Necrotizing pneumonia due to *Staphylococcus aureus* strains producing Panton-Valentine leukocidin

Gerard Lina
(gerard.lina@chu-Lyon.fr)
Déclaration de conflits d’intérêts

• Brevet
  ✓ bioMérieux R&D immunodiagnostic

• Bourse de recherche
  ✓ bioMérieux
  ✓ Novartis
  ✓ Pfizer

• Consulting
  ✓ bioMérieux
  ✓ Novartis

• Congrès, visites de laboratoires
  ✓ bioMérieux
  ✓ Copan
Panton-Valentine leukocidin (PVL)

- PVL = pore forming toxin
  - Produce by *S. aureus* (5 to 50%)
  - Human and rabbit specific
  - Target polymorphonuclear cells, monocytes and macrophages
  - Dose-dependent effects:
    - Release of pro-inflammatory and chemotactic mediators
    - Kill cells by apoptosis or necrosis
  - In rabbit induce leukopenia and tissues necrosis

- Clinical presentation of PVL infection
  - Old studies
    - skin infections/soft tissue abscesses…
    - chronic bone infections
  - In Prevost et al.
    - skin infections

Panton LA et al. Lancet 1932;i:56
Towers AG et al. Lancet 1958;ii:1192
Involvement of Panton-Valentine Leukocidin–Producing *Staphylococcus aureus* in Primary Skin Infections and Pneumonia

Gerard Lina,¹ Yves Piémont,² Florence Godail-Gamot,¹ Michèle Bes,¹ Marie-Odile Peter,³ Valérie Gauduchon,¹ François Vandenesch,¹ and Jerome Etienne¹

From the ¹Centre National de Référence de Toxémies Staphylocoociques, Faculté de Médecine, Lyon; ²Institut de Bactériologie, Université Louis Pasteur, Faculté de Médecine, Strasbourg; and ³Hôpital E. Muller-Moenschberg, Mulhouse, France

Table 1. Production of Panton-Valentine leukocidin by 171 *Staphylococcus aureus* strains associated with various clinical syndromes.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>No. of strains tested</th>
<th>No. (%) of PVL-positive strains</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>13</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Community-acquired</td>
<td>27</td>
<td>23 (85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Skin infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial folliculitis</td>
<td>10</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>Impetigo</td>
<td>4</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Finger pulp (felon)</td>
<td>15</td>
<td>2 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Cutaneous abscess</td>
<td>6</td>
<td>3 (50)</td>
<td>.03</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>9</td>
<td>5 (55)</td>
<td>.01</td>
</tr>
<tr>
<td>Furunculosis</td>
<td>30</td>
<td>28 (93)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

PVL associated with severe community-acquired pneumonia
Specific clinical features of PVL-associated pneumonia in case/control studies?

<table>
<thead>
<tr>
<th></th>
<th>PVL + N = 16</th>
<th>PVL- N = 36</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>14.8</td>
<td>70.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td>0</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>12</td>
<td>3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6</td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Blood leucocyte count</td>
<td>1.8</td>
<td>7.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Purulent expectoration</td>
<td>3</td>
<td>30</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


Survival of patients
Deaths: PVL+ 75%, PVL- 47%

Median survival time
PVL+: 4 days (young patients)
PVL-: 25 days (old patients)
P = 0.005

PVL+ infections died of respiratory failure or sepsis!
Necropsy: necrotizing pneumonia

- Larynx +
- Trachea:
  - abundant cocci + mucosal necrosis
- Lung:
  - few cocci + massively hemorrhagic
Memory from pediatric text books

• *S. aureus* pneumonia generally has:
  – as predisposing factor viral respiratory diseases (measles, influenza and adenovirus)
  – but :
    ¬ no haemoptysis!
    ¬ no leucopenia!
    ¬ mortality rate of 10%!

PVL-pneumonia is another disease: the necrotizing pneumonia.

