Traitement des infections liées à

*P. aeruginosa*

Benoit Guery
CHUV Lausanne
✓ *Pseudomonas aeruginosa* was the most common Gram-negative organism isolated in all pneumonia classes

- HCAP, 22/199 (11.1%)
- HAP, 28/379 (7.4%)
- VAP, 57/606 (9.4%);
✓ Patients with ICU-acquired Gram-negative bacteremia from 2004 to 2012 reviewed retrospectively
✓ Seventy-eight cases of ICU-acquired Gram-negative bacteremia occurred in 74 patients.
Multicenter observational study underwent in 68 medical institutions worldwide during a six-month study period (October 2012-March 2013).

1898 patients
- Mean age of 51.6 years (range 18-99)
- 777 patients (41%) were women

Community-acquired IAIIs: 1,645 (86.7%) healthcare-associated infections: 253 (13.3%)

Intraperitoneal specimens were collected from 1,190 (62.7%) of the enrolled patients.
Plan

✓ Sensibilité aux principales molécules et nouvelles molécules
✓ Le trio hôte-molécule-pathogène
✓ PK/PD
✓ Durée
✓ Associations
✓ Thérapeutiques alternatives
Table 1. Chromosomally encoded or imported resistance mechanisms of *P. aeruginosa*.

<table>
<thead>
<tr>
<th>Location</th>
<th>Resistance mechanisms</th>
<th>Targeted antibiotics</th>
<th>Type of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic (chromosomal)</td>
<td>AmpC–type cephalosporinase</td>
<td>β-lactams</td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class D oxacillinase OXA-50</td>
<td>β-lactams</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides inactivating enzymes</td>
<td>Aminoglycosides</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Efflux systems (overexpression)</td>
<td>Multiple antibiotic classes</td>
<td></td>
<td>Efflux systems</td>
</tr>
<tr>
<td>Decreased membrane permeability</td>
<td>Multiple antibiotic classes</td>
<td></td>
<td>Membrane permeability and purines</td>
</tr>
<tr>
<td>DNA gyrase and topoisomerase IV</td>
<td>Fluoroquinolones</td>
<td></td>
<td>Target modification</td>
</tr>
<tr>
<td>LPS modification</td>
<td>Colistin</td>
<td></td>
<td>Target modification</td>
</tr>
<tr>
<td>Imported (Mobile genetic elements)</td>
<td>Class A serine β-lactamases (PSE, CARB, TEM)</td>
<td>β-lactams</td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class A serine ESBL (TEM, SHV, CTX-M, PER, VEB, GES, IBC)</td>
<td>β-lactams</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class D ESBL (OXA-types)</td>
<td>β-lactams</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class B Metallo-β-lactamase (IMP, VIM, SPM, GIM)</td>
<td>Carbapenems</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class A serine carbapenemase (KPC)</td>
<td>Carbapenems</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Class D carbapenemase (OXA-types: OXA-40)</td>
<td>Carbapenems</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Aminoglycosides inactivating enzymes</td>
<td>Aminoglycosides</td>
<td></td>
<td>Antibiotic inactivation</td>
</tr>
<tr>
<td>Ribosomal methyltransferase enzymes</td>
<td>Aminoglycosides</td>
<td></td>
<td>Target modification</td>
</tr>
</tbody>
</table>
**Antibiotiques avec une activité contre *Pseudomonas***

### β-lactamines
- ticarcilline ± clavu
- pipéracilline ± tazo
- aztréonam
- cefsulodine
- céfopérazone
- ceftazidime
- cefpirome
- cefépime
- ceftolozane-tazobactam
- ceftazidime-avibactam
- imipénème
- méropénème
- doripénème

### Aminosides
- gentamicine
- nértilmicine
- tobramycine
- amikacine
- isépamicine

### Fluoroquinololones
- ofloxacine
- ciprofloxacine
- lévofloxacine
- delafloxacine

### Autres
- colistine
- polymyxine B
- rifampicine
- fosfomycine
<table>
<thead>
<tr>
<th>Statut</th>
<th>Ceftazidime-avibactam</th>
<th>Ceftolozane-tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMM juin 16 (IIA et IU) (2 g/500 mg x 3/j, en 2 h)</td>
<td>AMM oct 2015 (IIA et IU) (1 g/500 mg x 3/j, en 1 h)</td>
<td></td>
</tr>
<tr>
<td>Forces</td>
<td>Activité sur :</td>
<td>Activité sur :</td>
</tr>
<tr>
<td></td>
<td>• BLSE</td>
<td>• BLSE (coli +++, Kp ±)</td>
</tr>
<tr>
<td></td>
<td>• AmpC</td>
<td>• P. aeruginosa - R cefta et imipénème</td>
</tr>
<tr>
<td></td>
<td>• Carbapénémases (KPC, OXA 48)</td>
<td></td>
</tr>
<tr>
<td>Faiblesses</td>
<td>Pas d’activité sur :</td>
<td>Pas d’activité sur :</td>
</tr>
<tr>
<td></td>
<td>• Anaérobies</td>
<td>• Anaérobies</td>
</tr>
<tr>
<td></td>
<td>• Metallo-carbapénémases</td>
<td>• Carbapénémases</td>
</tr>
<tr>
<td></td>
<td>• Oxacillinases d’Acinetobacter</td>
<td>• AmpC hyperproduite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oxacillinases d’Acinetobacter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pk ≠ molécule et l’inhibiteur</td>
</tr>
</tbody>
</table>
**In vitro activity of ceftolozane/tazobactam versus antimicrobial non-susceptible *Pseudomonas aeruginosa* clinical isolates including MDR and XDR isolates obtained from across Canada as part of the CANWARD study, 2008–16**

Andrew Walkty¹–³*, Heather Adam²,³, Melanie Baxter², Philippe Lagacé-Wiens²,³, James A. Karlowsky²,³, Daryl J. Hoban²,³ and George G. Zhanel²

3229 *P. aeruginosa* isolates

<table>
<thead>
<tr>
<th>Organism (n)/antimicrobial agents</th>
<th>MIC₉₀ (mg/L)</th>
<th>MIC₉₀ (mg/L)</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa, all (n = 3229)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftolozane/tazobactam</td>
<td>0.5</td>
<td>1</td>
<td>98.3</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>amikacin</td>
<td>4</td>
<td>16</td>
<td>93.3</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>4</td>
<td>32</td>
<td>83</td>
<td>6</td>
<td>11.0</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>0.25</td>
<td>4</td>
<td>77.3</td>
<td>7.7</td>
<td>15.0</td>
</tr>
<tr>
<td>colistin</td>
<td>1</td>
<td>2</td>
<td>95.2</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>2</td>
<td>8</td>
<td>83.5</td>
<td>7.3</td>
<td>9.2</td>
</tr>
<tr>
<td>meropenem</td>
<td>0.5</td>
<td>8</td>
<td>81</td>
<td>7.1</td>
<td>11.9</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>4</td>
<td>64</td>
<td>84.1</td>
<td>8.6</td>
<td>7.3</td>
</tr>
<tr>
<td>MDR P. aeruginosa (n = 462)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftolozane/tazobactam</td>
<td>1</td>
<td>4</td>
<td>90.5</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>amikacin</td>
<td>8</td>
<td>64</td>
<td>76.4</td>
<td>9.1</td>
<td>14.5</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>32</td>
<td>&gt;32</td>
<td>19.5</td>
<td>22.7</td>
<td>57.8</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>4</td>
<td>&gt;16</td>
<td>24.9</td>
<td>20.6</td>
<td>54.5</td>
</tr>
<tr>
<td>colistin</td>
<td>1</td>
<td>2</td>
<td>93.5</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>8</td>
<td>&gt;32</td>
<td>47</td>
<td>13.6</td>
<td>39.4</td>
</tr>
<tr>
<td>meropenem</td>
<td>8</td>
<td>32</td>
<td>22.5</td>
<td>20.6</td>
<td>56.9</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>64</td>
<td>256</td>
<td>21.4</td>
<td>38.3</td>
<td>40.3</td>
</tr>
<tr>
<td>XDR P. aeruginosa (n = 84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftolozane/tazobactam</td>
<td>2</td>
<td>16</td>
<td>78.6</td>
<td>8.3</td>
<td>13.1</td>
</tr>
<tr>
<td>amikacin</td>
<td>16</td>
<td>&gt;64</td>
<td>51.2</td>
<td>14.3</td>
<td>34.5</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>0</td>
<td>26.2</td>
<td>73.8</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>8</td>
<td>&gt;16</td>
<td>0</td>
<td>20.2</td>
<td>79.8</td>
</tr>
<tr>
<td>colistin</td>
<td>1</td>
<td>4</td>
<td>89.3</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>32</td>
<td>&gt;32</td>
<td>1.2</td>
<td>19</td>
<td>79.8</td>
</tr>
<tr>
<td>meropenem</td>
<td>16</td>
<td>&gt;32</td>
<td>0</td>
<td>15.5</td>
<td>84.5</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>128</td>
<td>512</td>
<td>0</td>
<td>42.9</td>
<td>57.1</td>
</tr>
</tbody>
</table>
✓ Rapport concentration ceftolozane plasma/alvéole : 2/1
✓ *P. aeruginosa* dans plus de 30 % des PAVM
✓ *P. aeruginosa* R si CMI > 4 mg/l
✓ Rapport concentration ceftolozane plasma/alvéole : 2/1
✓ *P. aeruginosa* dans plus de 30 % des PAVM
✓ *P. aeruginosa* R si CMI > 4 MG/L
✓ Rapport concentration ceftolozane plasma/alvéole : 2/1
✓ *P. aeruginosa* dans plus de 30 % des PAVM
✓ *P. aeruginosa* R si CMI > 4 MG/L

✓ Il faut sans doute x 2 la posologie dans les PAVM
✓ Surtout que dans ce cas, la concentration du tazobactam reste > MEC (concentration minimale efficace) pdt 100 % du temps entre 2 injections

✓ Etude actuellement en cours

\[ fT > \text{CMI} : \geq 50 \% \]... objectif modeste
Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study

Benjamin Miller, Myra W. Popejoy, Ellie Hershberger, Judith N. Steenbergen, John Alverdy

