Farmacologia dei vecchi e nuovi antibiotici nelle polmoniti; terapia aerosolica?

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The inadequate tissue penetration hypothesis

In respiratory medicine, there are many publications on tissular concentrations to promote the idea that some antibiotics having a high tissular concentration accumulate in biophase (quinolones, macrolides) and are more efficacious as suggested by their low or undetectable plasma concentrations.
The inadequate tissue penetration hypothesis: Schentag 1990

• Two false assumptions
  1. tissue is homogenous
  2. bacteria are evenly distributed through tissue

⇒ spurious interpretation of all important tissue/serum ratios in predicting the antibacterial effect of AB

Schentag, 1990
Tissue concentrations: do we ever learn?

Johan W. Mouton¹, Ursula Theuretzbacher², William A. Craig³, Paul M. Tulkens⁴, Hartmut Derendorf⁵ and Otto Cars⁶

Statements such as ‘concentrations in tissue x h after dosing are much higher than the MICs for common pathogens that cause disease’ are meaningless

Mouton & al JAC 2007
Q1: Where are located the pathogens
Where are located the pathogens

**ISF**

Most bacteria of clinical interest

- S. pneumoniae
- E. coli
- Klebsiella
- Pseudomonas

**Cell**

(most often in phagocytic cell)

- mycoplasma (some)
- Chlamydiae
- Brucella
- Cryptosporidiosis
- Listeria monocytogene
- Salmonella
- Mycobacteria

S. Aureus

Legionella
Q2: Where is the biophase
The interstitial space fluid is the biophase

1. Most bacterial infections are located in the extracellular compartment.

2. Except few cases, In acute infections in non-specialized tissues, where there is no abscess formation, interstitial space fluid (ISF) must be considered as the actual target space for anti-infective agents

3. ISF concentrations are of primary interest

Muller et al. AAC, 2004, 48: 1441-1453
Q3: what is a tissue & what is a tissular concentration
In the past, it was used to characterize the **total concentration in a homogenized biopsy sample**

It was assumed that:
- tissue is homogenous
- that antibiotics is evenly repartited in tissue
- That bacteria are evenly repartited in tissue

Each of these assumptions is false and can be very misleading
Why a total drug tissue concentrations may be misleading?

1. Drug distributed mainly extracellurally
   - β-lactams and aminoglycosides,
   - grinding up the tissue means dilution of the drug by mixing intracellular and extracellular fluids, resulting in underestimation of its concentrations at the site of infection.

2. Drug accumulated by cells
   - fluoroquinolones or macrolides
   - assay of total tissue levels will lead to gross overestimation of the extracellular concentration.
   - The opposite is true for intracellular infections.
Methods for studies of target site drug distribution in antimicrobial chemotherapy
“Tissue concentrations”

- **Total tissue**
  - homogenates
  - biopsies

- **Extracellular fluids**
  - implanted cages
  - implanted threads
  - wound fluid
  - blister fluid
  - ISF (Microdialysis, Ultrafiltration)
Plasma (total, free) concentration vs interstitial concentration (muscle, adipose tissue) (Moxifloxacin)

Muller AAC, 1999
Plasma (total, free) concentration vs muscle (free) concentration

Protein binding?

Liu J.A.C. 2002

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What we learnt with animal and human MD studies

• MD studies showed that:
  1. The concentrations in ISF of selected antibiotics correspond to unbound concentrations in plasma
  2. They are generally much lower than total concentrations reported from whole-tissue biopsy specimens especially for macrolides and quinolones
What we learnt with MD studies:
Inflammation
Tissue concentrations of levofloxacin in inflamed and healthy subcutaneous adipose tissue

**Hypothesis:** Accumulation of fibrin and other proteins, oedema, changed pH and altered capillary permeability may result in local penetration barriers for drugs.

**Methods:** Free Concentrations measured in six patients by microdialysis after administration of a single intravenous dose of 500 mg.

**Results:** The penetration of levofloxacin into tissue appears to be unaffected by local inflammation. Same results obtained with others quinolones.

