Des pneumonies communautaires sévères à Staphylococcus aureus

F. Vandenesch, MD, PhD
Disclosure

Research Grants, consulting:

Astra Zeneca, Novartis, bioMérieux,
Sanofi-Pasteur, IRT Bioaster
Staphylococcus aureus, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30% of carriers

Lancet Infect Dis 2005; 5: 751-62
nasal carriage of *S. aureus* and the development of staphylococcal infection are linked

- rates of infection are higher in carriers than in non-carriers
- individuals are usually infected with their own carriage isolate
- temporary eradication of carriage following the use of topical mupirocin has been shown to reduce nosocomial infection
**Staphylococcus aureus**, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30% of carriers
- Responsible for a large number of diseases
  - Suppurative infections
**Staphylococcus aureus**, from commensalism to pathogenicity

- Gram-positive bacteria
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  - Toxemia
**Staphylococcus aureus**, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30% of carriers
- Responsible for a large number of diseases
  - Suppurative infections
  - Toxemia: toxic shock syndrome, staphylococcal scarlet fever = SAGs
Staphylococcus aureus, from commensalism to pathogenicity

- Gram-positive bacteria

- Commensal: 30% of carriers

- Responsible for a large number of diseases
  - Suppurative infections
  - Toxemia: bullous impetigo and SSS = exfoliative toxins
**Staphylococcus aureus**, from commensalism to pathogenicity

- Gram-positive bacteria

- Commensal: 30% of carriers

- Responsible for a large number of diseases
  - Suppurative infections
  - Toxemia
  - Food poisoning: TIAC

- Community & Hospital acquired
The burden of *S. aureus* infections

- **Frequency**
  - 25 to 40% of community-acquired infections
  - 25% of nosocomial infections
- **The burden for nosocomial infections**
  - Inpatients with *S. aureus* infection:
    - 3 times the length of hospital stay (14.3 vs 4.5 days; P<.001),
    - 3 times the total charges (48,824 US dollars vs 14,141 US dollars; P<.001),
    - 5 times the risk of in-hospital death (11.2% vs 2.3%; P<.001) than inpatients without this infection

Arch Intern Med 2005;165(15):1756-61
**Staphylococcus aureus**, from commensalism to pathogenicity

- Gram-positive bacteria
- Commensal: 30% of carriers

### Median survival time
- PVL+: 4 days
- PVL-: 25 days

\[ P = 0.005 \]
*S.aureus*, a diversity of secreted and cell-wall associated virulence factors

- **Adhesion**: >20 adhesins including MSCRAMs: Microbial Surface components Recognizing Adhesive matrix molecules

- **Acquisition of nutrients**: e.g. hemolysins & siderophores

- **Immune escape and subversion**:
  - Opsonisation inhibition: e.g. Prot A
  - Chemotaxis inhibition: e.g. CHIPS
  - Non-specific immune activation: superantigens
  - Hemolysins, pore-forming toxins and membrane-damaging peptides
Des pneumonies communautaires sévères à *Staphylococcus aureus*

F. Vandenesch, MD, PhD
Starting point: case report

- Yves Piémont, Strasbourg, 1998
- Jeune fille 14 ans sans ATCD
- J1: consultation état pseudo grippal
- J2: admission en réanimation SDRA, leucopénie, hémoptysie
- J3: décès.
  - *S.aureus*
  - Autospsie: nécrose extensive
  - Microbio: *S.aureus* Panton Valentine positif
CNR des staphylocoques

- Label DGS-InVS
- Expertise, surveillance, alert toward resistance or emerging staphylococcal diseases
- Ca 100 different french hospitals
- Ca 3000 strains expertised each year
G. Lina

- Retrospective analysis of *S. aureus* isolates from the CNR
- PCR targeting Panton Valentine leukocidin
- Results stratified according to known clinical informations
### 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><strong>Pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>13</td>
<td>0 (0)</td>
<td>—^a</td>
</tr>
<tr>
<td>Community-acquired</td>
<td>27</td>
<td>23 (85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Skin infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial folliculitis</td>
<td>10</td>
<td>0 (0)</td>
<td>—^b</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>
<tr>
<td><strong>Other infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>21</td>
<td>0 (0)</td>
<td>—^c</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>13</td>
<td>3 (23)</td>
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# Involvement of Panton-Valentine Leukocidin–Producing *Staphylococcus aureus* in Primary Skin Infections and Pneumonia