 ✓ Ceftolozane-tazobactam + metronidazole vs meropenem

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P. aeruginosa at baseline (n = 72)</th>
<th>No P. aeruginosa at baseline (n = 734)</th>
<th>Total (n = 806)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline APACHE II score category (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>61 (84.7)</td>
<td>596 (81.2)</td>
<td>657 (81.5)</td>
</tr>
<tr>
<td>≥10</td>
<td>11 (15.3)</td>
<td>137 (18.7)</td>
<td>148 (18.4)</td>
</tr>
<tr>
<td>Anatomic site of infection (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td>43 (59.7)</td>
<td>341 (46.5)</td>
<td>384 (47.6)</td>
</tr>
<tr>
<td>Biliary cholecystitis/cholangitis</td>
<td>5 (6.9)</td>
<td>138 (18.8)</td>
<td>143 (17.7)</td>
</tr>
<tr>
<td>Stomach/duodenum</td>
<td>4 (5.6)</td>
<td>75 (10.2)</td>
<td>79 (9.8)</td>
</tr>
<tr>
<td>Colon</td>
<td>17 (23.6)</td>
<td>101 (13.8)</td>
<td>118 (14.6)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 (1.4)</td>
<td>41 (5.6)</td>
<td>42 (5.2)</td>
</tr>
<tr>
<td>Parenchymal (liver)</td>
<td>1 (1.4)</td>
<td>32 (4.4)</td>
<td>33 (4.1)</td>
</tr>
<tr>
<td>Parenchymal (spleen)</td>
<td>0</td>
<td>4 (0.5)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.4)</td>
<td>15 (2.0)</td>
<td>16 (2.0)</td>
</tr>
</tbody>
</table>
FIG 1 MIC distribution and clinical outcomes with ceftolozane-tazobactam and meropenem. (A) Distribution of ceftolozane-tazobactam and meropenem MICs for 69 *Pseudomonas aeruginosa* isolates identified at the screening visit (microbiological intent-to-treat population). (B) Clinical cure rate at the test-of-cure visit for patients with and without baseline *P. aeruginosa* infection, by treatment group (microbiologically evaluable population, which includes patients with pathogens at baseline who were susceptible or resistant to study drug).
✓ Retrospective study
✓ Consecutive patients treated with C/T for XDR-PA infection at a tertiary referral hospital
✓ Thirty-eight patients included
✓ At completion of treatment, 33 (86.8%) patients showed clinical response
✓ Clinical cure associated to:
  o Lower C/T MIC
  o Adequate source control

*In this patient a lung transplant was performed during the course of pneumonia, so we considered that the focus of infection had been controlled and resolved.
21 patients treated with ceftolozane-tazobactam for MDR-\textit{P. aeruginosa} infections.

Eighteen (86\%) patients were treated for respiratory tract infections.

Ceftolozane-tazobactam failure rate was 29\% (6/21).

Ceftolozane-tazobactam resistance emerged in 3 (14\%) patients.

Resistance was associated with de novo mutations, rather than acquisition of resistant nosocomial isolates.

ampC overexpression and mutations were identified as potential resistance determinants.
Ceftolozane-tazobactam resistance induced in vivo during the treatment of MDR Pseudomonas aeruginosa pneumonia.

✔ Case report
- Septic shock on fecal peritonitis: mero/vanco
- Pneumonia *P. aeruginosa*: Pip-taz and cefta (isolate 1)
- Isolate 2 following week: cefto-tazo (1,5g/8h)
- Relapse isolate 3
Nine *P. aeruginosa* strains
- 2 reference strains (PAO1 and PA14)
- 7 clinical strains: 3 clinical multisusceptible strains, 1 MDR strain, 3MDR high-risk clones (ST111, ST235 and ST175).

Mouse peritonitis model
The increasing threat of *Pseudomonas aeruginosa* high-risk clones
Antonio Oliver*, Xavier Mulet, Carla López-Causapé, Carlos Juan
Bacteraemia due to extensively drug-resistant *Pseudomonas aeruginosa* sequence type 235 high-risk clone: Facing the perfect storm

Raúl Recio$^{a,*}$, Jennifer Villa$^a$, Esther Viedma$^a$, María Ángeles Orellana$^a$, Jaime Lora-Tamayo$^b$, Fernando Chaves$^a$

- Retrospective analysis
- 64 patients with bacteremia
  - Non-XDR (40)
  - XDR
    - 10 VIM-2 CP (ST175)
    - 11 GES-5 CP (ST235)
    - 3 no CP
- ST235: 100 ExoU+
- Susceptibility XDR
  - Cefta-avi 58.3%
  - Cefto-tazo 12.5%
- 30d mortality
  - XDR: 62.5%
  - Non-XDR: 30%

- 30d mortality
  - ST175 30%
  - ST235 82%

![Graph showing survival over time]
✓ Etude rétrospective monocentrique
✓ 37 inf. à EPC (dont 31 KPC) traitées par cefta/avibactam
  – IGS II = 34, SOFA = 5
  – 12 inf. pulmonaires (dont 6 PAVM), bactériémies (n=10)
✓ Monothérapie dans 70 % des cas
  – J30 : succès clinique 59 %, avec 23 % récurrence à J90
  – Mortalité globale : 24 % à J30, 38 % à J90
  – Echecs microbiologiques 27 %
    • Dont 33 % de souches cefta/avibactam-R
✓ Meilleur tolérance (rénale) que alternatives (coli et/ou carbapénèmes et ou aminosides
Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

Yehuda Corneli, Jon Armstrong, Peter J Laup, Paul Newell, Greg Stone, Angela Wardman, Leanne B Gasink

- Pathogen-directed, international, randomised, open-label, phase 3, 16 countries worldwide
- 18–90 years with complicated urinary tract infection or complicated intra-abdominal infection caused by ceftazidime-resistant Enterobacteriaceae or Pseudomonas aeruginosa
- Treatment:
  - ceftazidime-avibactam (2000 mg/500 mg), 2-h intravenous infusion every 8 h
  - best available therapy
- Primary endpoint: clinical response
  - at the test-of-cure visit,
  - 7–10 days after last infusion of study therapy

Lancet inf Dis 2016, 16:661-73
163 (97%) of 168 patients in the best available therapy group received a carbapenem, 161 (96%) as monotherapy.

Conclusion: efficacy of ceftazidime-avibactam as a potential alternative to carbapenems in patients with ceftazidime-resistant Enterobacteriaceae and P aeruginosa.
Adults with nosocomial pneumonia including ventilator-associated pneumonia

136 centres in 23 countries

Treatment:
- 2000 mg ceftazidime and 500 mg avibactam (by 2 h intravenous infusion every 8 h)
- 1000 mg meropenem (by 30-min intravenous infusion every 8 h) for 7–14 days

879 patients included
- Klebsiella pneumoniae (37%)
- Pseudomonas aeruginosa (30%); 28% were ceftazidime-non-susceptible

Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia.
Systematic review and meta-analysis including RCTs evaluating ceftazidime/avibactam versus comparator for the treatment of any infection

Primary outcome was 30 day all-cause mortality

Seven publications (eight trials, 4093 patients) were included

![Table of study results](image-url)

![Diagram of meta-analysis](image-url)

Figure 2. All-cause mortality at late follow-up. M-H, Mantel-Haenszel.
Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: “We’re Gonna Need a Bigger Boat”

Editorial qui souligne :

• Ceftazidime pas forcément le meilleur partenaire (émergence de BLSE +++)
• Dans les études pivot du dossier d’AMM : très peu de souches carbapénème-R
• Résultats décevants de Shields et al en « en vraie vie »
  o mortalité élevée (alors que IGS II à 34 et SOFA à 5 ➔ prédiction mortalité entre 5 et 10 %)
  o émergence rapide de la résistance

Spellberg B  CID 2016; 63 : 1619
Plan

✓ Sensibilité aux principales molécules et nouvelles molécules
✓ Le trio hôte-molécule-pathogène
✓ PK/PD
✓ Durée
✓ Associations
✓ Thérapeutiques alternatives
271 patients/ Emergence de résistance chez 28 (10,2%)

**TABLE 2. Multivariable Cox hazard models for the emergence of resistance to any of the four study drugs**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Events (no./total Rx)</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Culturing score</td>
<td>NI</td>
<td>2.5 (1.1–6.0)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>13/77</td>
<td>0.8 (0.4–2.0)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>10/125</td>
<td>0.7 (0.3–1.7)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>12/98</td>
<td>0.8 (0.3–2.0)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>11/37</td>
<td>2.8 (1.2–6.6)</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>9/91</td>
<td>1.7 (0.7–4.1)</td>
</tr>
</tbody>
</table>

*Rx, treatment; CI, confidence interval; NI, not included.*
Table 2. Univariate analysis of therapies, including ceftazidime, piperacillin, imipenem, ciprofloxacin, and aminoglycosides, as risk factors for antibiotic-specific resistance in 267 bacteremic strains of *Pseudomonas aeruginosa*.

Table 3. Multivariate association, averaged across antipseudomonal agents, of previous exposure to an agent, and resistance to that same agent in 267 bacteremic strains of *Pseudomonas aeruginosa*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous monotherapy with the agent</td>
<td>2.5 (1.3–4.8)</td>
<td>.006</td>
</tr>
<tr>
<td>Previous combination therapy including the agent</td>
<td>1.8 (0.55–5.6)</td>
<td>.34</td>
</tr>
<tr>
<td>Severe sepsis or septic shock</td>
<td>1.6 (0.94–2.6)</td>
<td>.08</td>
</tr>
</tbody>
</table>

**NOTE.** Stratified logistic regression analysis in which each episode of bacteremia contributed 5 times to the model (i.e., once per antipseudomonal agent). Variance estimates were adjusted for the resulting dependence among observations.

267 bactériémies, 25% avec une exposition à un anti-pyo
Plan

- Sensibilité aux principales molécules et nouvelles molécules
- Le trio hôte-molécule-pathogène
- PK/PD
- Durée
- Associations
- Thérapeutiques alternatives
Aminosides

\[ \frac{C_{\text{max}}}{\text{CMI}} \]

24 h
Aminosides
Relation Cmax/CMI - Guérison clinique

Taux de guérison clinique

Cmax/CMI

Moore, JID 1987
Importance de la première dose d’aminoside sur l’évolution clinique
Résistance adaptative
CMI; modèle statique *in vitro*

(Karlowsky et al, JAC 1994)
Résistance adaptative

\[ \Delta \log \text{CFU/ml/90min} \]

AMK in vivo : 80 mg/kg

(Xiong et al, AAC 1997)
Résistance adaptative
Mucoviscidose

Bactéricidie (log10 CFU/ml)

- Patient n° 1
- Patient n° 2
- Patient n° 3

P. aeruginosa
tobramycine
1 dose = 80 mg

(Barclay et al, JAC 1996)
Prospective randomised controlled study

Severe sepsis or septic shock treated with 15 mg/kg versus 25 mg/kg amikacin.

