Anti-toxin therapy: Is it enough to kill the bug?

Panton-Valentine Leukocydine

Porto, 2009

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UCIM - HSFX
Community acquired SAMR

- Eight MRSA infections among 5 of 58 players, all at sites of turf abrasions
- All had Panton-Valentine leukocidin and genes for mec type IVa resistance
Antibiotic Resistant *St. aureus*
Age groups and gender

Table 1. Comparison of community-associated and health care–associated methicillin-resistant Staphylococcus aureus (MRSA).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Community-associated MRSA</th>
<th>Health care–associated MRSA</th>
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<tbody>
<tr>
<td>SCC mec type</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>Lineage</td>
<td>USA 300, USA 400</td>
<td>USA 100, USA 200</td>
</tr>
<tr>
<td>Toxin-producing</td>
<td>More</td>
<td>Fewer</td>
</tr>
<tr>
<td>Panton-Valentine leukocidin–</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>producing</td>
<td>Less frequent</td>
<td>More frequent</td>
</tr>
</tbody>
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NOTE. SCC, staphylococcal chromosome cassette; TMP-SMZ, trimethoprim-sulfamethoxazole.
Panton-Valentine Leukocidin

Panton-Valentine leukocidin (PVL)

- Hemolysin first reported in 1932 by Panton and Valentine
- Located on mobile phage
- 2 co-transcribed genes, `lukS-PV` and `lukF-PV`
- The two subunits form a hexameric pore-forming cytolytic toxin with a high affinity for PMNs and macrophages

- Carried by 5 different phages
- Few strains susceptible to infection
- **Community *S. aureus* (MSSA & MRSA)**

Narita. Gene 2001; 268: 195
Panton-Valentine Leukocidin

Boyle-Vavra. Lab Invest 2007; 87: 3

Neutrophils lise

Abcess Formation
Susceptibility Patterns

- **CA-MRSA**
  - carries a gene encoding PVL
  - Staphylococcal chromosomal cassette (SCC) *mec* element types IV or V (code for methicillin resistance)

- Most USA300 strains of MRSA are resistant only to β-lactams and macrolides (93%)
  - recently mupirocin, tetracycline, clindamycin and fluoroquinolone resistance

- A case of CA-MRSA pneumonia with lessened vancomycin susceptibility in Italy
Panton-Valentine Leukocidin

- PVL producing strains associated with skin and soft tissue infections and necrotizing pneumonia
- Rarely associated with osteomyelitis, bacteraemia, or endocarditis
- Rare HA-MRSA strains with PVL have similar clinical syndrome
- Usually only 2% of all *S. aureus* isolates produce PVL but found in the majority of epidemic CA-MRSA strains
Presentation of CA-MRSA

**Skin and Soft tissue infections**

(>90% of cases)

- In a study in Oakland, MRSA was present in 51% of cultured skin and soft-tissue infections.
- **Strongest predictor of MRSA was presence of a furuncle**
- CA-MRSA commonly presents as an abscess or may be mistaken for a "spider bite" [Frazee. Ann Emerg Med 2005; 45: 311]

- Hospitalization – about 16%
- Mortality - <1%

The most common presentation of soft tissue infections are boils, abscesses, furuncles, carbuncles, etc. [Klevens. JAMA 2007; 298: 1763]
Therapy

Cephalexin versus placebo after drainage of non-complicated soft tissue infections

<table>
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<tr>
<th>Study group and outcome</th>
<th>No. of isolates</th>
<th>Cures/PVL positive</th>
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<tbody>
<tr>
<td>Cephalexin (n = 82)</td>
<td>MRSA</td>
<td>PVL positive/ tested</td>
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<tr>
<td>MRSA</td>
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<tr>
<td>PVL positive/ tested</td>
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- Surgical drainage, rather than antibiotic therapy, is the single most important intervention for a CA-MRSA abscess
- Positive clinical outcomes were seen among MRSA patients treated with abscess drainage alone or concomitant therapy with penicillins inactive against CA-MRSA

Young. Arch Surg 2004; 139: 947
Use of antibiotics

- Complicated abscesses (with fever, lymphangitis, or significant surrounding cellulitis)
- Rapidly progressive or severe local disease
- Abscess diameter greater than 5 cm
- Severe sepsis or shock
- Inability to completely drain an abscess cavity
- Extremes of age
- Failed prior I&D

PVL-associated Staphylococcal pneumonia

Incidence

- The true incidence is unknown
  - cases published is underestimated
  - cases may go unrecognized

- 71 cases of fatal pneumonia have been reported on reviewing the literature of case reports or small series. **The mortality rate approaches 75%**.

- In a series of patients with MRSA pneumonia, 100% \((n = 5)\) of PVL-positive patients died compared with 47% of PVL-negatives, a relatively increased risk of 1.56.