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

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</table>

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G. Lina

- Analyse rétrospective des souches de S.aureus reçues au CNR
- PCR ciblant la leucocidine de Panton Valentine
- Catégorisation / renseignement clinique connus

-> PVL significativement associé au caractère communautaire des pneumonies à S.aureus

Panton Valentine Leucocididine

- Phage encoded
- Two components -> hetero-octamer
- beta-barrel pore forming toxin

Panton LA, Lancet 1932;i:56
Panton Valentine Leucocidicine

- Phage encoded
- Two components -> hetero-octamer
- Beta-barrel pore forming toxin
- Apoptosis and necrosis

Genestier et al, J Clin Invest 2005;115:3117
Panton Valentine Leucocidin

- Phage encoded
- Two components -> hetero-octamer
- Beta-barrel pore forming toxin
- Apoptosis and necrosis
- Cell type specificity: neutrophils and macrophages
- Species specificity: human > rabbit > monkey > mice

Löffler et al. PLoS Pathog 2010
PVL induces rapid activation and cell death in human and rabbit neutrophils, but not in murine or simian cells

Panton Valentine Leucocidine

- Phage encoded
- Two components -> hetero-octamer
- Beta-barrel pore forming toxin
- Apoptosis and necrosis
- Cell type specificity: neutrophils and macrophages
- Species specificity: human > rabbit > monkey > mice
- Receptor on myeloid cells identified: C5aR > C5L2

András Spaan et al, Cell Host Microbes, 2013
LukS-PV binds to C5aR and C5L2 transfected cells
C5aRs Determine PVL Cell Specificity

C5aR is most abundantly expressed on neutrophils and monocytes but not on lymphocytes.

András Spaan et al, Cell Host Microbes, 2013
PVL Targets C5a Receptors

PVL induced pore formation (PI incorporation) is mediated by C5aR and C5L2

András Spaan et al, Cell Host Microbes, 2013
C5aR Determines PVL Species Specificity

HEK Cells transfected with C5aR from various species

András Spaan et al, Cell Host Microbes, 2013
LukS-PV is a potent inhibitor of the human C5aR

András Spaan et al, Cell Host Microbes, 2013
Panton Valentine Leucocidine

- Phage encoded
- Two components -> hetero-octamer
- beta-barrel pore forming toxin
- Apoptosis and necrosis
- Cell type specificity: neutrophils and macrophages
- Species specificity: human > rabbit > monkey > mice
- Receptor on myeloid cells identified: C5aR > C5L2
- -> facteur de sévérité des pneumonies communautaires?
Panton Valentine Leucocidin

- Phage encoded
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- Apoptosis and necrosis
- Cell type specificity: neutrophils and macrophages
- Species specificity: human > rabbit > monkey > mice
- Receptor on myeloide cells identified: C5aR > C5L2
- Prevalence: 2% of MSSA, ca 80% of CA-MRSA
PVL-SA: Genetic diversity

Courtesy Angela Kearns, Health Protection Agency, London, UK
• Does PVL production correlate with community acquired pneumonia?
• Does PVL production correlate with severity?
• -> Prospective observational study
  – 1 year, 76 hospitals
  – 16 PVL+ cases, 36 PVL- controls
### Clinical and biological features

<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 (5.4–24.0)</td>
<td>70.1 (59.2–81.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Risk factor (underlying disorder)</td>
<td>0</td>
<td>20</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Influenza-like illness (2 days before adm)</td>
<td>12</td>
<td>3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>6</td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Median trough leucocyte count (×109/L)</td>
<td>1.85 (0.6–6.4)</td>
<td>7.4 (4.9–9.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Survival of patients (16 cases, 36 controls)
Deaths: PVL+ 75%, PVL- 47%

Median survival time
PVL+: 4 days
PVL-: 25 days
$P = 0.005$
necrotizing pneumonia: a new clinical entity
–Median age 14 year, no risk factors
–Preceded by flu-like illness
–Typical symptoms: hemoptysis, leucopenia
–Mortality 75%
–Panton Valentine leucocidin

Lancet 2002; 359: 753-759
necrotizing pneumonia: a new clinical entity
–Median age 14 year, no risk factors
–Preceded by flu-like illness
–Typical symptoms: hemoptysis, leucopenia
–Mortality 75%
–Panton Valentine leucocidin

Lancet 2002; 359: 753-759. Times Cited: 726 (from Web of Science)
Is it a new syndrome?