The primary outcome target attainment defined as Cpeak/MIC ≥ 8

104 patients included. The target was attained in 76% vs. 40% of patients assigned to the 25 mg/kg vs. 15 mg/kg dose groups (P < 0.0001).
Bêtalactamamines: paramètres pharmacodynamiques

temps de contact à $C > CMI$

$T = t_1 + t_2 + t_3 (%24h) > CMI$

concentrations

cmi

t_1 > CMI  t_2 > CMI  t_3 > CMI  24 h

(Craig et al, CID 2001)
Idealized sketch of serum or tissue drug concentration after administration of a single dose of antibiotic to a patient. MIC and mutant prevention concentration (MPC), determined in laboratory studies, are indicated. The area between MPC and MIC (shaded) represents the mutant selection window.
✓ 18 patients de réanimation
✓ Dose de charge 12mg/kg, suivie de 6 g/24 h de ceftazidime
   – soit en continu (n=8)
   – soit en 3 bolus de 2g/8h (n = 10)
✓ Durant les 8 premières heures, concentrations sériques < 40 mg/L (5 fois la conc. crit. inf):
   – groupe perfusion continue: 1 patient / 8 (38 mg/L)
   – groupe bolus: 8 patients / 10 (2 - 33 mg/L)
✓ Durant les 40 heures suivantes, temps avec des concentrations sériques > 40 mg/L:
   – groupe perfusion continue: 100%
   – groupe bolus: 20 - 30%

Lipman, JAC 1999; 43: 309-11
Extended-Infusion Cefepime Reduces Mortality in Patients with Pseudomonas aeruginosa Infections

Karri A. Bauer, a Jessica E. West, b James M. O’Brien, c Debra A. Goff a

- Single-center study compared cefepime for bacteremia and/or pneumonia
  - admitted from 1 January 2008 through 30 June 2010 (a 30-min infusion of 2 g every 8 h)
  - admitted from 1 July 2010 through 31 May 2011 (a 4-h infusion of 2 g every 8 h).
- Extended infusion was associated to
  - Decreased mortality (20% versus 3%; p=0.03).
  - Decreased mean length of stay of 3.5 days less
  - Decreased mean length of stay was significantly less in the extended-infusion group (18.5 days versus 8 days; P0.04).
- Decreased Hospital costs were $23,183 less per patient,
- Extended-infusion treatment with cefepime provides increased clinical and economic benefits in the treatment of invasive P. aeruginosa infections.
Étude sur cohorte de 194 patients

- Deux modalités d’administration
  - 3.375g en 30 min toutes les 4 à 6 H
  - 3.375g en 4 H toutes les 8 H

- Analyse de 2 paramètres en fonction du Score Apache II
  - Mortalité
  - Durée d’hospitalisation

Lodise et al, CID, 2007
Mode d’administration de la pipera-tazocilline et mortalité à J14

![Bar chart showing mortality rates for different Apache II scores and modes of administration.](cid:lodise2007)
Multicenter clinical trial, 11 Spanish hospitals

Treatment:
- continuous infusion of piperacillin–tazobactam
- 30% higher dose administered by intermittent infusion

Primary efficacy endpoint:
- percentage of patients having a satisfactory clinical response at completion of treatment, defined as clinical cure or clinical improvement.
✓ No difference between the 2 groups but.....

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th></th>
<th>Intermitent</th>
<th></th>
<th>Continuous</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>No sepsis</td>
<td>60</td>
<td>76.9</td>
<td>29</td>
<td>76.3</td>
<td>31</td>
<td>77.5</td>
<td>0.992</td>
</tr>
<tr>
<td>Sepsis</td>
<td>16</td>
<td>20.5</td>
<td>8</td>
<td>21.1</td>
<td>8</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>2</td>
<td>2.6</td>
<td>1</td>
<td>2.6</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

✓ No definition of sepsis

<table>
<thead>
<tr>
<th>Clinical focus of actual infection</th>
<th>Total</th>
<th></th>
<th>Intermitent</th>
<th></th>
<th>Continuous</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>19.2</td>
<td>8</td>
<td>21.1</td>
<td>7</td>
<td>17.5</td>
<td>0.691</td>
</tr>
<tr>
<td>Tracheobronchitis</td>
<td>3</td>
<td>3.8</td>
<td>2</td>
<td>5.3</td>
<td>1</td>
<td>2.5</td>
<td>0.610$^*$</td>
</tr>
<tr>
<td>Urological</td>
<td>4</td>
<td>5.1</td>
<td>2</td>
<td>5.3</td>
<td>2</td>
<td>5.0</td>
<td>0.999$^*$</td>
</tr>
<tr>
<td>Abdominal</td>
<td>11</td>
<td>14.1</td>
<td>6</td>
<td>15.8</td>
<td>5</td>
<td>12.5</td>
<td>0.677</td>
</tr>
<tr>
<td>Biliary</td>
<td>17</td>
<td>21.8</td>
<td>6</td>
<td>15.8</td>
<td>11</td>
<td>27.5</td>
<td>0.211</td>
</tr>
<tr>
<td>Bacteremia with or without focus</td>
<td>3</td>
<td>3.8</td>
<td>1</td>
<td>2.6</td>
<td>2</td>
<td>5.0</td>
<td>0.999$^*$</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>15</td>
<td>19.2</td>
<td>7</td>
<td>18.4</td>
<td>8</td>
<td>20.0</td>
<td>0.860</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>5.1</td>
<td>2</td>
<td>5.3</td>
<td>2</td>
<td>5.0</td>
<td>0.999$^*$</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>7.7</td>
<td>4</td>
<td>10.5</td>
<td>2</td>
<td>5.0</td>
<td>0.425$^*$</td>
</tr>
</tbody>
</table>
Meropenem Dosing Based on a Population Pharmacokinetic–Pharmacodynamic Model in Elderly Patients with Infection of the Lower Respiratory Tract

Qing-Tao Zhou¹ · Bei He¹ · Ning Shen¹ · Ying Liang¹ · Li-Na Sun¹

✓ Prospective single-center open-label randomized controlled trial
✓ 79 elderly patients with an LRTI caused by Gram-negative bacilli
✓ Treatment
  • Meropenem according to a regimen decided by the attending physician.
  • Individualized meropenem therapy with a dosing strategy based on software developed from a meropenem population PK/PD model (prolonged 3h infusion)
✓ Primary endpoint: clinical response

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n = 79)</th>
<th>Study group (n = 39)</th>
<th>Control group (n = 40)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily meropenem dose (g)</td>
<td>1.5 (1.5–3.0)</td>
<td>1.5 (1.5–2.0)</td>
<td>2.0 (1.5–3.0)</td>
<td>–</td>
<td>0.017</td>
</tr>
<tr>
<td>Duration of meropenem therapy (days)</td>
<td>9.0 (7.0–13.0)</td>
<td>10.0 (7.0–13.0)</td>
<td>9.0 (7.0–13.0)</td>
<td>–</td>
<td>0.665</td>
</tr>
<tr>
<td>Total meropenem dose (g)</td>
<td>18.0 (10.5–26.0)</td>
<td>15.0 (7.5–24.0)</td>
<td>19.0 (12.0–29.5)</td>
<td>–</td>
<td>0.090</td>
</tr>
<tr>
<td>$T_{&gt;MIC}$</td>
<td>98.9 (76.3–100.0)</td>
<td>98.9 (77.1–100.0)</td>
<td>79.7 (52.3–100.0)</td>
<td>–</td>
<td>0.105</td>
</tr>
<tr>
<td>Clinical success</td>
<td>63 (79.7)</td>
<td>35 (89.7)</td>
<td>28 (70.0)</td>
<td>0.780 (0.620–0.981)</td>
<td>0.029</td>
</tr>
<tr>
<td>Bacteriologic success</td>
<td>52 (65.8)</td>
<td>28 (71.8)</td>
<td>24 (60.0)</td>
<td>0.836 (0.607–1.151)</td>
<td>0.269</td>
</tr>
</tbody>
</table>
RCT comparing mortality or clinical efficacy of prolonged (continuous or ≥3 h) versus short-term (≤60 min) infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was eligible

2196 articles were identified and screened, and 22 studies (1876 patients) were included in the meta-analysis
Prolonged infusion of antipseudomonal β-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than short-term infusion.
Fluoroquinolones

\[ \frac{C_{\text{max}}}{CMI} \]

ASC 24h

ASC 24h/CMI

Cmax/CMI

temps
Fluoroquinolones

Relation ASC 24h/CMI et efficacité

Forrest, AAC 1993

64 patients
ciprofloxacine

Clinical
Bacteriologic

Forrest, AAC 1993
Table 1. Relationship of the ratio of 24-h area under the curve to MIC (24-h AUC/MIC ratio) and monotherapy and combination therapy to the emergence of resistant organisms during therapy with β-lactams and ciprofloxacin.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>24-h AUC/MIC ratio</th>
<th>Patients with resistance/total patients (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All patients</td>
<td>Ciprofloxacin treatment</td>
<td>β-Lactam treatment</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>&lt;100</td>
<td>14/17 (82)</td>
<td>12/14 (86)</td>
<td>2/3 (67)</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>≥100</td>
<td>17/84 (20)</td>
<td>4/44 (9)</td>
<td>13/40 (31)</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>≥100</td>
<td>1/27 (4)</td>
<td>0/16 (0)</td>
<td>1/27 (4)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Relationship of the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistant *Pseudomonas* and other gram-negative bacilli (GNB) during monotherapy with ciprofloxacin and β-lactams.

