Problématique du Sepsis et des Infections à Pseudomonas aeruginosa dans un Centre de Brûlés

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Séminaire de Pathologie Infectieuse

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Decreased Mortality From Major Thermal Injury Has Been Due To Advances In:

- Resuscitation
- Control of Infection
- Support of the Hypermetabolic Response To Trauma
- Early Closure of the Burn Wound
## Burn Mortality
*(TBSA associated with LD50)*

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-14</td>
<td>15-44</td>
<td>45-64</td>
<td>&gt;65</td>
<td>0-14</td>
</tr>
<tr>
<td>Bull &amp; Fisher (1942-52) 2807 Patients</td>
<td>49 n = 1366</td>
<td>46 n = 967</td>
<td>27 n = 330</td>
<td>10 n = 144</td>
<td>64 n = 962</td>
</tr>
<tr>
<td>Bull 1967-70 1917 Patients</td>
<td>64 n = 962</td>
<td>56 n = 565</td>
<td>40 n = 246</td>
<td>17 n = 144</td>
<td>77 n = 803</td>
</tr>
<tr>
<td>Curreri &amp; Abston 1975-79 1508 Patients</td>
<td>77 n = 803</td>
<td>63 n = 413</td>
<td>38 n = 178</td>
<td>23 n = 114</td>
<td>98 n = 1524</td>
</tr>
<tr>
<td>SBI/UTMB 1980-89 2164 Patients</td>
<td>98 n = 1524</td>
<td>70 n = 450</td>
<td>46 n = 127</td>
<td>19 n = 63</td>
<td>98 n = 1524</td>
</tr>
<tr>
<td>SBI/UTMB 1989-2005 Patients 1722</td>
<td>98 n = 1524</td>
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<td>19 n = 63</td>
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</tr>
</tbody>
</table>
Deaths from Sepsis

Years

Deaths

66-70 71-75 76-80 81-85 86-90 91-95 97-02
Invasive Burn Wound Infections
1991-2004

Admissions: 3,876

Patients with Invasive Wound Infections

Bacterial:
  Gram negative bacilli: 20
  Gram positive cocci: 5  25

Fungal:
  Aspergillus sp.: 47
  Mucor sp.: 16 65
  Candida sp.: 2

Incidence 2.3%
Mortality 55/90 (61%)
## Increased Deaths from Sepsis Due to Antibiotic Resistant Organisms 1997-2002

<table>
<thead>
<tr>
<th>Organism</th>
<th># Deaths</th>
<th>Mean % Burn</th>
<th>Mean LOS (days)</th>
<th>Antibiotic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusarium</td>
<td>7</td>
<td>72%</td>
<td>28</td>
<td>Amphotericin</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>14</td>
<td>73%</td>
<td>29</td>
<td>Colistin</td>
</tr>
<tr>
<td>Vancomycin Resistant Enterococcus and Pan Resistant Pseudomonas</td>
<td>6</td>
<td>76%</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Fusarium: 7 deaths out of 8 patients admitted from mass disaster.
Mortality associated with Fungal Infection in Burns

• 30% of Burn Patients Become Colonized With Candida Sp. At Some Time During Their Acute Hospital Stay.

* $p = 0.004$
Decreased Mortality From Major Thermal Injury Has Been Due To Advances In:

- Resuscitation
- Control of Infection
- Support of the Hypermetabolic Response
- Early Closure of the Burn Wound

The Three Last are Related
Effect of Delay to Excision and Grafting on Protein Catabolism

Critically ill patients with sepsis showed:

- increases in metabolic rate
- loss of body protein associated with loss of skeletal hence respiratory muscle
- impaired immune response
- poor wound healing

Voerman et al
Effect of Burn Sepsis on Metabolic Rate and Protein Catabolism

Enteral Feeding Intolerance and Sepsis

Association Between EFI and Sepsis

<table>
<thead>
<tr>
<th>Neither</th>
<th>EFI</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>2</td>
<td>13</td>
</tr>
</tbody>
</table>

EFI and sepsis are associated at p < .0001

Mortality Rates for Patients with EFI and Sepsis

* denotes significant difference from those with neither EFI or sepsis
Decreased Mesenteric Blood Flow