*Figure 1*
Concentration vs time profiles for total (●) and free levofloxacin (——) in plasma (n = 7), and inflamed (△) and healthy tissue (▽) (n = 6). Data are presented as means ± SD.

Bellmann & al Br J Clin Pharmacol 2004 57

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In acute infections in non-specialized tissues, where there is no abscess formation, free serum levels of antibiotics are good predictors of free levels in tissue fluid.
The issue of lung penetration
Antibiotic penetration to the site of infection

Alveolar macrophages
Epithelial lining fluid
Colonising encapsulated bacteria
Infected lung
Antibiotic penetration
Cefpodoxime at steady state: plasma vs. ISF (muscle & Lung)

Free muscle concentrations of cepodoxime were similar to free lung concentration and therefore provided a surrogate measure of cefpodoxime concentration at the pulmonary target site.

Liu et al., JAC, 2002 50 Suppl: 19-22.
The major finding of this study was the observation of virtually superimposed free IPM concentration-versus-time profiles in the three media investigated,

- This result not only is in agreement with theory but also is consistent with most of the data in the literature.
Lung infections

• Uncertainty of the relevant actual location of proliferating bacteria
  – Alveoli, pulmonary interstitium, bronchioles, blood??

• What is the biophase??
  – Epithelium lining fluid (ELF)
  – Lung IF, alveolar macrophages, tissue biopsies, blood, bronchial secretion, sputum??

• ELF seems the most relevant specimen but potential sources of error: dilution, release of AB from alveolar macrophage in the sample
The blood-alveolar barrier

- Fenestrated pulmonary capillary bed
  - expected to permit passive diffusion of antibiotics with a molecular weight 1,000

The alveolar epithelial cells would not be expected to permit passive diffusion of antibiotics between cells, the cells being linked by tight junctions.
Drug passage through the alveolar epithelial cells will depend on the lipophilicity and diffusibility of the antibiotics, similar to the drug entry into the central nervous system.
ELF concentration: possible bias

- Measurement problems may confound the interpretation of the ELF concentrations of antibiotics.
- Cells, especially AM cells (that constitute 3.8 to 10.0% of ELF volume) are included in the composition of ELF.
- The cells may be lysed during the measurement of antibiotic concentration in BAL-derived fluids.


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Measured ELF concentrations of the beta-lactams are well below serum concentrations, and their respective concentrations in AM cells were negligible.

The low measured ELF concentrations of beta-lactams in comparison to their corresponding serum levels could be the result of low capacity of their unbound free fractions for penetration through the alveolar epithelial cell barriers.

GLICOPEPTIDES

Measured ELF concentrations of the glicopeptides are well below serum concentrations, and their respective concentrations in AM cells were negligible.

The low measured ELF concentrations of glicopeptides in comparison to their corresponding serum levels could be the result of low capacity of their unbound free fractions for penetration through the alveolar epithelial cell barriers. Moreover, its penetration is slow.

Measured ELF concentrations of macrolides and ketolides and their derived AUCs were consistently higher than serum levels by as much as 10-fold. The high ratios of ELF concentration to serum concentration for macrolides and ketolides could not be explained solely on the basis of good penetration across the alveolar epithelium.

The high concentrations of macrolides and ketolides in ELF might be explained by the possible contamination of intracellular antibiotics occurring during the process of BAL.

Fluoroquinolones achieved higher ELF levels than their free serum concentrations.

Effects of sepsis on serum drug concentrations

SEPSIS

- Increased cardiac index
- Increased capillary permeability
- Fluids shifts
- End organ dysfunction
- Increased clearances
- Increased volume of distribution
- Increased drug half-lives
- Decreased clearances

Low serum drug concentrations
- Consider an increase of dose

High serum drug concentrations
- Consider a decrease of dose

Hydrophilic and lipophilic antibiotics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hydrophilic</th>
<th>Lipophilic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Vd</strong></td>
<td>• Predominant renal CL</td>
<td>• Predominant hepatic CL</td>
</tr>
<tr>
<td><strong>Low intracellular penetration</strong></td>
<td></td>
<td>• Good intracellular penetration</td>
</tr>
<tr>
<td><strong>↑ Vd</strong></td>
<td>• CL ↑ or ↓ dependent on renal function</td>
<td>• Vd largely unchanged</td>
</tr>
<tr>
<td><strong>↑ or ↓ CL</strong></td>
<td></td>
<td>• CL ↑ or ↓ dependent on hepatic function</td>
</tr>
</tbody>
</table>

