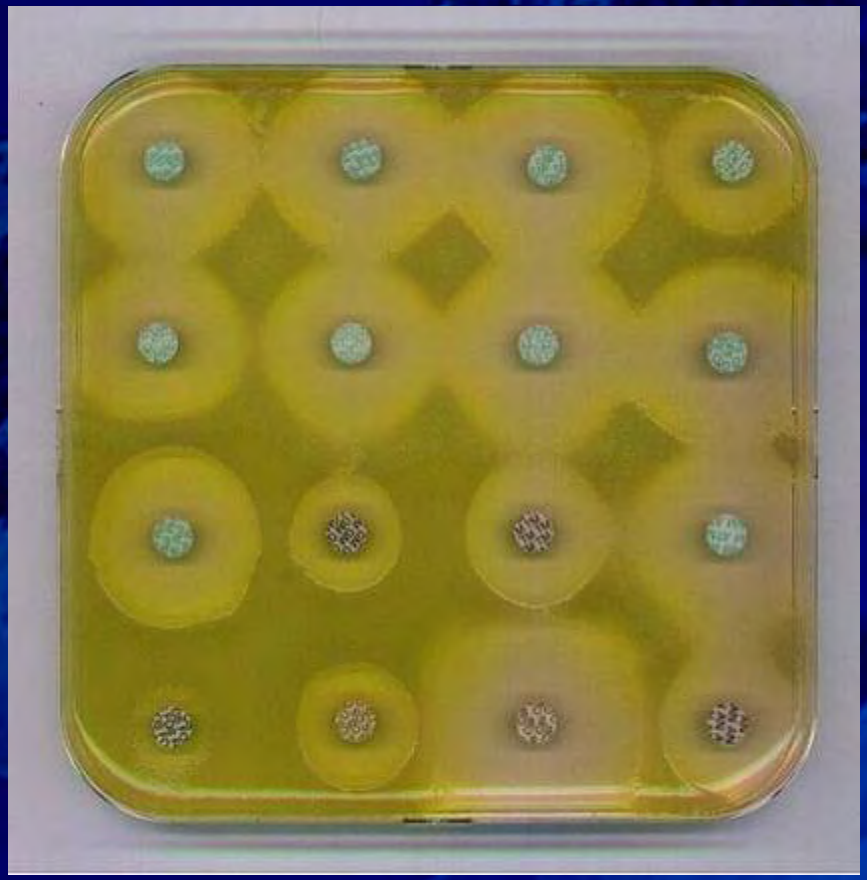
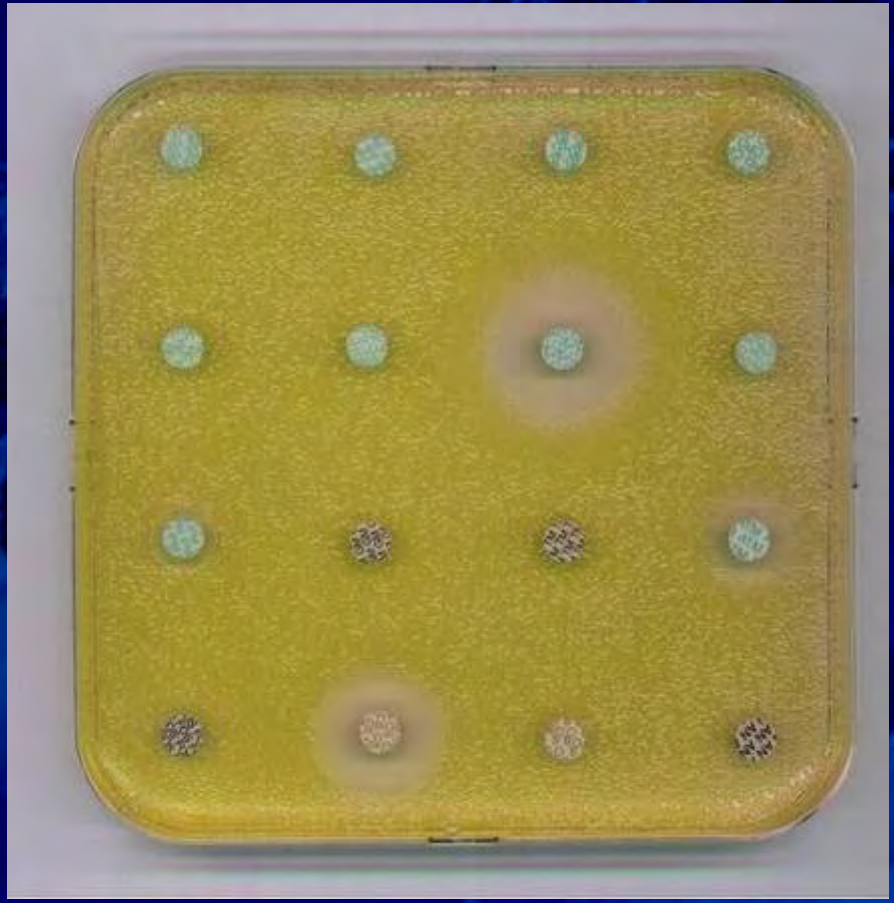
# Attitude thérapeutique dans les Infections à Pseudomonas Toto-résistants