Probable cases as early as 1930

PNEUMONIA IN RELATION TO AN EPIDEMIC OF "MILD" INFLUENZA, WITH THE REPORT OF THREE FULMINATING CASES APPARENTLY DUE TO STAPHYLOCOCCUS AUREUS*

BY ALEX. M. BURGESS, M.D.,† AND CHARLES-F. GORMLY, M.D.† NEJM 1930

First report CA-MRSA PVL+ infections

Vol. 48 / No. 32 MMWR 707

Four Pediatric Deaths from Community-Acquired Methicillin-Resistant Staphylococcus aureus — Minnesota and North Dakota, 1997–1999
Factors Predicting Mortality in Necrotizing Community-Acquired Pneumonia Caused by *Staphylococcus aureus* Containing Panton-Valentine Leukocidin

Yves Gillet,1,2,3 Philippe Vanhems,1,4 Gerard Lina,1,2,3 Michèle Bes,1,2,3 François Vandenesch,1,2,3 Daniel Floret,1,3 and Jerome Etienne1,2,3

- 50 PVL+ cases recruited via the NRC network
- Analysis of clinical and biological characteristics according to vital outcome

Factor associated with lethality: clinical parameters

- Hemoptysis: 42%
  - median survival time when + : 2 days
  - median survival time when - : 35 days
  - $p < 0.01$

Factor associated with lethality: biological parameters

Probability of survival

Range of leucocytes

- 11-74
- 4-10
- 1-3
- 0-1

Days after admission

p<0.001

Factor associated with lethality: biological parameters

Table 3. Multivariate analysis of factors associated with death among patients with Panton-Valentine leukocidin-positive *Staphylococcus aureus* pneumonia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Relative Hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count at hospital admission, leukocytes/mL</td>
<td></td>
</tr>
<tr>
<td>11,000–74,000</td>
<td>1.0</td>
</tr>
<tr>
<td>4000–10,000</td>
<td>1.29 (0.21–7.80)</td>
</tr>
<tr>
<td>&gt;1000–3000</td>
<td>7.99 (1.66–38.43)</td>
</tr>
<tr>
<td>0–1000</td>
<td>7.38 (1.60–34.02)</td>
</tr>
</tbody>
</table>

Severe leukopenia in *Staphylococcus aureus*-necrotizing, community-acquired pneumonia: risk factors and impact on survival

Nagham Khanafer\(^1,2\)*, Nicolas Sicot\(^3\), Philippe Vanhems\(^1,2\)*, Oana Dumitrescu\(^3\), Vanina Meyssonier\(^4\), Anne Tristan\(^3\), Michèle Bès\(^3\), Gérard Lina\(^3\), François Vandenesch\(^3,5\), Yves Gillet\(^3,6\) and Jérôme Etienne\(^3,5\)*

- 148 cases of CA PVL+ pneumonia
- study population divided into 2 groups:
  - leukocyte count \(\leq 3,000\) leukocytes/mL, \(n=62\)
  - \(>3,000\) leukocytes/mL, \(n=86\)
Khanafer et al. BMC Infectious Diseases (2013)
Table 2 Factors associated with severe leukopenia among patients with Panton-Valentine leukocidin-positive *Staphylococcus aureus*-associated necrotizing pneumonia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratios (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous influenza-like illness</td>
<td>4.45 (1.67-11.88)</td>
<td>0.003</td>
</tr>
<tr>
<td>Age &gt;30 years</td>
<td>2.69 (1.08-6.68)</td>
<td>0.033</td>
</tr>
<tr>
<td>Airway hemorrhage</td>
<td>4.53 (1.85-11.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Personal history of furuncles</td>
<td>0.11 (0.01-0.96)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