Examples:
- β-lactam
- Aminoglycosides
- Glycopeptides
- Colistin
- Fluoroquinolones
- Macrolides
- Lincosamides
- Tigecycline
- Linezolid

Vd, volume of distribution; CL, clearance; ICU, intensive care unit

**Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis**


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**Table 3**

Comparison of total ertapenem pharmacokinetic data after a single 1 g infusion obtained in critically ill patients with severe sepsis versus published data for critically ill patients with early-onset ventilator-associated pneumonia [7] and healthy volunteers [9,17].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>This study (n=8)</th>
<th>Burkhardt et al. [7] (n=17)</th>
<th>Majumdar et al. [9] (n=16)</th>
<th>Pletz et al. [17] (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.D.</td>
<td>Geometric mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>5.7 ± 4.9</td>
<td>4.5</td>
<td>4.15 ± 1.33</td>
<td>3.8</td>
</tr>
<tr>
<td>$V_{ss}$ (L)</td>
<td>59.4 ± 85.7</td>
<td>26.8</td>
<td>14.8 ± 3.78</td>
<td>8.2 ± 1.5</td>
</tr>
<tr>
<td>$CL_t$ (mL/min)</td>
<td>200.5 ± 306.9</td>
<td>88.6</td>
<td>43.2 ± 23.7</td>
<td>29.5 ± 3.4</td>
</tr>
<tr>
<td>$CL_R$ (mL/min)</td>
<td>72.5 ± 98.3</td>
<td>33.2</td>
<td>31.8 ± 23.3</td>
<td>12.9 ± 4.3</td>
</tr>
<tr>
<td>$f_o$ (% of dose)</td>
<td>45.1 ± 30.3</td>
<td>36.7</td>
<td>54.8 ± 19.09</td>
<td>44.4 ± 14.8</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (mg h/L)</td>
<td>317.7 ± 274.6</td>
<td>188.0</td>
<td>418.5 ± 171.6</td>
<td>572.1 ± 68.6</td>
</tr>
<tr>
<td>$C_{max}$ (mg/L)</td>
<td>94.1 ± 79.0</td>
<td>52.3</td>
<td>90.5 ± 26.1</td>
<td>154.9 ± 22.0</td>
</tr>
</tbody>
</table>
Comparison of main PK parameters for linezolid 600 mg iv

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Septic Shock</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>14.23 ± 3.45</td>
<td>13.32 ± 5.03</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>4.92 ± 2.08</td>
<td>4.73 ± 2.08</td>
</tr>
<tr>
<td>$\text{AUC}_{0-24}$</td>
<td>70.78 ± 28.12</td>
<td>78.30 ± 24.97</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>9.81 ± 4.32</td>
<td>8.59 ± 3.38</td>
</tr>
</tbody>
</table>

Mean ± standard deviation

Thallinger C et al JAC. 2008;61:173-176;
# Tissue penetration (% tissue / serum)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Vancomycin</th>
<th>Teicoplanin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>7-13%</td>
<td>50-60%</td>
<td>60%</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0-18%</td>
<td>10%</td>
<td>70%</td>
</tr>
<tr>
<td>Epithelial lining fluid (ELF)</td>
<td>11-17%</td>
<td>30%</td>
<td>450%</td>
</tr>
<tr>
<td>Inflammatory fluid</td>
<td>30%</td>
<td>77%</td>
<td>104%</td>
</tr>
<tr>
<td>Muscle</td>
<td>30%</td>
<td>40%</td>
<td>94%</td>
</tr>
<tr>
<td>Peritoneal dialysis fluid</td>
<td>20%</td>
<td>40%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Graziani 1988; Matzke 1986; Albanese 2000; Georges 1997; Lamer 1993; Daschner 1987; Blevins 1984; Wilson 2000; Stahl 1987; Wise 1986; Franck 1997; Lovering 2002; Conte 2002; Gee 2001; Gendjar 2001
Conclusions 1° part:

1. In acute infections in non-specialized tissues, where there is no abscess formation, free plasma levels of antibiotics are good predictors of free levels in interstitial fluid.