Worldwide Emergence of PVL producing Community-associated MRSA

1. First detection PVL producing strain in France
   - Community MRSA
   - Genotype different from Hospital MRSA
   - MRSA multi-sensitive

2. Worldwide emergence of CA-MRSA producing PVL
   - Different genotypes
   - Different from HA-MRSA
PVL positive pneumonia in France

Passive survey by the CNR staphylocoques of PVL+ CA- S. aureus pneumonia

Nb of CA-MRSA pneumonia cases increased from 0% to 47%!
Addition of CA-MRSA pneumonia to CA-MSSA pneumonia
Clinical features of PVL-associated pneumonia

<table>
<thead>
<tr>
<th></th>
<th>CA-MRSA (n=35)</th>
<th>CA-MSSA (n=113)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median</td>
<td>22 (0.1 to 86 yrs)</td>
<td>22 (0.1 to 83 yrs)</td>
<td>ns</td>
</tr>
<tr>
<td>Sex Ratio</td>
<td>54%</td>
<td>58%</td>
<td>ns</td>
</tr>
<tr>
<td>No underling condition</td>
<td>57%</td>
<td>70%</td>
<td>ns</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>60%</td>
<td>61%</td>
<td>ns</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>23%</td>
<td>44%</td>
<td>ns</td>
</tr>
<tr>
<td>Purulent expectoration</td>
<td>47%</td>
<td>61%</td>
<td>ns</td>
</tr>
<tr>
<td>Skin rash</td>
<td>6%</td>
<td>8%</td>
<td>ns</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>43%</td>
<td>44%</td>
<td>ns</td>
</tr>
<tr>
<td>Leukopenia, median</td>
<td>4.4 (0.3 to 28.8)</td>
<td>8.8 (0.3 to 74.0)</td>
<td>ns</td>
</tr>
<tr>
<td>ARDS</td>
<td>31%</td>
<td>47%</td>
<td>ns</td>
</tr>
<tr>
<td>Septic shock</td>
<td>17%</td>
<td>13%</td>
<td>ns</td>
</tr>
<tr>
<td>Lethality</td>
<td>37%</td>
<td>44%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Identical presentation of PVL+ CA-MRSA and CA-MSSA pneumonia
7/13 deaths occurred in the 24 first hours of hospitalization!
12/13 within the 1st week!
There is no time to lost!
Marker linked to severity

1- Clinical: hemoptysis

<table>
<thead>
<tr>
<th>Hemoptyis</th>
<th>Survival OR (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CA-MRSA (n=35)</td>
</tr>
<tr>
<td>No</td>
<td>2.9 (0.9-10)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.35 (0.2-0.7)</td>
</tr>
</tbody>
</table>

P=0.032

P<0.001

* Hemorrhage from respiratory tractus at admission

2- Biological: blood leukocytes count

Threshold for survivors: 3,000 leucocytes/mm3

Survival OR (CI95%)

<table>
<thead>
<tr>
<th>Leucocytes count minimum</th>
<th>CA-MRSA (n=35)</th>
<th>CA-MSSA (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3,0</td>
<td>3 (1.1-7.9)</td>
<td>4.1 (2.5-6.9)</td>
</tr>
<tr>
<td>≤ 3,0</td>
<td>0.5 (0.3-0.9)</td>
<td>0.2 (0.1-0.4)</td>
</tr>
</tbody>
</table>

P=0.032                        P<0.001

Can we inhibit *S. aureus* virulence in necrotizing pneumonia?

Antimicrobial agents?

Passive immunisation by hIV-IG?
Action of antibiotics on toxins expression

Antibiotic effect on PVL production by CA-MRSA

Strains:
4 ST8
4 ST1
1 ST59
Antibiotics in rabbit model of PVL-MSSA pneumonia

Strong reduction of the mortality by clindamycin, linezolid, cloxacillin but not by vancomycin.

Delphine Corisier et al. ECMID 2010
Antibiotics in rabbit model of PVL-CA-MRSA pneumonia

Strong reduction of the mortality by linezolid but not by vancomycin!