Decreased Gut Immune Function → Decreased Gut Mucosal Integrity

Decreased Ability to Prevent Bacterial Exodus from Lumen → Increase in Mucosal Permeability

Bacterial Translocation From The GI Tract
Complications of Catabolism

- Consequences associated with erosion of body mass\(^1\)

<table>
<thead>
<tr>
<th>% Lost</th>
<th>Altered Physiology</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>Impaired immune function</td>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
<td>Decreased wound healing</td>
<td>30%</td>
</tr>
<tr>
<td>30%</td>
<td>Pneumonia, pressure sores</td>
<td>50%</td>
</tr>
<tr>
<td>40%</td>
<td>Death (pneumonia)</td>
<td>100%</td>
</tr>
</tbody>
</table>

\(^1\)Chang, DeSanti, Demling. *SHOCK*. 1998
Scoring & Definitions should be Specific for Burns

- ABSI correlates better with mortality than APACHE II
- The clinical Pulmonary Infection score (CPIS) does not accurately predict the presence of pneumonia in burn patients, due to the systemic inflammation associated with injury. Pham et al. J Burn Care Res 2007; 28: 76-9.
- Sepsis definitions should be specific (see next)
Definition of *Sepsis*

**Burn**

- At least 3 of the following:
  - T > 38.5 or < 36.5°C
  - Progressive tachycardia
  - Progressive tachypnea
  - WBC > 12,000 or < 4,000
  - Refractory hypotension
  - Thrombocytopenia
  - Hyperglycemia
  - Enteral Feeding Intolerance

- **AND**
  - Pathologic tissue source identified

**Modified ACCP/SCCM**

- At least 2 of the following:
  - T > 38.5 or < 36.5°C
  - HR > 20% above NL for age
  - RR > 20% above NL for age or PaCO₂ < 32 torr
  - WBC > 12,000 or < 4,000

- **AND**
  - Bacteremia or fungemia
  - Pathologic tissue source identified
Effect of Ambient Temperature on Metabolic Rate

EFFECTS OF BURN INJURY ON IMMUNITY

- Decreased Neutrophils Chemotaxis
- T Cell Numbers Decreased
- Decreased Leukocyte Killing
- B Cell Numbers Normal or Increased
- Immunoglobulin Levels Variable
- Decreased Delayed Hypersensitivity
- Decreased Complement Levels
Burn-Associated Immunosuppression Associated with

Impairments in microbiocidal activities of:
- Natural Killer cells
- Macrophages
- T cells
- Neutrophils

Changes in relative Th1/Th2 cytokine levels

↓ Th1 (IFN-γ, IL-12, IL-15, IL-2)

↑ Th2 (IL-10 and IL-4)
WOUND CULTURES Jan - Mar 01 (N=81)

- **Gram +**
  - Staphylococcus aureus: 11
  - Staphylococcus albus: 11
  - MRSA: 9
  - Enterococcus spp: 6

- **Gram -**
  - Pseudomonas Aeruginosa: 16
  - Proteus spp: 4
  - Klebsiella spp: 3
  - E. coli: 2
  - Enterobacter spp: 1

Total: N = 81
CATHETER CULTURES Jan – Mar 01 (N=22)

- Staphylococcus albus: 9
- Staphylococcus aureus: 3
- MRSA: 2
- Pseudomonas aeruginosa: 5
- Enterobacter spp: 1
- Enterococcus spp: 1

Total:
- 68% of cultures were Staphylococcus albus
- 27% were Pseudomonas aeruginosa
- N = 22
- 17 venous
- 5 arterial
WOUND CULTURES Apr– Jun 01 (N=43)

Wound cultures APR- JUN 2001
n = 43

Candida albicans 4

Staphylococcus albus 5
MRSA 2
Enterococcus spp 7

Pseudomonas aeruginosa 18
Proteus spp 1
Klebsiella spp 2
E. coli 4

58%
9%
33%

Gram +
Gram -
Schimmel

N = 43
CATHETER CULTURES Apr – Jun 01 (N=17)