2. PK/PD indices predictive of antibiotic efficacy should be based on free plasma concentration.

3. People who truly understand tissue concentration work in corporate marketing departments (Apley, 1999).
Aerosolized antibiotics ?
The blood-alveolar barrier

- Fenestrated pulmonary capillary bed
  - expected to permit passive diffusion of antibiotics with a molecular weight 1,000

The alveolar epithelial cells would not be expected to permit passive diffusion of antibiotics between cells, the cells being linked by tight junctions.

Epithelial lining fluid (ELF) (protein:<10%)
Aerosolized antibiotics in the ICU

- **Systemic** antibiotics often have **poor** penetration into lung parenchyma limiting effectiveness against infections that require **higher** concentrations.
- To achieve these concentrations with **aminoglycosides**, the risk of **ototoxicity** and **nephrotoxicity**
- **Polymyxins** → **nephrotoxicity, neuromuscular blockade, and neurotoxicity**
- Inhaled therapy → the delivery of high antibiotic concentrations directly to the endobronchial tree to minimize the adverse effects of systemic therapy.
Inhaled antibiotics for long-term therapy in cystic fibrosis (CF)


Aerosolized tobramycin after 20 wks: increase in the FEV1, forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC, bodyweight, BMI and a decrease in lost school/work days due to disease.

10.1002/14651858.CD001021.pub2.
Aerosolized antibiotics for non-CF adult patients with bronchiectasis and tracheobronchitis

Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of Pseudomonas aeruginosa infections in adult bronchiectasis. Chest 2006; 130:1503–1510.

addition of inhaled tobramycin to a 14-day course of oral ciprofloxacin

The multiinstitutional, randomized controlled trial of 53 patients demonstrated a greater microbiologic response in the tobramycin group, but no statistical clinical efficacy difference was described at day 14 or 21.
Aerosolized antibiotics in the ICU

- **Aerosolized antibiotics**: ideal alternative to i.v. therapy in VAP
- → High drug dosage at the site of infection and limiting systemic absorption, reducing renal toxicity.

Palmer LB, Smaldone GC, Chen JJ, et al.
Aerosolized antibiotics and ventilator-associated tracheobronchitis in the ICU

Based on Gram stain of the tracheal aspirate, patients received aerosolized vancomycin or gentamycin for 14 days versus placebo.

Reduced clinical signs of respiratory infection, pulmonary infection score, progression to VAP, reduced bacterial resistance, reduced use of systemic antibiotics, and earlier discontinuation of mechanical ventilation.
Aerosolized antibiotics in the ICU


1950 – 2005: Meta-analysis of 5 RCTs (414 pts)
ICU-acquired pneumonia was statistically less common in the cohorts receiving aerosolized antibiotic prophylaxis.


Monotherapy via the inhaled route should be considered when i.v. therapy is unavailable or limited by complications.
Aerosolized antibiotics in the ICU


Low systemic concentrations of aminoglycosides after inhalation.


The use of inhaled tobramycin in addition to a systemic β-lactam cured all patients with pseudomonas or acinetobacter VAP, whereas the cohort with i.v. tobramycin had two failures.
Aerosolized antibiotics in the ICU

Meta-analysis of 5 RCTS

Ioannidou E, Siempos II, Falagas ME. Administration of antibiotics via the respiratory tract for the treatment of nosocomial pneumonia: a meta-analysis.