Benoît GUERY
JNI Dijon
Juin 2007

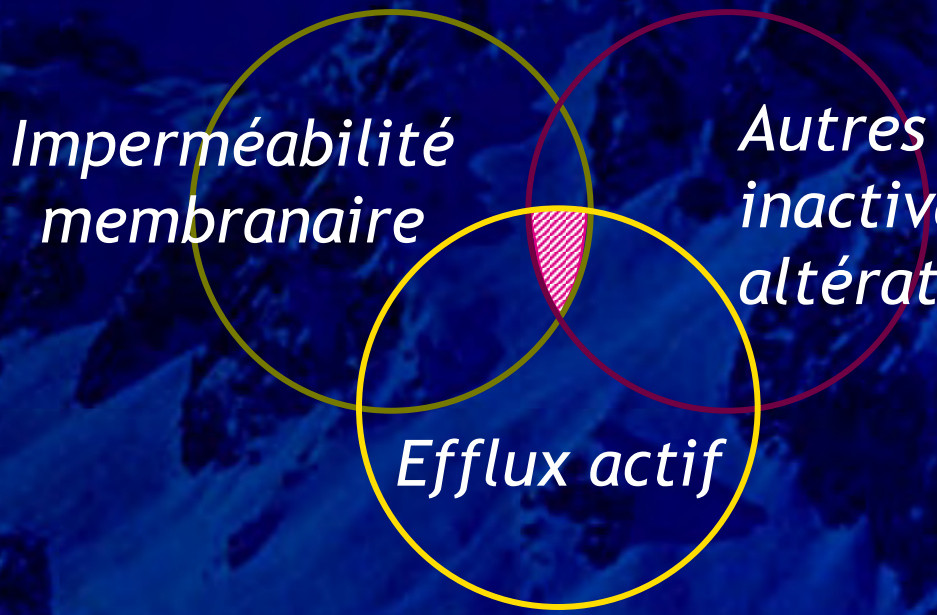
# Phénotype sauvage



# Phénotype multirésistant



# Multirésistance



# Émergence de la résistance sous traitement

| | Céph Total | Péni | Quin | Ipm | AGs | Ass |
|---|---|---|---|---|---|---|
| *E. coli* | 0<br>0.7 | 2.7 | 0 | 0 | 8 | 0.6 |
| *Proteus* sp. | 0<br>0.5 | 0.9 | 0 | 1.6 | 4 | 0 |
| *Klebsiella* | 3.2<br>2.7 | 6 | 2.8 | 1.4 | 1.5 | <2 |
| *Enterobacter* | 10.1<br>6.8 | 10 | 4.1 | 4.1 | 26.1 | 2.4 |
| *Serratia* | 5.8<br>7.8 | 20 | 11.7 | 4 | 21.7 | 5 |
| *Acinetobacter* | 16.7<br>Nd | 25 | Nd | Nd | Nd | Nd |

***Fish 1995***
***Pooling de 173 études***

# Toto-résistance

- Les facteurs de la résistance
- La prise en charge thérapeutique
  - Utilisation de la colistine
  - Les autres associations
  - L'inhalation
- Les pistes thérapeutiques

# Facteurs associés à la résistance

- 52 637 *Pseudomonas aeruginosa*
- 10 antibiotiques évalués
- Facteurs retrouvés
  - Isolement d'une réanimation
  - Age entre 18 & 39 ans
  - Site: voies respiratoires inférieures
- MDR
  - Maisons de retraite (29.9%)
  - Réanimation (29.5%)