<table>
<thead>
<tr>
<th>24-h AUC/MIC ratio</th>
<th>Patients with resistance/total patients (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ciprofloxacin therapy</td>
<td>β-Lactam therapy</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em></td>
<td>Other GNB</td>
</tr>
<tr>
<td>&lt;100</td>
<td>10/10 (100)</td>
<td>2/4 (50)</td>
</tr>
<tr>
<td>≥100</td>
<td>2/8 (25)</td>
<td>2/28 (7)</td>
</tr>
<tr>
<td>( P )</td>
<td>.002</td>
<td>.07</td>
</tr>
</tbody>
</table>
Fish et al, JAC 2002

(a) Ciprofloxacine

- Cefep
- Cefta
- Cipro
- Cefep-Cipro
- Cefta-Cipro

(b) Levofloxacine

- Cefta-Levo
Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*

Eric R. Ocheretyaner\(^a\)\(^b\) and Tae Eun Park\(^c\)

Table 2. Susceptibility test interpretive criteria for delafloxacin [4].

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum inhibitory concentrations ((\mu g/mL))</th>
<th>Disk diffusion (zone diameter in mm)</th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>(\leq0.25)</td>
<td>(0.5)</td>
<td>(\geq1)</td>
<td>(\geq23)</td>
<td>(20–22)</td>
<td>(\leq19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
<td>(\leq0.25)</td>
<td>(0.5)</td>
<td>(\geq1)</td>
<td>(\geq24)</td>
<td>(21–23)</td>
<td>(\leq20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>(\leq0.06)</td>
<td>(0.12)</td>
<td>(\geq0.25)</td>
<td>(\geq20)</td>
<td>(\leq19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>(\leq0.06)</td>
<td>(0.12)</td>
<td>(\geq0.25)</td>
<td>(\geq20)</td>
<td>(\leq19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus anginosus Group</em></td>
<td>(\leq0.06)</td>
<td>(0.12)</td>
<td>(\geq0.25)</td>
<td>(\geq20)</td>
<td>(\leq19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>(\leq0.12)</td>
<td>(0.25)</td>
<td>(\geq0.5)</td>
<td>(\geq21)</td>
<td>(19–20)</td>
<td>(\leq18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>(\leq0.25)</td>
<td>(0.5)</td>
<td>(\geq1)</td>
<td>(\geq22)</td>
<td>(19–21)</td>
<td>(\leq18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>(\leq0.5)</td>
<td>(1)</td>
<td>(\geq2)</td>
<td>(\geq23)</td>
<td>(20–22)</td>
<td>(\leq19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S = susceptible; I = intermediate; R = resistant.

Table 5. Clinical outcomes of delafloxacin for acute bacterial skin and skin-structure infections in Phase III trials [4,19,20,22].

<table>
<thead>
<tr>
<th>Trial</th>
<th>Delafloxacin</th>
<th>Vancomycin 15 mg/kg + Aztreonam</th>
<th>Treatment difference (2-sided 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>300-mg intravenous</td>
<td></td>
<td>-2.6 (-8.8 to 3.6)</td>
</tr>
<tr>
<td>Total N</td>
<td>331</td>
<td>329</td>
<td></td>
</tr>
<tr>
<td>Clinical response, (%)</td>
<td>259 (78.2%)</td>
<td>266 (80.9%)</td>
<td></td>
</tr>
<tr>
<td>Success ITT, (%)</td>
<td>270 (81.6%)</td>
<td>274 (83.3%)</td>
<td>-1.7 (-7.6 to 4.1)</td>
</tr>
<tr>
<td>Success CE, (n/N)</td>
<td>232/240</td>
<td>238/244 (97.5%)</td>
<td>-0.9 (-4.3 to 2.4)</td>
</tr>
<tr>
<td>Trial 2</td>
<td>300-mg intravenous</td>
<td>300-mg and oral</td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>423</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Clinical response, (%)</td>
<td>354 (83.7%)</td>
<td>344 (80.6%)</td>
<td>3.1 (-2 to 8.3)</td>
</tr>
<tr>
<td>Success ITT, (%)</td>
<td>369 (87.2%)</td>
<td>362 (84.8%)</td>
<td>2.5 (-2.2 to 7.2)</td>
</tr>
<tr>
<td>Success CE, (n/N)</td>
<td>339/353</td>
<td>319/329 (97%)</td>
<td>-0.9 (-3.9 to 2)</td>
</tr>
<tr>
<td>Trial 3</td>
<td>300-mg intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>331</td>
<td>329</td>
<td></td>
</tr>
<tr>
<td>Objective response, (%)</td>
<td>259 (78.7%)</td>
<td>266 (80.9%)</td>
<td>-2.6 (-8.78 to 3.57)</td>
</tr>
<tr>
<td>Investigator assessed cure, (%)</td>
<td>172 (52%)</td>
<td>166 (50.5%)</td>
<td>1.5 (-6.11 to 9.11)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ITT = intent-to-treat and includes all randomized patients; CE = clinically evaluable consisted of all ITT patients who had a diagnosis of ABSSI, received at least 80% of expected doses of study drug, did not have any protocol deviations that would affect the assessment of efficacy and had investigator assessment at the follow-up visit.
Is fluoroquinolone monotherapy a useful alternative treatment for *Pseudomonas aeruginosa* bacteraemia?

Ping-Feng Wu¹², Yi-Tsung Lin¹³, Fu-Der Wang¹³, Tsuey-Ching Yang⁴, Chang-Phone Fung⁵

- Retrospective study between Nov 2013 and Nov 2014 at Taipei Veterans General Hospital.
- 105 patients enrolled, 78 patients received beta-lactams and 27 received fluoroquinolones (20 with ciprofloxacin and 7 with levofloxacin)
- Primary bacteraemia (39.0%) and urinary tract infections (37.1%) were the most common sources of bacteraemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (N=105)</th>
<th>Fluoroquinolone group (N=27)</th>
<th>Beta-lactam group (N=78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>28 (26.7)</td>
<td>3 (11.1)</td>
<td>25 (32.1)</td>
<td>0.062</td>
</tr>
<tr>
<td>Bacteraemia-associated mortality</td>
<td>21 (20.0)</td>
<td>3 (11.1)</td>
<td>18 (23.1)</td>
<td>0.289</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>35 (33.3)</td>
<td>5 (18.5)</td>
<td>30 (38.5)</td>
<td>0.097</td>
</tr>
<tr>
<td>Duration of definitive therapy, daysᵃ</td>
<td>11.5 ± 4.9</td>
<td>11.6 ± 4.6</td>
<td>11.5 ± 5.1</td>
<td>0.731</td>
</tr>
</tbody>
</table>

- The 28-day mortality rate between the two groups stratified by APACHE II and Pitt bacteraemia scores showed no significant differences in each category
- Fluoroquinolone might be an alternative to beta-lactam as a definitive monotherapy for *P. aeruginosa* bacteraemia provided they are active in vitro
<table>
<thead>
<tr>
<th>Drug</th>
<th>Current clinical indications</th>
<th>Usual clinical dosage for serious infections</th>
<th>Other comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefidercol</td>
<td>Complicated UTI</td>
<td>2 g intravenous every 8 hours</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cephalosporin + β-lactamase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftolozane-tazobactam</td>
<td>Complicated UTI and IAI</td>
<td>Loading dose 1.5 g or 3 g intravenous in 1 hour, followed by 1.5 g or 3 g intravenous every 8 hours</td>
<td>Extended infusion (over 3 h) 1.5 g or 3 g every 8 hours is recommended</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>Complicated UTI and IAI, HAP and VAP and Gram-negative infections when other treatments might not work</td>
<td>Loading dose 2.5 g intravenous in 1 hour, followed by 2.5 g intravenous every 8 hours</td>
<td>Extended infusion (over 3 h) 2.5 g every 8 hours is recommended</td>
</tr>
<tr>
<td><strong>Carbapenem + β-lactamase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem-vaborbactam</td>
<td>Complicated UTI</td>
<td>2 g/2 g intravenous every 8 hours</td>
<td>Not active against MDR strains</td>
</tr>
<tr>
<td>Imipenem-relebactam</td>
<td>Not yet approved by any regulatory authority</td>
<td>500 mg/250 mg intravenous every 6 hours</td>
<td>Not active against MDR strains</td>
</tr>
<tr>
<td><strong>Aminoglycoside</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Not yet approved by any regulatory authority</td>
<td>15 mg/kg every 24 hours</td>
<td>-</td>
</tr>
</tbody>
</table>
Plan

✓ Sensibilité aux principales molécules et nouvelles molécules
✓ Le trio hôte-molécule-pathogène
✓ PK/PD
✓ Durée
✓ Associations
✓ Thérapeutiques alternatives
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Jean Chastre, MD
Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franck Thomas, MD
Delphine Wermert, MD
Eva Clementi, MD
Jesus Gonzalez, MD
Dominique Jusserand, MD
Pierre Asfar, MD
Dominique Perrin, MD
Fabienne Fieux, MD
Sylvie Aubas, MD
for the PneumA Trial Group

Chastre et al, JAMA 2003
Taux de récidive de l'infection pulmonaire (%) en fonction de l'infection à *P. aeruginosa*.

- **“8 jours”** (n=58): 40.6%
- **“15 jours”** (n=62): 25.4%

La différence est statistiquement significative avec un *p*-value de 0.06.

Chastre et al, JAMA 2003
Rechute

RR: 13.8
(7.8-19.7)

8j

Surinfection

RR: 7.6 (1.1-14.2)

15j

Chastre et al, JAMA 2003
The impact of the duration of antibiotics on clinical events in patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia (iDIAPASON) trial is a randomized, open-labeled non-inferiority controlled trial, conducted in 34 French intensive care units (ICUs), comparing two groups of patients with PA-VAP according to the duration (8 days or 15 days) of effective antibiotic therapy against PA.

The primary outcome is a composite endpoint combining day 90 mortality and PA-VAP recurrence rate during hospitalization in the ICU.
Plan

✓ Sensibilité aux principales molécules et nouvelles molécules

✓ Le trio hôte-molécule-pathogène

✓ PK/PD

✓ Durée

✓ Associations

✓ Thérapeutiques alternatives
Pourquoi faire une association?

✓ Le patient?