- **Staphylococcus albus**: 5
- **MRSA**: 1
- **Enterococcus spp**: 1
- **Pseudomonas aeruginosa**: 8
- **Proteus spp**: 1
- **E. coli**: 1

- Gram +
- Gram -
- Schimmel

- N = 17
- 15 venous
- 2 arterial
WOUND CULTURES Jul - Sep 01 (N=67)

- Staphylococcus aureus: 4
- Staphylococcus albus: 7
- MRSA: 1
- Enterococcus spp: 8
- Pseudomonas aeruginosa: 20
- Proteus spp: 8
- E. coli: 9
- Klebsiella spp: 5
- Enterobacter spp: 3
- Acinetobacter spp: 1

n = 67
CATHETER CULTURES Jul – Sep 01 (N=29)

- Staphylococcus aureus 1
- Staphylococcus albus 7
- Enterococcus spp 2
- Pseudomonas aeruginosa 11
- Proteus spp 2
- Klebsiella spp 2
- E. coli 2
- Enterobacter spp 1
- Acinetobacter spp 1
- Candida albicans 1

N = 29
24 venous
5 arterial
WOUND CULTURES Oct - Dec 01 (N=26)

- Staphylococcus aureus: 4
- Staphylococcus albus: 4
- Enterococcus spp: 5
- Pseudomonas aeruginosa: 6
- Proteus spp: 2
- E. coli: 2
- Klebsiella spp: 1
- Enterobacter spp: 1
- Citrobacter: 1

n = 26
CATHETER CULTURES OCT - DEC 01 (N=12)

- **Gram +**
  - Pseudomonas aeruginosa: 4
  - E. coli: 1
- **Gram -**
  - Staphylococcus aureus: 1
  - Staphylococcus albus: 4
  - Enterococcus spp: 2
- **Schimmel**: 58%

- Total: 12
- Venous: 11
- Arterial: 1
Wound vs Catheter Jan-Jun

Wound cultures APR-JUN 2001
n = 43

Gram +
Gram -
Schimmel
Wound vs Catheter Jul-Dec
HAEMOCULTURES 2001

- Trim 1: n = 2
- Trim 2: n = 5
- Trim 3: n = 7
- Trim 4: n = 4

Categories: Gram +, Gram -, Fungi

Legend:
- Yellow: Gram +
- Green: Gram -
- Cyan: Fungi

Y-axis: Count (0-6)
X-axis: Trims
Conclusions

• Skin colonisations correlate with catheters’ cultures, both are frequent

• Hemocultures bring few positive results

• The was a shift Gram+/-% during the year (was not identical in 2002)

• Conclusions:
  - Aim as 1st priority at reducing the bacterial load on the colonized skin (bath therapy, topical, excision)
  - Treat empirically IV if septic aiming at the germs found in the skin colonization
  - Change catheters if septic and use antimicrobial impregnated catheters
Control of Infection

- Prevention
- Topical Antimicrobials
- Regular cleansing of wounds
- Excision
- Systemic Antimicrobials
Are Topical Antimicrobials Useful?
### Quantitative Bacteriology of the Burn Wound

(Autopsy - Total Burn > 50%)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. Cases</th>
<th>No. Wound Samples</th>
<th>Bacteria per Gram Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average</td>
</tr>
<tr>
<td>1963</td>
<td>12</td>
<td>43</td>
<td>$6 \times 10^7$</td>
</tr>
<tr>
<td>(No Sulfamylon)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>9</td>
<td>38</td>
<td>$8.4 \times 10^4$</td>
</tr>
<tr>
<td>(Sulfamylon)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
## Invasive Burn Wound Sepsis

<table>
<thead>
<tr>
<th>Wound Treatment</th>
<th>Incidence as Autopsy Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No topical therapy</td>
<td>60%</td>
</tr>
<tr>
<td>Topical Therapy</td>
<td>28%</td>
</tr>
<tr>
<td>Topical Therapy plus Early Excision</td>
<td>6%</td>
</tr>
</tbody>
</table>
Topical Therapy of the Burn Wound