Flamm et al, AAC 2004

# Facteurs d'acquisition d'un MDR

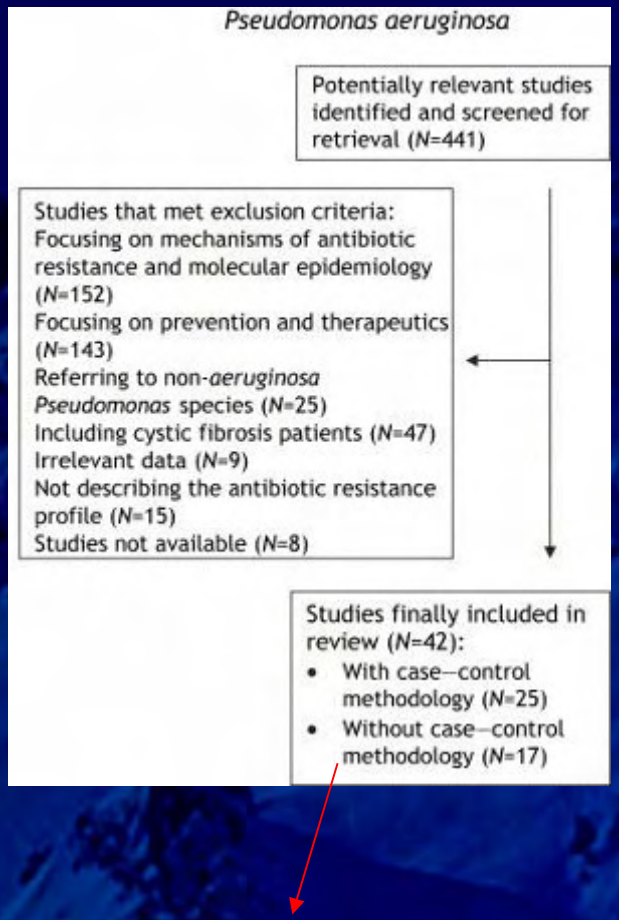
Acquisition of Multidrug-Resistant *Pseudomonas aeruginosa* in Patients in Intensive Care Units: Role of Antibiotics with Antipseudomonal Activity

Elisabeth Paramythiotou[1,a], Jean-Christophe Lucet,[2] Jean-François Timsit,[3,6] Dominique Vanjak,[1] Catherine Paugam-Burtz,[4] Jean-Louis Trouillet,[5] Stéphanie Belloc,[1] Najiby Kassis,[1] Andreas Karabinis,[7] and Antoine Andremont[1]

- Etude cas-control (34/34)
- Analyse multivariée
  - Durée du traitement par ciprofloxacine
  - Valeur borderline pour l'imipénème

Paramythiotou et al, CID 2004

# Isolement d'un MDR: revue systématique




Environnement (13/17)

- 17 multivariées /8 univariées
- Utilisation prélable d'antibiotiques (15/17)
  - Carbapenem (6)
  - Fluoroquinolones (6)
  - C3G, puis BL
- Ventilation mécanique (5)
- Durée d'hospitalisation (6)
- Comorbidité

Falagas et al, J Hosp Inf 2006

**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.**

| Therapy | 24-h AUC/MIC ratio | Patients with resistance/ total patients (%) | | |
|---|---|---|---|---|
| | | All patients | Ciprofloxacin treatment | β-Lactam treatment |
| Monotherapy | <100 | 14/17 (82) | 12/14 (86) | 2/3(67) |
| Monotherapy | ⩾100 | 17/84 (20) | 4/44 (9) | 13/40 (31) |
| Combination | ⩾100 | 1/27 (4) | 0/16 (0) | 1/27 (4) |

Craig et al CID 2001

**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.**

| 24-h AUC/MIC ratio | Patients with resistance/total patients (%) | | | |
|---|---|---|---|---|
| | Ciprofloxacin therapy | | β-Lactam therapy | |
| | *Pseudomonas* | Other GNB | *Pseudomonas* | Other GNB |
| <100 | 10/10 (100) | 2/4 (50) | 2/3 (67) | |
| ⩾100 | 2/8 (25) | 2/28 (7) | 2/3 (67) | 10/28 (36) |
| *P* | .002 | .07 | 2/3 (67) | |