✓ Le pathogène?
A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD

<table>
<thead>
<tr>
<th>Group</th>
<th>Monotherapy Mortality (%)</th>
<th>Combination Therapy Mortality (%)</th>
<th>Odds Ratio</th>
<th>I² (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-shock</td>
<td>86/660 (12.6)</td>
<td>96/666 (14.4)</td>
<td>1.06 (0.73-1.52)</td>
<td>13.7</td>
<td>.7721</td>
</tr>
<tr>
<td>shock</td>
<td>96/188 (51.1)</td>
<td>177/422 (41.9)</td>
<td>0.56 (0.39-0.83)</td>
<td>0.8</td>
<td>.0043</td>
</tr>
<tr>
<td>non-critically ill</td>
<td>23/313 (7.3)</td>
<td>35/339 (10.3)</td>
<td>1.10 (0.46-2.60)</td>
<td>45.3</td>
<td>.8321</td>
</tr>
<tr>
<td>critically ill</td>
<td>32/64 (50.0)</td>
<td>34/128 (26.6)</td>
<td>0.33 (0.15-0.74)</td>
<td>0</td>
<td>.0067</td>
</tr>
<tr>
<td>non-shock/non-critically ill</td>
<td>109/993 (11.0)</td>
<td>131/1005 (13.0)</td>
<td>1.06 (0.76-1.47)</td>
<td>19.1</td>
<td>.7178</td>
</tr>
<tr>
<td>shock/critically ill</td>
<td>128/252 (50.1)</td>
<td>211/550 (38.4)</td>
<td>0.51 (0.36-0.72)</td>
<td>0</td>
<td>.0002</td>
</tr>
<tr>
<td>overall</td>
<td>237/1245 (19.0)</td>
<td>342/1555 (22.0)</td>
<td>0.76 (0.57-1.02)</td>
<td>33.8</td>
<td>.0622</td>
</tr>
</tbody>
</table>
Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis


A total of 4662 eligible cases of culture-positive, bacterial septic shock treated with combination or monotherapy from which 1223 propensity-matched pairs were generated.
The use of aminoglycoside (AG), fluoroquinolone (FQ), or a macrolide/clindamycin (ML/CL) in addition to a -lactam was associated with a reduced hazard ratio for death compared to -lactam alone.

No other drug combinations demonstrated evidence of significant benefit.
✓ Retrospective study, monomicrobial septic shock patients 2010–15.
✓ 576 monomicrobial septic shock
✓ All-cause mortality at 7, 15 and 30 days was similar in patients with monomicrobial septic shock receiving empirical double-active combination therapy and active monotherapy
✓ Beneficial influence of empirical double-active combination on mortality in patients with neutropenia and those with *P. aeruginosa* infection
Pourquoi faire une association?

✓ Le patient?
  – Donc Oui!

✓ Le pathogène?
  – En dehors de BHR bien sur!
ETUDES CLINIQUES PAVM
Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

183 épisodes de VAP à *P. aeruginosa*

<table>
<thead>
<tr>
<th>Tt final</th>
<th>Survivants n=106</th>
<th>Décédés n=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>18.7</td>
<td>19.8</td>
</tr>
<tr>
<td>Choc septique</td>
<td>38 (35.8)</td>
<td>52 (67.5)</td>
</tr>
<tr>
<td>Monothérapie</td>
<td>22 (19.9)</td>
<td>12 (15.6)</td>
</tr>
<tr>
<td>Association</td>
<td>84 (81.1)</td>
<td>60 (84.4)</td>
</tr>
</tbody>
</table>
Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

<table>
<thead>
<tr>
<th></th>
<th>aHR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01–1.04</td>
<td>.005</td>
</tr>
<tr>
<td>Chronic cardiac failure</td>
<td>1.90</td>
<td>1.04–3.47</td>
<td>.035</td>
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<tr>
<td>Effective empirical therapy</td>
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<td></td>
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</tr>
<tr>
<td>Combined therapy</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>0.90</td>
<td>0.50–1.63</td>
<td>.73</td>
</tr>
<tr>
<td>Inappropriate therapy</td>
<td>1.85</td>
<td>1.07–3.10</td>
<td>.02</td>
</tr>
</tbody>
</table>

aHR, adjusted hazard ratio; CI, confidence interval.
Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Monotherapy n/N</th>
<th>Combination Therapy n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1984</td>
<td>11/18</td>
<td>9/16</td>
<td>13.39</td>
<td>1.09</td>
<td>[0.62, 1.92]</td>
</tr>
<tr>
<td>Kjucar 1987</td>
<td>0/16</td>
<td>1/17</td>
<td>0.44</td>
<td>0.35</td>
<td>[0.02, 8.08]</td>
</tr>
<tr>
<td>Cometta 1994</td>
<td>13/91</td>
<td>12/86</td>
<td>8.17</td>
<td>1.02</td>
<td>[0.49, 2.12]</td>
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<tr>
<td>Sieger 1997</td>
<td>10/104</td>
<td>17/107</td>
<td>8.04</td>
<td>0.61</td>
<td>[0.29, 1.26]</td>
</tr>
<tr>
<td>Manhold 1998</td>
<td>13/28</td>
<td>6/23</td>
<td>6.84</td>
<td>1.78</td>
<td>[0.80, 3.94]</td>
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<tr>
<td>Alvarez-Lerma 2001</td>
<td>16/69</td>
<td>20/71</td>
<td>13.40</td>
<td>0.82</td>
<td>[0.47, 1.45]</td>
</tr>
<tr>
<td>Heyland 2005</td>
<td>67/370</td>
<td>71/369</td>
<td>47.66</td>
<td>0.94</td>
<td>[0.70, 1.27]</td>
</tr>
<tr>
<td>Damas 2006</td>
<td>2/24</td>
<td>9/50</td>
<td>2.05</td>
<td>0.46</td>
<td>[0.11, 1.98]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>720</td>
<td>739</td>
<td>100.00</td>
<td>0.94</td>
<td>[0.76, 1.16]</td>
</tr>
</tbody>
</table>

Total events: 132 (Monotherapy), 145 (Combination Therapy)
Test for heterogeneity: Chi² = 5.72, df = 7 (P = 0.57), I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)

Figure 4. Mortality in pooled trials comparing monotherapy to combination therapy. There is no evidence that combination therapy improves survival when compared with monotherapy. RR, relative risk; CI, confidence interval.
Etude rétrospective de cohorte 1994-2014

- 100 patients: 85 association/15 monothérapie, 9 inadequates
- SAPS 2: 46, 45% choc, Colonisation 60%, Multi-R 31%
- Mortalité associée (HR)
  - SAPS>40: 3.08
  - Choc: 4.71

L’associationaugmente la probabilité d’antibiothérapie appropriée sans impact sur la mortalité
✓ 314 patients avec 393 VAP à *P. aeruginosa*
✓ 112 échec de traitement
✓ Facteurs associés avec un échec de traitement
  – Age (P . 0.02);
  – Présence d’au moins une pathologie chronique (P . 0.02);
  – Limitation de soins (P . 0.0004);
  – Score de défaillance d’organe élevé (P , 0.0001);
  – Bacterémie à *P. aeruginosa* (P .0.003);
  – previous use of FQ before the first PA-VAP (P . 0.0007).
✓ Risque d’échec non influencé par le profil de résistance de la souche ou par la prescription d’une association
✓ Risque d’échec diminue si le Tt initial inclus une fluoroquinolone
✓ Nécessité d’évaluer le potentiel bénéfice des quinolones dans une étude randomisée
ETUDES CLINIQUES
bactériémies
Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapper et al(^1)</td>
<td>0.56 (0.17, 1.75)</td>
</tr>
<tr>
<td>Kregler et al(^2)</td>
<td>1.04 (0.63, 1.73)</td>
</tr>
<tr>
<td>Piccart et al(^3)</td>
<td>1.50 (0.13, 21.72)</td>
</tr>
<tr>
<td>de La Torre et al(^4)</td>
<td>0.89 (0.27, 2.88)</td>
</tr>
<tr>
<td>McCue et al(^5)</td>
<td>2.31 (1.10, 4.82)</td>
</tr>
<tr>
<td>Bouza et al(^6)</td>
<td>0.19 (0.01, 1.98)</td>
</tr>
<tr>
<td>McCue et al(^7)</td>
<td>2.78 (0.90, 8.48)</td>
</tr>
<tr>
<td>Hiff et al(^8)</td>
<td>0.42 (0.19, 0.90)</td>
</tr>
<tr>
<td>Feidman et al(^9)</td>
<td>0.00 (0.00, 0.29)</td>
</tr>
<tr>
<td>Chow et al(^10)</td>
<td>1.14 (0.37, 3.49)</td>
</tr>
<tr>
<td>Korvick et al(^11)</td>
<td>1.14 (0.56, 2.34)</td>
</tr>
<tr>
<td>Mendelson et al(^12)</td>
<td>0.45 (0.06, 3.66)</td>
</tr>
<tr>
<td>DePauw et al(^13)</td>
<td>1.75 (0.11, 104.80)</td>
</tr>
<tr>
<td>Lebovici et al(^14)</td>
<td>1.18 (0.83, 1.66)</td>
</tr>
<tr>
<td>Igga et al(^15)</td>
<td>0.92 (0.08, 6.08)</td>
</tr>
<tr>
<td>Kuikka et al(^16)</td>
<td>0.55 (0.21, 1.36)</td>
</tr>
<tr>
<td>Kim et al(^17)</td>
<td>1.45 (0.52, 3.98)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.96 (0.70, 1.32)</td>
</tr>
</tbody>
</table>

Favoring combination therapy  Odds ratio (95% confidence interval)  Favoring monotherapy
Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

**Etudes prospectives uniquement**

<table>
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<td>Hiff et al</td>
<td>0.42 (0.19, 0.90 )</td>
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<tr>
<td>Feldman et al</td>
<td>0.00 (0.00, 0.29)</td>
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<tr>
<td>DePauw et al</td>
<td>1.75 (0.11, 104.80)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.85 (0.50, 1.48)</td>
</tr>
</tbody>
</table>
Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

Bactériémies à *P. aeruginosa*

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapper et al(^{35})</td>
<td>0.56 (0.17, 1.75)</td>
</tr>
<tr>
<td>Igra et al(^{45})</td>
<td>0.92 (0.08, 6.08)</td>
</tr>
<tr>
<td>Mendelson et al(^{43})</td>
<td>0.45 (0.06, 3.66)</td>
</tr>
<tr>
<td>Kuikka et al(^{46})</td>
<td>0.55 (0.21, 1.36)</td>
</tr>
<tr>
<td>Hiff et al(^{19})</td>
<td>0.42 (0.19, 0.90)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.50 (0.32, 0.79)</td>
</tr>
</tbody>
</table>