- Silver Sulfadiazine Cream
- Dressing with Silver Micro-crystals
- Isobetadine (Polyvidon Iod 10%)
- Furacin Solution (Nitrofural 0.2%)
- Colistin Milk (Colistin Sulf 0.5%)
Molecular Epidemiology of 
*Pseudomonas Aeruginosa* Colonization 
in the Brussels Burn Unit

Setting

- ICU: 8 single-bed rooms, MCU: 12 double-bed rooms
- Daily hydrotherapy and Daily application of 1% Silver Sulphadiazine (SSD)
- Surgical excision starting within 1st week after admission
- Sampling: twice a week (ICU), weekly (MCU)
- 5 August 1998: outbreak MDR *Ps. Aeruginosa*
- 1999: epidemic strain disappeared (occupancy rate: 10%)
Outbreak Analysis

Exogenous source initially suspected

→ Screening of patients

→ Environmental survey

→ Retrospective analysis frozen stock

**Methods:**

- Standard microbiology procedures
- Serotyping and drug susceptibility testing (antibiotics and topical agents)
- Genotyping: RAPD-PCR and AFLP
366 *Ps. Aeruginosa* isolates (incl. 45 environmental): 48 genotypes

48 AFLP patterns and dendrogram of the *Ps. Aeruginosa* genotypes
DNA genotyping: Results (1)

- 48 different AFLP genotypes
  - N patient = 70 (100%)
    - 21 exclusively from environment
    - 15 from only one patient
    - 12 from several patients (N = 57), of which 2 in environment

Conclusion:
- No ongoing *P. Aeruginosa* reservoir in environment
- But, 57 events of cross-acquisition

Concentrating on the genotypes found in n patients
- 27% of the patients colonized by 2 to 4 strains
- And, 2 genotypes were found in 60% of the patients
  - AFLP 35: 131 isolates, 29 patients
  - AFLP 8: 76 isolates, 19 patients
Characteristics of *P. Aeruginosa* colonized patients

- Most of them were colonized in the unit, so the main factor was the length of stay (LOS).
- Out of 441 patients, 70 patients (16%) colonized,
- 12 (17%) at admission, 58 (83%) later (nosocomially).
- Colonization versus hospitalization length, age and TBSA.
Patient P13 (age 25, TBSA 75%, 10 month hospitalization)

Simultaneously colonized with 4 genotypes (incl. AFLP 35 and AFLP 8)
Drug susceptibility testing - AFLP 35 & 8

- **Antibiotics**
  - Most strains susceptible to most antibiotics
  - 4 genotypes (incl. AFLP 35) were MDR

- **Topical agents**
  - AFLP 8: antibiotic sensitive but SSDR
Analysis of an Outbreak of *Ps. Aeruginosa*,

Conclusions:

- Patient P13: continuous reservoir of AFLP 35 and AFLP 8
- AFLP 35 and AFLP 8 were highly successful (60% of the patients with Ps Ae) due to acquired resistance to antibiotics or topical antimicrobial
- No inanimate reservoir and patients colonized via cross-acquisition
The project for a New Unit:

A burn center must be renovated every 15 years, this means planning and budgeting after ten years…

This project was designed to reduce the bacteriological risk.
B4. Medische Organisatie : Algemeen
Organisation Médicale : Généralités

HIGH CARE

ONTHAAL ACCUEIL

MEDIUM CARE

LOW RISK

AMBULANTE KLINIEK

CLINIQUE PATIENTS AMBULATOIRES
Sepsis with MR Ps Aeruginosa

• Colistine IV (Colistineb®) is used (again) since 2006
  - 6-8 Mio./24 Hr in three dosis
  - Toxicity:
    • Follow Renal (RF) function and adjust dosis
    • Toxicity increased by concommittent use of an aminoglycoside
    • In 15% has an impact on RF (reversibility)
    • In 4-6% is neurotoxic (reversibility and not dosis related)
  - From in vitro studies: the parenteral form and long dosage intervals may be problematic for treatment of infections by colistin resistant A. baumanii

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- Slides 3-14, 16-20: D HERNDON, MD
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- Slides 49-50: S WEYGERS