Craig et al CID 2001

# Pic/CMI

- Un ratio Pic/CMI proche de 8-10
  - Fluoroquinolones
  - Aminosides

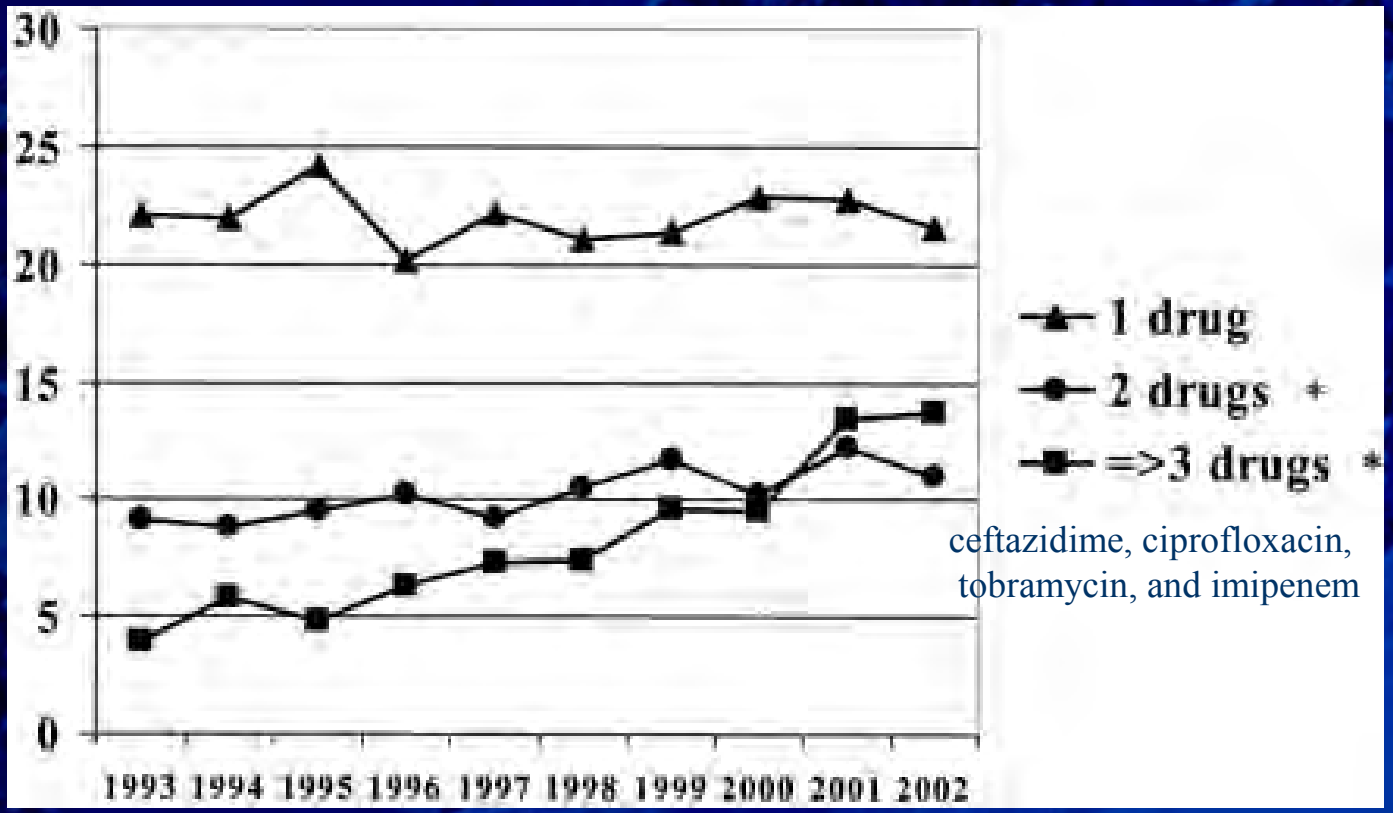
**Table 3. Relationship of peak/MIC or the 24-h area under the curve to MIC (24-h AUC/MIC ratio) to the emergence of resistance during monotherapy with ciprofloxacin.**

| PK/PD parameter | Patients with or without resistance/total patients (%) | |
|---|---|---|
| | Emergence of resistance | No resistance |
| Peak/MIC >8 or 24-h AUC ⩾100 | 3/31 (10) | 28/31 (90) |
| Peak/MIC <8 or 24-h AUC/MIC <100 | 8/10 (80) | 2/10 (20) |

**NOTE.** Data obtained from reference [28]. AUC, area under the curve; PK/PD, pharmacokinetic/pharmacodynamic. $P<.001$ by Fisher exact test.