*Variables were adjusted to gender, mechanical ventilation, platelet count, pleural effusion, and time elapsed between onset of symptoms and hospitalization.*

Table 3 Factors associated with death among patients with Panton-Valentine leukocidin-positive *Staphylococcus aureus* pneumonia

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<tr>
<th>Variables</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1-year increase)</td>
<td>1.02 (1.01-1.03)</td>
<td>0.015</td>
</tr>
<tr>
<td>Airway hemorrhage</td>
<td>2.05 (1.18-3.59)</td>
<td>0.011</td>
</tr>
<tr>
<td>Severe leukopenia (≤3,000 leukocytes/mL)</td>
<td>4.50 (2.38-8.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Variables were adjusted to gender, mechanical ventilation, personal history of furuncles, platelet count, pleural effusion, and previous influenza-like illness.*
PVL in question
Controversy: factor of severity?

76 studies from 31 countries.
- PVL strongly associated with SSTI, but are rare in pneumonia.
- PVL-positive SSTI are more likely to be treated surgically.
- Children with PVL-positive musculoskeletal disease might have increased morbidity.

For other forms of disease [pneumonia,...] we identified no evidence that PVL affects outcome.
While PVL-positive strain might have a lesser propensity to cause pneumonia compared with SSTI, these meta-analyses cannot be used to make any inference regarding whether or not PVL contributes to the pathogenesis and outcomes of pneumonia.
Complexity

- Community-acquired MRSA
  - Harbor *pvl* genes
  - Can be highly epidemic (USA300)
  - Outcompete HA-MRSA in the US

- PVL and MRSA often mixed up in many articles

- Virulence and capacity to disseminate may not be linked
Methicillin resistance is not a predictor of severity in community-acquired *Staphylococcus aureus* necrotizing pneumonia—results of a prospective observational study

N. Sicot\(^1\), N. Khanafer\(^2,3\), V. Meyssonier\(^4\), O. Dumitrescu\(^1\), A. Tristan\(^1\), M. Bes\(^1\), G. Lina\(^1\), F. Vandenesch\(^1\), P. Vanhems\(^2,3\), J. Etienne\(^1\) and Y. Gillet\(^1,5\)

- 29 cases of PVL-MRSA pneumonia
- 104 cases of PVL-MSSA pneumonia

**TABLE 2.** Cox regression analysis of factors associated with 30 days mortality in community-acquired, Panton-Valentine leukocidin-positive *Staphylococcus aureus* necrotizing pneumonia\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>Multivariate adjusted hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td>Airway haemorrhage</td>
<td>0.004</td>
<td>2.96 (1.41–6.25)</td>
</tr>
<tr>
<td>Leucocyte count ((10^9/L))(^b)</td>
<td>0.001</td>
<td>0.32 (0.17–0.61)</td>
</tr>
<tr>
<td>Antitoxicin treatment</td>
<td>0.002</td>
<td>0.11 (0.03–0.49)</td>
</tr>
</tbody>
</table>

\(^a\)The model was adjusted on severity and presence of the mecA gene.
\(^b\)In this model, natural logarithms of leucocyte counts were used.

**FIG. 1.** Kaplan-Meier survival curves after 30 days for patients with community-acquired, Panton-Valentine-positive, *Staphylococcus aureus* necrotizing pneumonia according to methicillin susceptibility.

Sicot et al. CMI (2013)
Necrotizing pneumonia: pending questions

• Why so infrequent (ca. 30 cases/year in France)
  – 5% PVL among 30% S.aureus nasal carriage

• Why children and young adults ?

• -> genetic predisposition to this disease ?
Human genetics of infectious diseases

Rare, monogenic primary immunodeficiencies: one gene, multiple infections

Jean-Laurent Casanova, et al. EMBO J. 2007
Human genetics of infectious diseases

Common infectious diseases associated with polygenic inheritance of numerous susceptibility genes:
- one « common » infection, multiple genes

Jean-Laurent Casanova, et al. EMBO J. 2007
Human genetics of infectious diseases

Novel monogenic PIDs predispose the individual to a principal or single type of infection: -> one gene, one infection

Jean-Laurent Casanova, et al. EMBO J. 2007
A proposed age-dependent genetic architecture of infectious diseases