Review: Administration of antimicrobials via the respiratory tract for the treatment of nosocomial pneumonia: a meta-analysis
Comparison: 01 Antibiotics administered via the respiratory tract versus antibiotics administered systemically
Outcome: 01 Treatment success in ITT patients

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Aerosolized n/N</th>
<th>Systemic n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky et al.17</td>
<td>7/7</td>
<td>2/8</td>
<td></td>
<td>1972</td>
</tr>
<tr>
<td>Klastersky et al.16</td>
<td>14/18</td>
<td>9/20</td>
<td>4.28 [1.04, 17.66]</td>
<td>1979</td>
</tr>
<tr>
<td>Brown et al.13</td>
<td>24/45</td>
<td>10/40</td>
<td>1.60 [0.59, 3.28]</td>
<td>1990</td>
</tr>
<tr>
<td>Le Conte et al.11</td>
<td>7/21</td>
<td>3/17</td>
<td>2.33 [0.50, 10.91]</td>
<td>2000</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>91</td>
<td>85</td>
<td>2.39 [1.29, 4.44]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 52 (aerosolized), 32 (systemic)
Total for heterogeneity: $\chi^2 = 5.07, df = 3 (P = 0.17), I^2 = 40.8\%$
Text for overall effect: $Z = 2.76 (P = 0.006)$

No difference was demonstrated for mortality, emergence of resistance, or adverse event.

### Table 1. Baseline Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>Aerosol (n = 20)</th>
<th>Intravenous (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean ± SD</td>
<td>58 ± 15</td>
<td>60 ± 17</td>
<td>0.71</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (75)</td>
<td>18 (90)</td>
<td>0.41</td>
</tr>
<tr>
<td>SAPS II, mean ± SD</td>
<td>33 ± 13</td>
<td>30 ± 10</td>
<td>0.47</td>
</tr>
<tr>
<td>SOFA, median (IQR)</td>
<td>3.5 (2.5–7.5)</td>
<td>3.0 (2.5–5.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>CPIS, median (IQR)</td>
<td>8 (7–8)</td>
<td>9 (8–9)</td>
<td>0.01</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>3 (15)</td>
<td>4 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Circulatory shock, n (%)</td>
<td>5 (25)</td>
<td>2 (10)</td>
<td>0.41</td>
</tr>
<tr>
<td>Admission category, n (%)</td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Trauma</td>
<td>7 (35)</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>12 (60)</td>
<td>10 (50)</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>Body temperature, mean ± SD</td>
<td>38.2 ± 0.6</td>
<td>38.5 ± 0.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Leukocyte count (cells/mm³), mean ± SD</td>
<td>12,470 ± 5,582</td>
<td>13,205 ± 5,116</td>
<td>0.67</td>
</tr>
<tr>
<td>PaO₂/FIO₂, mean ± SD</td>
<td>266 ± 79</td>
<td>250 ± 66</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Aerosol (n = 20)</td>
<td>Intravenous (n = 20)</td>
<td>P Value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Cure of <em>P. aeruginosa</em> VAP on Day 9, n (%)</td>
<td>14 (70)</td>
<td>11 (55)</td>
<td>0.33</td>
</tr>
<tr>
<td>Day 9: Positive BAL $\geq 10^4$ cfu·ml$^{-1}$ or mini-BAL $\geq 10^3$ cfu·ml$^{-1}$, n</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Persisting <em>P. aeruginosa</em> VAP on Day 9, n (%)</td>
<td>3 (15)</td>
<td>6 (30)</td>
<td>0.26</td>
</tr>
<tr>
<td>VAP caused by superinfection on Day 9, n (%)</td>
<td>3 (15)</td>
<td>3 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrence of <em>P. aeruginosa</em> VAP, n</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrence of VAP caused by superinfection, n</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of MV, median (IQR)</td>
<td>29 (22–38)</td>
<td>18 (13–31)</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of MV after inclusion, median (IQR)</td>
<td>14 (7–22)</td>
<td>8 (6–12)</td>
<td>0.18</td>
</tr>
<tr>
<td>Length of stay in ICU, median (IQR)</td>
<td>38 (29–55)</td>
<td>29 (18–44)</td>
<td>0.08</td>
</tr>
<tr>
<td>Length of stay in ICU after inclusion, median (IQR)</td>
<td>24 (18–48)</td>
<td>16 (11–23)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mortality on Day 28, n (%)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Aerosolized antibiotics in the ICU

Cosa abbiamo in mano?

La somministrazione di antibiotici per aerosol può essere un utile complemento alla terapia sistemica

Non ci sono dati sufficienti per definire la validità della sola terapia per aerosol

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