(Peloquin et al Arch Intern Med 1989)

# National surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* isolates obtained from intensive care unit patients from 1993 to 2002




13999 souches

Obritsch et al, AAC 2004

TABLE 3. Resistance of P. aeruginosa isolates to both agents in potential combination regimens[a]

| Yr | Cefepime | | | Imipenem | | | Piperacillin-tazobactam | | | Aztreonam | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CIP | TOB | AK | CIP | TOB | AK | CIP | TOB | AK | CIP | TOB | AK |
| 1993 | NA | NA | NA | 5 | 3 | 2 | NA | NA | NA | 7 | 4 | 4 |
| 1994 | NA | NA | NA | 6 | 5 | 6 | NA | NA | NA | 11 | 8 | 8 |
| 1995 | NA | NA | NA | 6 | 3 | 3 | NA | NA | NA | 10 | 5 | 5 |
| 1996 | NA | NA | NA | 6 | 4 | 3 | NA | NA | NA | 10 | 6 | 6 |
| 1997 | NA | NA | NA | 9 | 4 | 3 | 5 | 2 | 2 | 11 | 5 | 5 |
| 1998 | 10 | 5 | 4 | 8 | 5 | 2 | 7 | 4 | 3 | 14 | 6 | 5 |
| 1999 | 15 | 10 | 6 | 10 | 6 | 4 | 8 | 6 | 3 | 16 | 9 | 6 |
| 2000 | 16 | 8 | 6 | 10 | 6 | 3 | 8 | 4 | 3 | 17 | 7 | 6 |
| 2001 | 19 | 11 | 9 | 13 | 8 | 5 | 9 | 5 | 4 | 20 | 10 | 8 |
| 2002 | 17 | 11 | 6 | 16 | 9 | 5 | 7 | 4 | 4 | 17 | 11 | 7 |
| P value[b] | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0002 | 0.013 | <0.0001 | <0.0001 | <0.0001 |

[a] AK, amikacin; CIP, ciprofloxacin; TOB, tobramycin; NA, not available. Data presented as percentages.

[b] P values representative of available resistance data over the 10-year period.

Obritsch et al, AAC 2004

# Toto-résistance

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- Les pistes thérapeutiques

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

# Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas[corr] and Sofia K. Kasiakou

[1]Alfa Institute of Biomedical Sciences (AIBS) and [2]Department of Medicine, "Henry Dunant" Hospital, Athens, Greece, and [3]Tufts University School of Medicine, Boston, Massachusetts

The emergence of multidrug-resistant gram-negative bacteria and the lack of new antibiotics to combat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice. Most of the reintroduction of polymyxins during the last few years is related to colistin. The polymyxins are active against selected gram-negative bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species. These drugs have been used extensively worldwide for decades for local use. However, parenteral use of these drugs was abandoned ~20 years ago in most countries, except for treatment of patients with cystic fibrosis, because of reports of common and serious nephrotoxicity and neurotoxicity. Recent studies of patients who received intravenous polymyxins for the treatment of various *P. aeruginosa* and *Acinetobacter baumannii* infections of various types, including pneumonia, bacteremia, and urinary tract infections, have led to the conclusion that these antibiotics have acceptable effectiveness and considerably less toxicity than was reported in old studies.