Binh Diep et al. Submitted
Can we inhibit *S. aureus* virulence in necrotizing pneumonia?

Antimicrobial agents?

Passive immunisation by hIV-IG?
Human IVIG contains high level of neutralising anti-PVL antibodies

Abs against-PVL  Anti-PVL Abs are neutralising

Untreated

PVL  PVL + IVIG

Leucocytes

A single dose of human IVIG (0.2 g/kg) protects against lethal necrotizing pneumonia in rabbit model
CFU Titers in Organs

![Graph showing CFU titers in different organs with various treatments like Saline, IVIG, and Vancomycin. The y-axis represents log cfu/g, and the x-axis shows different organs: Lungs, Spleen, and Kidneys. The graph displays scatter plots and line graphs for each treatment group.]
Guidelines for PVL pneumonia

• Guideline for CA-MRSA pneumonia only in UK:
  – combination of clindamycin 1.2 g iv qds, linezolid 600 mg iv bd and rifampicin 600 mg bd until the patient has improved and is clinically stable when continuation therapy with linezolid plus rifampicin, or with clindamycin plus rifampicin
  – 1-2g/kg of IVIG, be repeated after 48 h if there is still evidence of sepsis, or failure to respond

• Guideline for MRSA pneumonia:
  – US, American Thoracic Society/Infectious Disease Society of America: vancomycin trough concentrations of 15–20 mg/mL and linezolid as alternative choice.
  – France, Société de pathologie infectieuse de langue française: no recommendation…
**Nouveau :** PHRC PVL et pneumonies communautaires sévères à *Staphylococcus aureus*

Inclusion : toute pneumonie communautaire à *S. aureus* nécessitant une hospitalisation en unité de soin intensif ou de réanimation.
Remerciements

France
Lyon. Hospices Civil de Lyon – Université Lyon1 –
INSERM U85, CNR Staphylocoques Lyon : Y Gillet,
D Floret, P Delguidice, B Issartel, N Rouzic, N
Sicot, E Javouhey, P Vanhems, L Genestier, F
Vandenenesch, J Etienne, Michèle Bes, V
Gauduchon, P Dufour, ME Reverdy, AL Genestier, A
Tristan, S Boisset, M Dumitrescu, O Dauwalder, H
Meugnier, M Croze, C Badiou, F Cozon, JP
Razigade, AM Frediere, F Laurent…
Strasbourg. Service de Microbiologie, Centre
Hospitalo-Universitaire de Strasbourg: Y Piemont
Paris. Hôpital R. Poincaré - Université Versailles Saint
Quentin en Yvelines : A Saleh-Mghir , A-C Crémieux
Hôpital Necker - Enfants Malades-Université René
Descartes : JC Fournet, N Brousse
Dijon. Département d’Infectiologie : D Hayez, S
Rousseau, D Croisier, P Chavanet

Belgique
Faculty of Veterinary Medicine, Ghent University, Ghent :
K Hermans, U Lipinska

UK
London, AM Kearns, E Boakes

Greece
Department of Microbiology, School of Medicine,
University of Patras: I Spiliopoulou, E Drougka

Algeria
Service de Microbiologie, Centre Hospitalo-
Universitaire Mustapha Bacha: N Ramdani-
Bouguessa, M Tazir

USA
Laboratory of Human Bacterial, Pathogenesis, NIH,
Hamilton : F Deleo
University of Texas School of Public Health, Houston
: ARN Forbes, M-G Bowden
Department of Pediatrics, Baylor College of Medicine,
Houston : KG Hulten
San Francisco General Hospital, University of California,
San Francisco : B Diep, HF Chambers

Australia
Division of Microbiology, Pathology Queensland
Central Laboratory, Herston Hospitals Complex,
Herston, Brisbane, Queensland: N George, GR
Nimmo

Singapore
Department of Medicine, National University of
Singapore: LY Hsu

«plus tous ceux que j’ai oubliés et les futures collaborateurs...»