PVL-associated Staphylococcal pneumonia

Pathogenesis

PVL-producing *S. aureus*
- has a propensity to attach to exposed collagen of damaged bronchial mucosa, especially basement membrane

> Necrotising vasculitis with massive areas of infarction and haemorrhage

- Protease and cytotoxic α haemolysins
- Leukocidin protects *Staphylococci* by destroying approaching polymorphs
Survival of patients according to PVL genotype

Contribution of PVL to virulence

Gillet Lancet 2002; 359: 753
PVL-associated Staphylococcal pneumonia

Clinical Presentation

- Young patient with a previous flu-like illness

- Toxic shock:
  - Fever >39 °C
  - Haemoptysis
  - Tachycardia >140 bpm
  - Marked leukopenia
  - Hypotension
  - High CRP (often >200–350 g/L)
  - Sputum smear reveals sheets of *Staphylococci*

Gillet. Lancet 2002; 359: 753
PVL-associated Staphylococcal pneumonia

Chest X-Ray

- Multilobar infiltrates on CXR, accompanied by effusions and often cavitation (may be normal in the first 24-48h)
  - single or multiple opacities < 3 cm diameter
  - several small rounded areas of consolidation cavitating within 96 h
  - coalescence of small cavities
  - pneumatocele, fistulae, empyema or necrosis

- The incidence of complicated pneumonia is far higher than with non PVL producing Staphylococcal pneumonia.
Massive acute intra-alveolar and interstitial hemorrhages and infarction

- Completely necrotic lung with liquefaction in patients who take longer to die.

- Microscopically, sheets of Gram-positive cocci, often with a paucity of neutrophils, are characteristic.
PVL-associated Staphylococcal pneumonia

Antibiotic Therapy

Antibiotics

Act in cell wall
- Beta-lactams
- Glycopeptides
- Lypopeptides

Act in protein synthesis
- Oxazolidinones
- Lyncosamines
- Glycilcicles

Inhibit Toxin production

- Lung antibiotic concentration may be impaired by tissue necrosis and abscess formation
PVL-associated Staphylococcal pneumonia

Antibiotic Therapy

- β-Lactams not to cover PVL producing *Staphylococci* (even sensitive)

PVL-associated Staphylococcal pneumonia

Antibiotic Therapy

- **Vancomycin:**
  - inadequate lung concentrations
  - **no effect on exotoxin synthesis**
  - Gentamicin may be synergic

- **Daptomycin:**
  - extremely rapidly bactericidal in vitro
  - **no effect on exotoxin synthesis**
  - inactivation by surfactant (limits its usage to non-pneumonic infections)
PVL-associated Staphylococcal pneumonia

**Antibiotic Therapy**

- **Clindamycin:**
  - concentration-dependent decrease of PVL levels
  - stops alpha toxin production
  - decreases TSST-1 production

  Some clones present **Inducible Resistance:**

  *S. aureus* resistant to erythromycin but clindamycin-sensitive must be “D tested” to exclude inducible clindamycin resistance.

- **Linezolid:**
  - active against MRSA, especially in CA-MRSA strains
  - Inhibits exotoxin synthesis

  3 patients with necrotising pneumonia failing vancomycin therapy responded to a change to linezolid and rifampicin.

PVL-associated Staphylococcal pneumonia

Antibiotic Therapy

- Other Antibiotics
  - Moxifloxacin, TMP-SMX, Tigecycline, Rifampicin
    - Limited experience

✓ Few guidelines available and no double-blind randomised controlled trials for the treatment of PVL-associated pneumonia

✓ Empirically use large doses (and combination) of antibiotics aimed at switching off exotoxin synthesis

✓ Avoid β-lactams even if it is methicillin-sensitive.
Adjunctive therapy for PVL-associated infections

- **Immunoglobulin:**
  - Neutralizes toxins already produced
    - Inhibits PVL pore formation and its cytopathic effect in vitro
  - Concentration dependent
  - The optimal dosage is uncertain
  - Use 2 g/kg in PVL associated pneumonia

- Activated protein C
- Granulocyte colony stimulating factor
- Extracorporeal membrane oxygenation

Is PVL responsible for increased virulence?

Panton-Valentine virulence

Soft tissue infections and PVL

Conclusions

- The prevalence of *S. aureus* producing Panton-Valentine Leukocidine is increasing
  - By far the most common infected tissue is soft tissue – surgical drainage is the treatment of choice
    
    **No improvement should be expected from blocking PVL**

- PVL related pneumonia is extremely severe and difficult to treat
  
  **Combination antibiotic therapy including blocking exotoxins is more effective**
Need to genotype MRSA isolates?

- “At the present time, there is no information to suggest that molecular typing or identification of toxin genes should impact clinical management decisions”

CDC Clinical Management of MRSA Report, March 2006
Treatment Option for the Management of Skin and Soft-Tissue Infection

NEJM Oct 9 2008  Management of Skin and Soft-Tissue Infection — Polling Results
Comparison of Cephalexin Versus Clindamycin for Empiric Treatment of Suspected CA-MRSA Skin Infections
This study is currently recruiting participants.
Verified by Johns Hopkins University, May 2008

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<th>Johns Hopkins University Thrasher Research Fund</th>
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<tr>
<td>ClinicalTrials.gov Identifier:</td>
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DIDN'T WASH HANDS

MEN