Falagas et al, CID 2005

## Outcome of colistin therapy for *Pseudomonas aeruginosa* infection

| Outcome | No. of patients |
|---|---|
| Favorable therapeutic outcome | 14/23 |
| Unfavorable therapeutic outcome | 9 |
| Died while receiving therapy | 7 |
| Experienced relapse[a] | 3 |
| **Survived** | |
| Through end of therapy | 16 |
| Through end of hospitalization | 9 |

5 mg/kg/j en 2 doses

(Linden et al, CID 2003)

Intensive Care Med (2005) 31:1058–1065
DOI 10.1007/s00134-005-2691-4

ORIGINAL

Rosa Reina
Elisa Estenssoro
Gabriela Sáenz
Héctor S. Canales
Romina Gonzalvo
Gabriela Vidal
Gustavo Martins
Andrea Das Neves
Oscar Santander
Carlos Ramos

# Safety and efficacy of colistin in *Acinetobacter* and *Pseudomonas* infections: a prospective cohort study

- Etude prospective
- 185 patients infectés avec *Acinetobacter baumannii* et *Pseudomonas aeruginosa*
- Hospitalisation> 48 h
  - 55 groupe colistine
  - 130 groupe non colistine
- Comparable sur age, APACHE II, antécédents, et score SOFA

| | *n* | Mortality |
|---|---|---|
| Colistin | 29 | 10 (34%) |
| *P. aeruginosa* | 14 | 5 (36%) |
| *Acinetobacter* | 15 | 5 (33%) |
| Noncolistin | 86 | 21 (24%) |
| *P. aeruginosa* | 34 | 5 (15%) |
| *Acinetobacter* | 52 | 16 (31%) |

Table 2 Outcomes and sites of infection in colistin and noncolistin groups (*LOS* length of stay)

| | Colistin group (*n*=55) | Noncolistin group (*n*=130) | *p* |
|---|---|---|---|
| Treatment duration (days) | 13±5 | 13±6 | 0.8 |
| Basal creatinine (mg/dl)[a] | 0.9±0.2 | 0.9±0.2 | 0.6 |
| End creatinine (mg/dl)[b] | 1.0±0.3 | 1.0±0.3 | 0.9 |
| Day of diagnosis of infection[c] | 12 (7–21) | 7 (6–13) | 0.0001[d] |
| Inappropriate empirical treatment | 55 (100%) | 10 (8%) | 0.00001 |
| Treatment delay (hours)[e] | 96±24 | 12±4 | 0.00001 |
| Alive at hospital discharge | 39 (71%) | 96 (74%) | 0.2 |
| Length of MV (days)[f] | 28 (15–48) | 20 (12–27) | 0.02[d] |
| LOS ICU (days)[f] | 40 (21–58) | 26 (16–43) | 0.03[d] |
| LOS hospital (days)[f] | 61 (29–88) | 36 (26–70) | 0.54[d] |
| *Acinetobacter* infections | 36 (65%) | 69 (53%) | 0.2 |
| Mortality | 10 (27%) | 21 (30%) | 0.8 |
| *Pseudomonas* infections | 19 (35%) | 61 (47%) | 0.3 |
| Mortality | 7 (37%) | 17 (28%) | 0.5 |
| Ventilator-associated pneumonia | 29 (53%) | 86 (66%) | 0.2 |
| Mortality | 10 (32%) | 21 (24%) | 0.2 |
| Primary bacteremia | 9 (16%) | 25 (19%) | 0.2 |
| Mortality | 2 (22%) | 9 (36%) | 0.1 |
| Urinary tract infection | 10 (18%) | 11 (8%) | 0.1 |
| Mortality | 2 (20%) | 2 (20%) | 0.2 |
| Other infections[g] | 7 (13%) | 8 (6%) | 0.3 |
| Mortality | 3 (43%) | 3 (38%) | 0.3 |

