Rifampicin (Aventis Pharma) on his fifth day of admission, while his inflammatory markers were peaking. Little progress was evident, until he received two days of anti-toxin treatment, 30 g (1 mg/kg) of intravenous immunoglobulin (Flebogamma 5%) infusions. He thereafter demonstrated clinical improvement and was extubated seven days subsequently. Ultrasound demonstrated soft tissue infection of right knee, left ankle and septic arthritis of left ankle.</td>
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His disease progressed despite being treated with antibiotics to which his strain was susceptible, until anti-toxin therapy was instituted on the fifth day of admission. No repeated drainage procedures were necessary and he discharged on the thirty-first day of admission, whilst receiving 2.4 g of intravenous Ceftriaxone by per-cutaneous catheter each morning, 300 mg of oral Rifampicin twice daily and 300 mg of oral Clindamycin four times daily. These antibiotics were continued for 18 weeks, whereupon he was discharged from the orthopedic team and his local physiotherapy service without known long-term sequel. Our case did not experience any hair loss or peeling of finger-tip skin throughout his illness. His mother and father were screened for S. aureus while he was admitted on intensive care, returning negative results and his household contacts underwent decolonization.

### Discussion

PVL+ staphylococcal sepsis with necrotizing pneumonia is difficult to manage. Early recognition and treatment with both antibiotic and anti-toxin therapy may optimize clinical outcomes for this aggressive disease.

Our case presented to Accident and Emergency without respiratory distress, re-presenting in shock 36 hours later and de-compensating shortly afterward with blood stained secretions aspirated on ventilation. His disease progressed despite being treated with antibiotics to which his strain was susceptible, until anti-toxin therapy was instituted on the fifth day of admission.

PVL Staphylococcal infection incidence is likely increasing and was estimated at 3.38 per 100,000 in 2009 [3]. Data from the UK Staphylococcus Reference Laboratory in 2005 demonstrated PVL S. aureus constituted 1.6% of bacteraemic isolates sent for analysis [4]. From 2005 to 2009, a ten-fold increase in number of PVL isolates was recorded. In contrast to the American experience, the majority of reported European isolates are methicillin susceptible [1,2,5]. The majority of methicillin susceptible PVL S. aureus isolates are associated with soft tissue infection and abscesses, and a proportion of these progresses to sepsis [5].

The progression of PVL+ staphylococcal sepsis may be attenuated by the combination of instituting both bactericidal treatment and anti-toxin therapy. In clinical practice, seemingly appropriate antibiotics identified through in vitro susceptibility profiling may not prevent considerable disease progression when used in isolation [1,2]. Therefore, early recognition of potential toxin driven disease is crucial, and risks of administering anti-toxin treatment should be balanced with their potentially life-saving capacity for patients presenting with toxin associated sepsis.

In vitro work has demonstrated that Clindamycin and Linezolid have protein-synthesis inhibiting characteristics capable of dramatically impairing the capacity of S. aureus strains to manufacture phenol-soluble modulin peptides [6]. Cases receiving prompt anti-toxin therapy in combination with appropriate antibiotic treatment appear to achieve beneficial outcomes in practice [7]. Without this, outcomes may be impaired, particularly where penicillin agents used below the minimum inhibitory concentration which may promote more rapid dispersal and manufacture of toxins [8].

The UK Health Protection Agency outlines that PVL S. aureus should be suspected amongst individuals and families with a history of repeated or severe soft tissue infection, necrotising pneumonia and close contacts thereof [9]. A recent UK case series highlights that minor preceding soft tissue injury, contact sport in young adolescents and adults, non-white ethnicity and preceding respiratory infection are risk factors for developing PVL S. aureus infection [10]. The authors also speculate that ascertaining such features in the history may aid earlier diagnosis [3]. However, such factors are commonplace amongst those attending primary and secondary healthcare facilities worldwide. Our case attended for emergency care whilst confused, unable to describe any preceding illness or injury. Nonetheless, a scab was dislodged from his left lower leg during his second day in intensive care, discharging PVL+ S. aureus. A pragmatic clinical approach must be recommended to clinicians in urgent care centers, emphasizing the importance of noting histories of preceding staphylococcal infection, recognising early sepsis and arranging prompt anti-toxin management early for such patients.

### References


### Table 1: Hematological parameters through acute deterioration and recovery.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 15</th>
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<tbody>
<tr>
<td>Haemoglobin g/dl</td>
<td>13.8</td>
<td>10.6</td>
<td>6.7</td>
<td>7.2</td>
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<tr>
<td>White cell x10⁶</td>
<td>4.4</td>
<td>1.6</td>
<td>1.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Neutrophils x10⁶</td>
<td>3.7</td>
<td>0.9</td>
<td>1.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Platelets x10⁹</td>
<td>127</td>
<td>82</td>
<td>74</td>
<td>87</td>
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<tr>
<td>Prothrombins secs</td>
<td>16.1</td>
<td>15.0</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>APTT secs</td>
<td>54.9</td>
<td>57.7</td>
<td>65.4</td>
<td>61.0</td>
</tr>
<tr>
<td>Fibrinogen g/L</td>
<td>5.05</td>
<td>4.56</td>
<td>4.4</td>
<td>4.1</td>
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<tr>
<td>INR</td>
<td>1.50</td>
<td>1.40</td>
<td>1.38</td>
<td>1.28</td>
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<tr>
<td>CRP</td>
<td>246</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;250</td>
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