Favoring combination therapy: Odds ratio Favoring monotherapy
(95% confidence interval)

MAIS
Dans 4 études sur 5 aminosides en monothérapie

Adéquation?
Risk factors associated with unfavorable short-term treatment outcome in patients with documented *Pseudomonas aeruginosa* infection

- **Etude rétrospective monocentrique**
  - Bactériémies et pneumonies
  - 117 patients
    - 40 (34%) évolution favorable à J5
    - 77 (66%) évolution défavorable à J5

<table>
<thead>
<tr>
<th>Monothérapies</th>
<th>Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pip-Tazobactam</td>
<td>Pip-Taz+Cipro</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Mero+Cipro</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Cefta+Cipro</td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
</tr>
<tr>
<td>Tobramycine</td>
<td></td>
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<tr>
<td>Ciprofloxacine</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopresseur</td>
<td>6</td>
<td>0.0003</td>
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<tr>
<td>Admission direct USI</td>
<td>2.9</td>
<td>0.052</td>
</tr>
<tr>
<td>&gt;2 Atb actifs</td>
<td>0.39</td>
<td>0.022</td>
</tr>
</tbody>
</table>

DiMondi et al Int J Clin Pharm 2015
Retrospective study analyzed data of 234 patients with *P. aeruginosa* bacteremia at a 1,200-bed tertiary teaching university hospital in South Korea between January 2010 and December 2012.
How to manage *Pseudomonas aeruginosa* infections

Matteo Bassetti MD, PhD\(^1\), Antonio Vena MD\(^1\), Antony Croxatto PhD\(^2\), Elda Righi MD, PhD\(^1\), Benoit Guery MD, PhD\(^3\)

---

**Figure 1.** Clinical approach to patients with suspected *P. aeruginosa* infection.

### Patient Risk Factors

**Critically ill or septic shock** AND/OR

- **Associated Comorbidities:**
  - Diabetes
  - COPD
  - Moderate/severe renal/liver disease
  - Immunosuppression/neutropenia
  - Elderly
  - Solid tumor
  - Structural lung disease
  - Trauma
  - Organ transplantation
  - Hemodialysis

**Risk factors for *P. aeruginosa***

- Receipt of broad-spectrum antimicrobial therapy in last 90 days (mainly cephalosporines, fluoroquinolones or carbapenems)
- History of prolonged hospitalization and/or LTCFs
- Invasive devices
- Immunosuppression
- Current or prior ICU admission

---

**At least one risk factor**

**Empirical Therapy**

- **BSI and VAP**
  - Ceftolozane/tazobactam-ceftazidime/avibactam
  - OR
  - carbapenem-piperacillin/tazobactam-cefepime-ceftazidime
  - PLUS
  - aminoglycoside/colistin/fosfomycin

- **Complicated UTI or IAI**
  - Ceftolozane tazobactam-ceftazidime/avibactam ± metronidazole
  - OR
  - carbapenem-piperacillin/tazobactam or cefepime-ceftazidime ± metronidazole
  - PLUS
  - aminoglycoside/colistin/fosfomycin

---

**No risk factors**

- **Local epidemiology for *P. aeruginosa* strains**
  - Resistance to third generation cephalosporin, piperacillin/tazobactam or carbapenem v(imipenem or meropenem) >25%

**De-escalate to single agent when the antimicrobial susceptibility testing becomes available**

---

**Empirical Therapy**

- **BSI and VAP, skin and soft tissue infections**
  - carbapenem-piperacillin/tazobactam-cefepime-ceftazidime

- **Complicated UTI**
  - carbapenem-piperacillin/tazobactam-cefepime-ceftazidime
  - aminoglycoside/colistin

---

BSI: Bloodstream infection; COPD: Chronic obstructive pulmonary disease; IAI: Intra-abdominal infections; LTCFs: Long term care facilities; UTI: Urinary tract infection; VAP: Ventilator associated pneumonia.

---

Drugs in context 2018
Plan

✓ Sensibilité aux principales molécules et nouvelles molécules
✓ Le trio hôte-molécule-pathogène
✓ PK/PD
✓ Durée
✓ Associations
✓ Thérapeutiques alternatives
Étape d’adhésion initiale

Reconnaissance de structures glycaniques épithéliales et muciniques via des lectines

Adhésion

Colonisation pulmonaire

Formation du biofilm
Les lectines de *P. aeruginosa*

- LecA (PA-IL)  
  ![LecA structure](image)
  (Cioci et al., 2003)

- LecB (PA-IIIL)  
  ![LecB structure](image)
  (Loris et al., 2003)

- D-galactose  
- L-fucose

✓ L’expression de LecA et LecB est régulée par le quorum sensing et par le facteur RpoS
Role of LecA and LecB Lectins in *Pseudomonas aeruginosa*-Induced Lung Injury and Effect of Carbohydrate Ligands

Chanez Chemani,¹ Anne Imberty,² Sophie de Bentzmann,³ Maud Pierre,¹,⁴ Michaela Wimmerová,⁵ Benoît P. Guery,¹⁺⁺ and Karine Faure¹⁺⁺

---

**A**

<table>
<thead>
<tr>
<th></th>
<th>CTR</th>
<th>PAO1</th>
<th>PAO1::lecA</th>
<th>PAO1::lecA/pMMBlecA</th>
<th>PAO1::lecB</th>
<th>PAO1::lecB/pMMBlecB</th>
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<tbody>
<tr>
<td><strong>125I-albumin in blood (%)</strong></td>
<td></td>
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**B**

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<th>PAO1::lecA/pMMBlecA</th>
<th>PAO1::lecB</th>
<th>PAO1::lecB/pMMBlecB</th>
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<td><strong>125I-albumin in lung (%)</strong></td>
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<tr>
<td>6.0</td>
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</tr>
</tbody>
</table>

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*Infection and Immunity, May 2009, p. 2065–2075*
Figure A: 
125-I-albumin in blood (%)

- CTR
- PA
- PA + Glc
- PA + Me-α-Fuc
- PA + GalNAc
- PA + Me-α-Gal
- PA + Me-α-Gal + Me-α-Fuc

**Significance Levels:**
- * p < 0.05
- ** p < 0.01
- *** p < 0.001

Figure B: 
125-I-albumin in lung (%)

- CTR
- PA
- PA + Glc
- PA + Me-α-Fuc
- PA + GalNAc
- PA + Me-α-Gal
- PA + Me-α-Gal + Me-α-Fuc

**Significance Levels:**
- * p < 0.05
- ** p < 0.01
- *** p < 0.001

**Time Points:**
- 6h
- 16h

INFECTION AND IMMUNITY, May 2009, p. 2065–2075
11 adult CF patients with chronic infection with *P. aeruginosa* treated twice daily with inhalation of a fucose/galactose solution for 21 days.

**Figure 2:** TNFα mRNA expression in sputum cells (A) and in PBMC (B) before (pre) and after (post) treatment with inhalation alone (p. i.) or combination of inhalation with antibiotics (p. i. + i. v.). Mean±SEM. *: P < 0.05 vs pre.
Facteurs extracellulaires de virulence

- Type I: Protéase alcaline, HasAp, AprX
- Type III: Exo-enzymes S, T, U, Y
- Type II: Protéases (élastases LasA, LasB), Exotoxin A, Phospholipases, Lipase, Phosphatase alcaline, Protéine de liaison de la chitine, Hémolysines

Alginate, Pili (Type IV), Flagellum
Type I  Type II  Type III

P. aeruginosa

AprA  ToxA  ExoY  ExoT  ExoU  ExoS

Membrane interne
Membrane externe
Membrane cytoplasmique

Cellule eucaryote

ExoY  ExoT  ExoU  ExoS

PcrV

Type I Type II Type III

P. aeruginosa

AprA  ToxA  ExoY  ExoT  ExoU  ExoS

Membrane interne
Membrane externe
Membrane cytoplasmique

Cellule eucaryote

ExoY  ExoT  ExoU  ExoS

PcrV
TTSS: a needle

Kubori et al. Science 1998, 280, 602
Persistent Infection with *Pseudomonas aeruginosa* in Ventilator-associated Pneumonia

Ali A. El Solh¹, Morohunfolu E. Akinnusi¹, Jeanine P. Wiener-Kronish², Susan V. Lynch², Lilibeth A. Pineda¹, and Kristie Szarpa¹

34 patients with VAP

25 TTSS+   9 TTSS-

- Adequate antimicrobial therapy

13/25 + at day 8

0/9 + at day 8
## Surmortalité et SST III

<table>
<thead>
<tr>
<th></th>
<th>Infection aiguë</th>
<th>Infection chronique</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTT [+ ]</td>
<td>89%</td>
<td>41%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SSTT [+ ]</th>
<th>SSTT [- ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortalité</td>
<td>21%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### RR décès

- **PcrV seule**: 7,4
- **PcrV + toxine(s)**: 8,7

(Roy Burman et al, J Infect Dis. 2001)
35 patients ventilés
Pneumonie à *P. aeruginosa*

Production de Protéines
Issues du système de sécrétion
de type III

+ 27/35

- 8/35

22 Sévère  (81%)
5 Modérées (19%)

3 Sévères  (38%)
5 Modérées (62%)

ExoU : 10/35 (29%) associée à 90% de formes sévères

(Hauser et al, Crit Care Med 2002)
a. Intravenous treatment 1 h after infection

- Anti-PcrV IgG (100 µg)
- Anti-PcrV IgG (50 µg)
- Anti-PcrV IgG (10 µg)
- Anti-PcrV F(ab')2 (100 µg)
- Anti-ExoU IgG (100 µg)
- Control IgG (100 µg)

Survival (%) vs Time (days after infection)

b. Intravenous treatment 4 h after infection

- Anti-PcrV IgG (100 µg)
- Anti-PcrV IgG (50 µg)
- Anti-PcrV IgG (10 µg)
- Control IgG (100 µg)

Survival (%) vs Time (days after infection)
Generation and Characterization of a Protective Monoclonal Antibody to *Pseudomonas aeruginosa* PcrV

Dara W. Frank,1 Amy Vallis,1
Jeanine P. Wiener-Kronish,2,3,4 Arup Roy-Burman,2,5
Edward G. Spack,6 Brian P. Mullaney,2,5
Mehdi Megdoud,2 James D. Marks,2 Robert Fritz,1
and Teiji Sawa2

1Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, Milwaukee; Departments of 2Anesthesia and Perioperative Care and 3Medicine, 4Cardiovascular Research Institute, and 5Division of Critical Care Medicine of the Department of Pediatrics, University of California, San Francisco, and 6Inter.Mune, Brisbane, California

---

**Diagram A**

- **Rab anti-PcrV**
  - MAb 166
  - MAb 203
  - MAb 3.3.5
  - MAb 179
  - MAb 248
  - MAb 3.75
  - MAb 1.82

**Graph A**

Survival (%) vs. Days after infection

- m166 50 µg
- m166 10 µg
- m166 1 µg
- m166 0.5 µg
- MOPC-141 50 µg
- Rab poly anti-PcrV IgG 10 µg
- Rab control IgG 10 µg
- PBS

**Graph B**

Survival (%) vs. Body temperature (°C)

- 4 h after infection
- 16 h after infection
Membrane disruption and toxin injection into cell

Pseudomonas aeruginosa

TTSS

PcrV Protein

Anti-PcrV Antibody (KB001)

Cell Membrane

Membrane disruption and toxin injection into cell
Safety and pharmacokinetics of an anti-PcrV PEGylated monoclonal antibody fragment in mechanically ventilated patients colonized with *Pseudomonas aeruginosa*: A randomized, double-blind, placebo-controlled trial*

Bruno François, MD; Charles-Edouard Luyt, MD, PhD; Anthony Dugard, MD; Michel Wolff, MD; Jean-Luc Diehl, MD, PhD; Samir Jaber, MD, PhD; Jean-Marie Forel, MD; Denis Garot, MD; Eric Kipnis, MD, PhD; Alexandre Mebazaa, MD, PhD; Benoit Misset, MD, PhD; Antoine Andremont, MD, PhD; Marie-Cécile Ploy, PharmD, PhD; Alan Jacobs, MD; Geoffrey Yarranton, PhD; Tillman Pearce, MD; Jean-Yves Fagon, MD, PhD; Jean Chastre, MD

![Figure 1. Trial flow chart. KB001, a PEGylated recombinant anti-*Pseudomonas aeruginosa* (Pa) PcrV Fab’ antibody.](Crit Care Med 2012 Vol. 40, No. 8)
Figure 2. Average serum and endotracheal aspirate (ETA) KB001 concentration-time curves. KB001, a PEGylated recombinant anti-
*Pseudomonas aeruginosa* PcrV Fab’ antibody.
Pneumonie
Survie 28j
Survie 28j sans Pa

3mg/kg
10mg/kg
Placebo

KB001
Two cohorts of 12 subjects were planned: each randomized 2:1 to receive a single intravenous (IV) infusion of KB001 or placebo.

Subjects randomized to receive KB001 received 3 mg/kg in the first cohort and 10 mg/kg in the second cohort.
Neutrophils
($\log_{10} /nL$ with 95% CI)

Macrophages
($\log_{10} /\mu L$ with 95% CI)

Interleukin-8
($\log_{10} \text{ ng/mL}$ with 95% CI)

Interleukin-1β
($\log_{10} \text{ ng/mL}$ with 95% CI)

Neutrophil Elastase
($\log_{10} \mu g/mL$ with 95% CI)

Myeloperoxidase
($\log_{10} \text{ pmol/mL}$ with 95% CI)

Baseline

Change at Day 28

Les INP. Le 18-55
Synthesis and structure–activity relationships of novel phenoxyacetamide inhibitors of the *Pseudomonas aeruginosa* type III secretion system (T3SS)


![Chemical structures](image)

**Figure 1.** T3SS hit compounds.

Table 1
Activity and cytotoxicity of T3SS inhibitors with varying substituents at the α-position

<table>
<thead>
<tr>
<th>Compound #</th>
<th>R</th>
<th>R'</th>
<th>Secretion IC₅₀ (µM)</th>
<th>Translocation IC₅₀ (µM)</th>
<th>Translocation CC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>7.8 ± 2.0</td>
<td>11 ± 2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>&gt;100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6b</td>
<td>Me</td>
<td>H</td>
<td>&gt;100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6c</td>
<td>Et</td>
<td>H</td>
<td>3.9 ± 1.3</td>
<td>3.0 ± 1.0</td>
<td>67 ± 18</td>
</tr>
<tr>
<td>6d</td>
<td>nPr</td>
<td>H</td>
<td>&gt;100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6e</td>
<td>iPr</td>
<td>H</td>
<td>&gt;100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>(R)-1</td>
<td>Me</td>
<td>H</td>
<td>4.3 ± 1.5</td>
<td>8.9 ± 5.5</td>
<td>61 ± 19</td>
</tr>
<tr>
<td>(S)-1</td>
<td>Me</td>
<td>H</td>
<td>&gt;100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

n.d.: value not determined.

Table 2
Activity and cytotoxicity of T3SS inhibitors with varying substituents on the phenoxyide ring

<table>
<thead>
<tr>
<th>Compound #</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>Secretion IC₅₀ (µM)</th>
<th>Translocation IC₅₀ (µM)</th>
<th>Translocation CC₅₀ (µM)</th>
</tr>
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<tr>
<td>1</td>
<td>CH</td>
<td>-Cl</td>
<td>-Cl</td>
<td>7.8 ± 2.0</td>
<td>11 ± 2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>12a</td>
<td>CH</td>
<td>-H</td>
<td>-Cl</td>
<td>7.8 ± 2.0</td>
<td>11 ± 2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>12b</td>
<td>CH</td>
<td>-H</td>
<td>-H</td>
<td>7.8 ± 2.0</td>
<td>11 ± 2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>12c</td>
<td>CH</td>
<td>-Cl</td>
<td>-H</td>
<td>34 ± 1</td>
<td>67 ± 18</td>
<td>67 ± 18</td>
</tr>
<tr>
<td>12d</td>
<td>CH</td>
<td>-Cl</td>
<td>-F</td>
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<tr>
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<td>67 ± 18</td>
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<tr>
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<tr>
<td>16</td>
<td>N</td>
<td>-Cl</td>
<td>-Cl</td>
<td>5.6 ± 0.2</td>
<td>22 ± 10</td>
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n.d.: value not determined.
Quorum Sensing
Azithromycin Blocks Quorum Sensing and Alginate Polymer Formation and Increases the Sensitivity to Serum and Stationary-Growth-Phase Killing of *Pseudomonas aeruginosa* and Attenuates Chronic *P. aeruginosa* Lung Infection in Cfr<sup>−/−</sup> Mice

Nadine Hoffmann, Baoleri Lee, Morten Hentzer, Thomas Bovbjerg Rasmussen, Zhijun Song, Helle Krogh Johansen, Michael Givskov, and Niels Høiby

### TABLE 1. Effect of AZM on virulence factor production by *P. aeruginosa* over 24 h of culture

<table>
<thead>
<tr>
<th>Virulence factor</th>
<th>AZM concn (µg/ml)</th>
<th>Activity per cell&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastase</td>
<td>0 (control)</td>
<td>0.075 ± 0.007&lt;sup&gt;*&lt;/sup&gt;</td>
<td>100</td>
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<tr>
<td></td>
<td>2</td>
<td>0.058 ± 0.008</td>
<td>77</td>
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<td>4</td>
<td>0.034 ± 0.009</td>
<td>45</td>
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<td>8</td>
<td>0.038 ± 0.010</td>
<td>51</td>
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<tr>
<td>Chitinase</td>
<td>0 (control)</td>
<td>188 ± 11</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>124 ± 18</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>29 ± 9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>18 ± 10</td>
<td>10</td>
</tr>
<tr>
<td>Pyocyanin</td>
<td>0 (control)</td>
<td>0.044 ± 0.004</td>
<td>100</td>
</tr>
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<td>2</td>
<td>0.019 ± 0.005</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.014 ± 0.003</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.007 ± 0.002</td>
<td>16</td>
</tr>
<tr>
<td>Alginate</td>
<td>0 (control)</td>
<td>612 ± 37.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>383 ± 38.9</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>340 ± 62.5</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>320 ± 9.8</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values are means ± standard deviations for three replicates. The specific activities are *A*<sub>600/OD<sub>600</sub> for elastase, *U*/OD<sub>600</sub> for chitinase, *A*<sub>520/OD<sub>600</sub> for pyocyanin, and µg/ml/OD<sub>600</sub> for alginate.
Azithromycin Blocks Quorum Sensing and Alginate Polymer Formation and Increases the Sensitivity to Serum and Stationary-Growth-Phase Killing of *Pseudomonas aeruginosa* and Attenuates Chronic *P. aeruginosa* Lung Infection in *Cftr*−/− Mice

Nadine Hoffmann,1* Baoleri Lee,1 Morten Hentzer,2 Thomas Bovbjerg Rasmussen,2 Zhijun Song,1 Helle Krogh Johansen,1 Michael Givskov,2 and Niels Høiby1

FIG. 3. Alcohol precipitation of alginate from liquid ox bouillon cultures of *P. aeruginosa* NH57388A after 24 h of incubation at 37°C. The precipitation of high-weight polymers of alginate in untreated cultures (a) versus that in cultures treated with 12 μg AZM/ml (b) was negative.
Once-weekly azithromycin in cystic fibrosis with chronic *Pseudomonas aeruginosa* infection

Gratiana Steinkamp a, Sabina Schmitt-Grohe b,*, Gerd Döring c, Doris Staab d, Dietmar Pfründer e, Gudrun Beck e, Ralf Schubert f, Stefan Zielen f

- Thirty-eight patients (21 AZM/17 placebo)
- Randomized double-blind, placebo-controlled trial AZM or placebo
- 1 per week for 8 weeks
Once-weekly azithromycin in cystic fibrosis with chronic *Pseudomonas aeruginosa* infection

Gratiana Steinkamp \(^a\), Sabina Schmitt-Grohe \(^b\,*\), Gerd Döring \(^c\), Doris Staab \(^d\), Dietmar Pfründer \(^e\), Gudrun Beck \(^e\), Ralf Schubert \(^f\), Stefan Zielen \(^f\)

**Figure 3** Alginate in sputum.

**Figure 4** Mean changes in quality of life.
Impact of Macrolide Therapy in Patients Hospitalized With *Pseudomonas aeruginosa* Community-Acquired Pneumonia