Current study

- Prospective observational study
- Nationwide level
- All cases of community-acquired pneumonia admitted to ICU caused by *S. aureus*
- Clinical and genetic informations collected
- Orfeome of 50 patients currently being analysed
Pneumonie Nécrosante : questions en suspens

• Pourquoi si rare (environ 30 cas/an en France)
• Pourquoi enfant et adulte jeune
• Comment améliorer l’évolution ?
  – Antibiotiques anti-toxiniques
  – Immunoglobulines intra-veineuses
  – Vaccin

-> PHRC recrutement National
-> ANR Blanc
Leucocidine de Panton Valentine :
Facteur indépendant de gravité des pneumonies à *Staphylococcus aureus*

Objectifs

- Confirmer le rôle de la PVL **comme facteur de gravité indépendant** des pneumonies à *S. aureus*
- Rechercher une **prédisposition génétique** rendant certains patients plus réactifs à l’effet de la PVL
- Impact de la prise en charge **thérapeutique** des patients sur l’évolution clinique
- Déterminer la proportion de **SARM-Co** responsables de pneumonie PVL+

Etude de cohorte

- volet observationnel adultes et enfants pneumonie communautaire grave à *S. aureus* hospitalisée en Réanimation
- volet interventionnel immunogénétique patients et famille: orfeome

Recueil

- Données cliniques
- Souche, Sérum, ADN
PHRC 2011 -2013
(F.Vandenesesch, L. Argaud, Y. Gillet)

Leucocidine de Panton Valentine :
Facteur indépendant de gravité des pneumonies à
*Staphylococcus aureus*
Objectives

✓ Investigate the role of PVL as an independent factor of severity in *S. aureus* CAP

✓ Identify clinical/biological factors associated with the disease prognostic

✓ Assess the level of antibiotic sensitivity of *S. aureus* strains

✓ Investigate the genetic susceptibility of the host
Inclusion criteria

• *S. aureus* CAP leading to hospitalization in ICU

Non-inclusion criteria

• HIV-positive
• Nosocomial pneumonia
• Hospitalization during three months prior to ICU admission for pneumonia
Data collection

- Demographic variables
- Medical history
- Signs and symptoms at presentation
- Radiological, laboratory and clinical findings during 7 days following hospitalization
- Biological sample: serum, total blood
2011 - 2013
114 cases enrolled
2011-2013
114 cases enrolled
CAP and influenza during influenza seasons

![Graph showing CAP and influenza cases over time.](image-url)
Characteristics of enrolled patients

✓ ♂/♀: 59/55
✓ 61 PVL+/53 PVL-
✓ 92 adults and 22 children <18 years old
✓ Serum available for all patients
✓ Blood samples for genetic analyses available for 53 patients (30 PVL+) and 37 family members
✓ CRF available for 70 patients
Interim analysis for 70 patients with available CRF
### Clinical and biological features at admission

<table>
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<tr>
<th>Variable</th>
<th>PVL-positive (n=38)</th>
<th>PVL-negative (n=32)</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>16 (42.1%)</td>
<td>22 (68.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (years), Median (min-max)</td>
<td>37.5 (0.2-79)</td>
<td>58 (16-82)</td>
<td>0.001</td>
</tr>
<tr>
<td>Purulent aspiration</td>
<td>15 (41.7%)</td>
<td>21 (65.6%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (15.8%)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Erythrodermia</td>
<td>8 (21%)</td>
<td>0</td>
<td>0.006</td>
</tr>
<tr>
<td>Median (min-max) CRP</td>
<td>291 (10-504)</td>
<td>203(20-486)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Antibiotic susceptibility of isolated strains

- **PVL-Negative**
  - MSSA 78.20%
  - MRSA 21.80%

- **PVL-Positive**
  - MSSA 81.20%
  - MRSA 18.80%

-> Severe CA pneumonia: MRSA = ca. 20%

- 6 CC80-MRSA-IV
- 3 CC5-MRSA-IV
- 3 ST8-MRSA-IV, USA300
- 3 CC88-MRSA-IV
Antibiotic susceptibility of isolated strains

PVL- Negative

MSSA 78.20%
MRSA 21.80%

PVL- Positive

MSSA 81.20%
MRSA 18.80%

-> Severe CA pneumonia: MRSA = ca. 20%
Clinical and biological features during hospitalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>PVL-Positive (n=38)</th>
<th>PVL-Negative (n=32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>24 (70.6%)</td>
<td>19 (61.3%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9 (25.7%)</td>
<td>8 (25.8%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Erythrodermia</td>
<td>9 (27.3%)</td>
<td>2 (6.3%)</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Pulmonary abscess</td>
<td>12 (38.7%)</td>
<td>5 (16.1%)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>6 (18.7%)</td>
<td>1 (3.3%)</td>
<td><strong>0.06</strong></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>18 (52.9%)</td>
<td>15 (48.4%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Unilateral condensation</td>
<td>15 (46.9%)</td>
<td>6 (19.4%)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Bilateral condensation</td>
<td>23 (69.7%)</td>
<td>27 (84.4%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Median (min-max) peak Leucocytes</td>
<td>15 (1.5-292)</td>
<td>13.2 (3.8-41.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>Median (min-max) trough Leucocytes</td>
<td>6.5 (0.7-117)</td>
<td>8.6 (0.4-18.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>28 (80.0%)</td>
<td>27 (87.1%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Treatment during the first 24h of hospitalization

✓ Appropriate empirical antibiotic therapy
PVL+: 93.3%
PVL-: 84.4%

✓ Antibiotic with antitoxin properties
PVL+: 30%
PVL-: 21.9%

No differences between the two groups
Mortality

Survival status known for 58 patients

Overall mortality rate

✓ No differences between PVL-positive and PVL-negative patients (40.0% vs 23.3%; p=0.2)

Mortality rate at Day-7

✓ Significantly higher among PVL-positive as compared to PVL-negative patients (31.6% vs 6.6%, p=0.009)
PVL affects mortality

Overall mortality
PVL+ 40%,
PVL- 23.3%, p=NS

Day-7 mortality
PVL+ 31.6%,
PVL- 6.6%, p=0.009
Factors associated with death regardless of PVL status

<table>
<thead>
<tr>
<th></th>
<th>Survival (n=37)</th>
<th>Death (n=21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pulmonary cancer</td>
<td>2 (2.2%)</td>
<td>5 (4.8%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoptysis during hospitalization</td>
<td>15 (40.5%)</td>
<td>13 (72.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Toxin eruption during hospitalization</td>
<td>2 (5.7%)</td>
<td>5 (27.8%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Currarisation at admission</td>
<td>5 (13.5%)</td>
<td>10 (50%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Curratisation during hospitalization</td>
<td>14 (38.9%)</td>
<td>13 (72.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Abscess at admission</td>
<td>9 (25%)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Abscess during hospitalization</td>
<td>15 (35.3%)</td>
<td>0</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Finding summary

✓ Characteristics of PVL-associated necrotizing CAP
  ✓ younger adults
  ✓ Rapid death at day-7
  ✓ Presence of Diarrhea and erythordermia at admission in 15% and 20% of these patients
  ✓ Higher rates of pneumothorax, erythrodermia and unilateral condensation during hospitalization
  ✓ High prevalence of MRSA
Finding summary

✓ Appropriate antibiotic therapy at admission in the large majority of patients
✓ regardless of PVL-status
   ✓ Death associated with haemoptysis and toxin eruption during hospitalization
   ✓ Survival associated with abscess at admission and during hospitalization
✓ Peaks of influenza seasons overlapped with an increase in the incidence of CAP
Perspectives

✓ Recruitment to be completed

✓ Study of genetic susceptibility of the host
  ✓ Orfeome of 50 patients currently being analysed

✓ Study of bacterial co-factors by Meta-genomic analysis
Conclusions

✓ Biological evidence and animal experiments converge toward a role of PVL in pathogenesis
✓ PVL remains a factor of severity in *S. aureus* CAP
✓ PVL-associated CAP: young adults and rapid death
✓ Severe leukopenia and airway haemorrhage associated with death
✓ Severe CA pneumonia: MRSA = ca. 20% regardless PVL -> optimize the empirical treatment
✓ Parallelism between influenza epidemics and higher incidence of CAP
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