Elena Laserna, MD; Oriol Sibila, MD; Juan Felipe Fernandez, MD; Diego Jose Maselli, MD; Eric M. Mortensen, MD; Antonio Anzueto, MD; Grant Waterer, MD; and Marcos I. Restrepo, MD, FCCP

---

**Flowchart:**

1. **P. aeruginosa Pneumonia (n=781)**
   - Excluded (n=379)
     - HCAP criteria (n=326)
     - Immunosuppression (n=25)
     - HCAP criteria + immunosuppression (n=28)
   - **P. aeruginosa CAP (n=402)**
     - Received a macrolide during the first 48 hours (n=171)
     - Did not receive macrolide therapy (n=231)

---

_CHEST 2014; 145(5):1114–1120_
Impact of Macrolide Therapy in Patients Hospitalized With *Pseudomonas aeruginosa* Community-Acquired Pneumonia

Elena Laserna, MD; Oriol Sibila, MD; Juan Felipe Fernandez, MD; Diego Jose Maselli, MD; Eric M. Mortensen, MD; Antonio Anzueto, MD; Grant Waterer, MD; and Marcos I. Restrepo, MD, FCCP

![Graph showing survival rate comparison between No-macrolide and Macrolide groups.](image)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nonmacrolide (n = 231)</th>
<th>Macrolide (n = 171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d mortality</td>
<td>38 (16.5)</td>
<td>32 (18.7)</td>
<td>.5</td>
</tr>
<tr>
<td>Use of mechanical ventilation</td>
<td>64 (27.7)</td>
<td>49 (28.7)</td>
<td>.8</td>
</tr>
<tr>
<td>Use of vasopressors</td>
<td>38 (16.5)</td>
<td>29 (17.0)</td>
<td>.8</td>
</tr>
<tr>
<td>Need of ICU</td>
<td>75 (32.5)</td>
<td>61 (35.7)</td>
<td>.5</td>
</tr>
<tr>
<td>Hospital LOS, d</td>
<td>20.3 ± 33.1</td>
<td>18.9 ± 23.5</td>
<td>.6</td>
</tr>
</tbody>
</table>
Macrolide Treatment Inhibits *Pseudomonas aeruginosa* Quorum Sensing in Non–Cystic Fibrosis Bronchiectasis

An Analysis from the Bronchiectasis and Low-Dose Erythromycin Study Trial

Lucy D. Burr¹,⁴, Geraint B. Rogers², Alice C.-H. Chen¹, Brett R. Hamilton³, Gertruida F. Pool³, Steven L. Taylor², Deon Venter³, Simon D. Bowler⁴, Sally Biga⁵, and Michael A. McGuckin¹

117 Randomized (stratified for *P. aeruginosa*)

- 58 Randomized to receive placebo
  - 53 Completed the treatment period
    - 5 Did not complete the treatment period
    - 2 Did not return for follow up
    - 1 Nausea
    - 1 Withdrawn by physician (respiratory deterioration)
    - 1 Unable to continue
  - 40 subjects provided adequate induced sputum samples
  - 21 subjects were PCR positive for *P. aeruginosa* after 48 weeks of treatment
    - 6 had insufficient housekeeper mRNA expression
  - 15 patients met criteria for whole sputum gene expression analysis

- 59 Randomized to receive erythromycin
  - 54 Completed the treatment period
    - 5 did not complete the treatment period
    - 2 did not return for follow up
    - 1 Possible QTc prolongation
    - 1 Moved
    - 1 Unable to continue
  - 40 subjects provided adequate induced sputum samples
  - 20 subjects were PCR positive for *P. aeruginosa* after 48 weeks of treatment
    - 9 had insufficient housekeeper mRNA expression
  - 11 patients met criteria for whole sputum gene expression analysis
**Lung bacterial load**

- **A** and **B**

- LasR (A) and PqsA (B) expression

Ann Am Thor Soc 2016, 13/169
Retrospective observational study

Severe COPD patients
- Azithromycin (PA) (250 mg, at least 3 times weekly for at least 6 months), n=126
- Not prescribed azithromycin (NPA), n=69

Long-term azithromycin reduces exacerbation numbers in severe COPD patients, and benefits persist beyond one year
Autoinducer production and quorum-sensing dependent phenotypes of *Pseudomonas aeruginosa* vary according to isolation site during colonization of intubated patients

Sabine Favre-Bonté, Eric Chamot, Thilo Köhler, Jacques-A Romand and Christian van Delden

**Elastase**

A

**Adhésion**

B

**Tracheal Asp**

C

**Intub Device**

3-oxo-C₁₂-HSL (μM)

0.1

8

12

13

C₁₂-HSL (μM)

1

8

12

13

**Biofilm**

D

E

F

**Biofilm (%)**

8

12

13

TA isolates

ID isolates

8

12

13

TA isolates

ID isolates

0

20

40

60

80

100

120

TA isolates

ID isolates

0

20

40

60

80

100

120

TA isolates

ID isolates

0

20

40

60

80

100

120

TA isolates

ID isolates
Microbiome and Immune system
✓ C57BL/6: ampicillin, vancomycin, neomycin sulfate, and metronidazole in drinking water for 4 wk before PR8 virus infection (10 pfu per mouse)
The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia

Ampicillin, neomycin, metronidazole and vancomycin
Mp alvéolaires

Neutrophiles circulants

Mp Pérétonéaux

Mp alvéolaires

LTA

LPS

Mp Pérétonéaux
Loss of Bacterial Diversity during Antibiotic Treatment of Intubated Patients Colonized with *Pseudomonas aeruginosa*^V^  

J. L. Flanagan,† E. L. Brodie,† L. Weng,§ S. V. Lynch,‡ O. Garcia,† R. Brown,† P. Hugenholtz,§ T. Z. DeSantis,‡ G. L. Andersen,‡ J. P. Wiener-Kronish,† and J. Bristow‡,*  

TABLE 1. Patient information and antimicrobial treatment  

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of days after enrollment (sample no.)</th>
<th>Sex</th>
<th>Patient age</th>
<th>Antimicrobial treatment Within 24 h before study enrollment</th>
<th>Antimicrobial treatment Following sampling (sensitivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (1)</td>
<td>Female</td>
<td>57 yr</td>
<td>Cefazolin, piperacillin-tazobactam</td>
<td>Pipracillin-tazobactam (S), fluconazole, cefazolin</td>
</tr>
<tr>
<td></td>
<td>7 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Cefazolin (S), fluconazole (S), levofloxacin (S)</td>
</tr>
<tr>
<td>2</td>
<td>1 (1)</td>
<td>Male</td>
<td>79 yr</td>
<td>Cefazolin, cefuzidime</td>
<td>Antifungal, cefazidime</td>
</tr>
<tr>
<td></td>
<td>11 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Cefazidime (R), vancomycin</td>
</tr>
<tr>
<td></td>
<td>15 (3)</td>
<td></td>
<td></td>
<td></td>
<td>Pipracillin-tazobactam (S), ciprofloxacin (S)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vancomycin, piperacillin-tazobactam, ciprofloxacin</td>
</tr>
<tr>
<td>3</td>
<td>1 (1)</td>
<td>Female</td>
<td>54 yr</td>
<td>None</td>
<td>Ciprofloxacin (S)</td>
</tr>
<tr>
<td></td>
<td>5 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>4</td>
<td>1 (1)</td>
<td>Male</td>
<td>55 yr</td>
<td>None</td>
<td>Pipracillin-tazobactam, vancomycin</td>
</tr>
<tr>
<td></td>
<td>7 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Pipracillin-tazobactam</td>
</tr>
<tr>
<td>5</td>
<td>1 (1)</td>
<td>Female</td>
<td>85 yr</td>
<td>Clindamycin</td>
<td>Clindamycin, pipracillin-tazobactam (S)</td>
</tr>
<tr>
<td></td>
<td>4 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Pipracillin-tazobactam (S), vancomycin, ciprofloxacin (S)</td>
</tr>
<tr>
<td></td>
<td>15 (3)</td>
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<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>18 (4)</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>23 (5)</td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>1 (1)</td>
<td>Female</td>
<td>45 yr</td>
<td>None</td>
<td>Meropenem (I), fluconazole, linezolid</td>
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<tr>
<td></td>
<td>23 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Tobramycin(S), imipenem (I), cefpirome, cefazolin, cefepime (I)</td>
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<tr>
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<td>102 (3)</td>
<td></td>
<td></td>
<td></td>
<td>Timentin, trimethoprim-sulfamethoxazole, imipenem, vancomycin, fluconazole, cefepime, cefpirome, amphotericin B, tobramycin</td>
</tr>
<tr>
<td>7</td>
<td>1 (1)</td>
<td>Female</td>
<td>2 mo</td>
<td>Ampicillin, gentamicin, trimethoprim-sulfamethoxazole</td>
<td>Ampicillin (R), gentamicin</td>
</tr>
<tr>
<td></td>
<td>82 (2)</td>
<td></td>
<td></td>
<td></td>
<td>Gentamicin (S)</td>
</tr>
</tbody>
</table>

*S*, sensitive; *R*, resistant; *I*, indeterminate.
We hypothesize that reduced microbial diversity under antibiotic selection in the airways may contribute directly to pathogen selection through the loss of microbial competition.
✓ Relative abundance of viable *P. aeruginosa* and non-pseudomonal species in sputa from 12 adult CF subjects

✓ Time points:
  - 21, 14, and 7 days prior to antibiotics
  - day 3 of treatment, the final day of treatment
  - 10–14 days afterward
Respiratory microbiota resistance and resilience to pulmonary exacerbation and subsequent antimicrobial intervention

Leah Cuthbertson¹², Geraint B Rogers³, Alan W Walker⁴⁵, Anna Oliver¹, Laura E Green⁶, Thomas WV Daniels⁷, Mary P Carroll⁷, Julian Parkhill⁴, Kenneth D Bruce⁵ and Christopher J van der Gast¹

✓ (B0) baseline pre-CFPE (n = 56)
✓ (E) CFPE, 30 days prior to treatment (n = 41)
✓ (T) CFPE treatment period (n = 67)
✓ (R) recovery, 30 days post-CFPE treatment (n = 32)
✓ (B1) baseline post-CFPE (n = 41)
CIBLER LA BACTERIE :
NI SUFFISANT
NI POSSIBLE