Int Care Med 2005

ORIGINAL ARTICLE

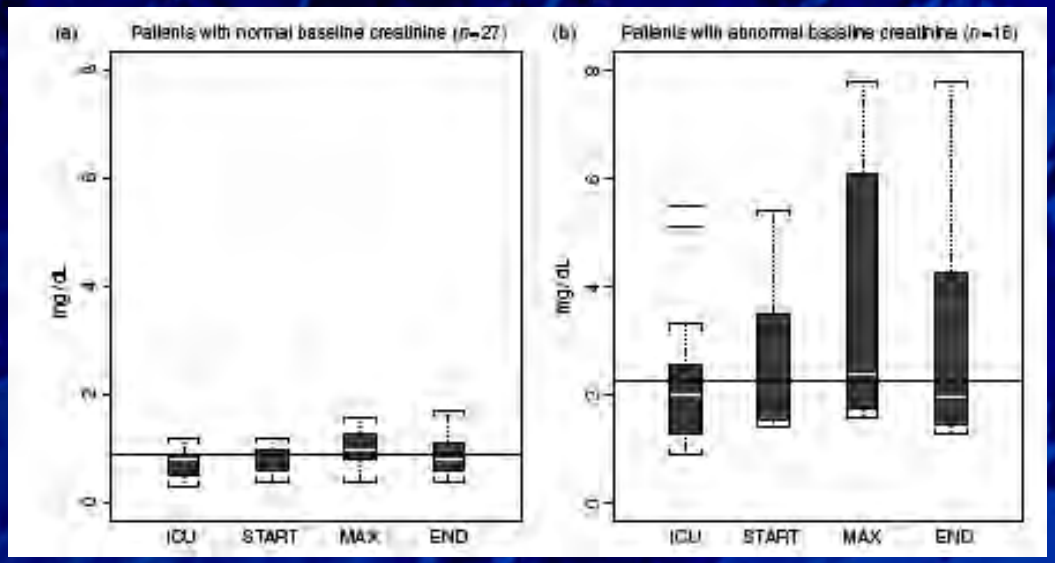
10.1046/j.1469-0691.2004.01043.x

**Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic**

*A. S. Michalopoulos[1], S. Tsiodras[2], K. Rellos[1], S. Mentzelopoulos[1] and M. E. Falagas[2,3,4]*

[1]Intensive Care Unit and [2]Department of Medicine, Henry Dunant Hospital, [3]Alfa HealthCare, Athens, Greece; and [4]Tufts University School of Medicine, Boston, MA, USA

- **Étude rétrospective**
- **43 patients en réanimation**
- **Bactéries multi-résistantes (*P aeruginosa-A baumanii*)**




- Réponse clinique: 74,4%
- Détérioration rénale 18,6%
- Mortalité 27,9%

La colistine est une option thérapeutique

Clin Microb Infect 2005

- Cohorte rétrospective
- 50 patients, Apache II: 16,1
- Dose journalière moyenne: 4,5 MU pdt 21,3j
- Localisation: Pneumonie (33%), bactériémie (27,8%), urines (11%), abdominal (11%)
- Pathogène: *A baumanii* (51,9%), *P aeruginosa* (42,6%), *K pneumoniae* (3,7%)
- Résultats
  - Réponse clinique: 66,7%
  - Néphrotoxicité: 8%

Kasiakou et al, AAC 2005

ELSEVIER

International Journal of Antimicrobial Agents 28 (2006) 366–369

International Journal of Antimicrobial Agents

Short communication

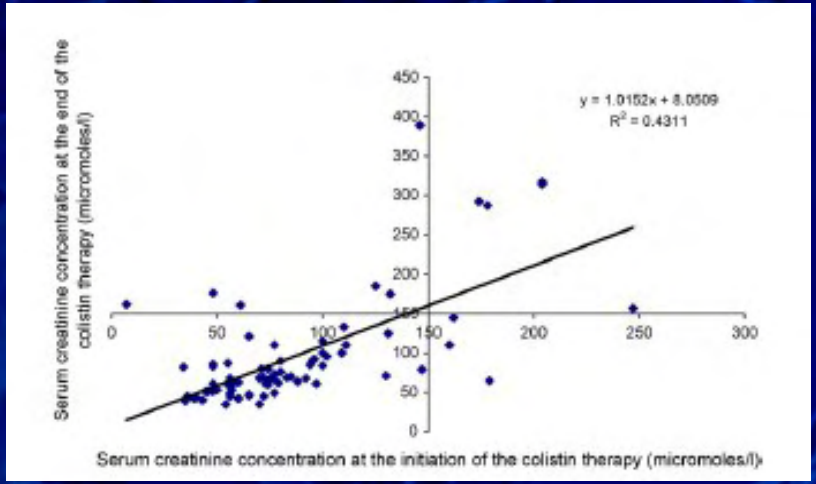
# Colistin as a salvage therapy for nosocomial infections caused by multidrug-resistant bacteria in the ICU

Hatem Kallel[a,*], Mabrouk Bahloul[a], Leila Hergafi[a], Malek Akrout[a], Wajdi Ketata[a], Hedi Chelly[a], Chokri Ben Hamida[a], Noureddine Rekik[a], Adnane Hammami[b], Mounir Bouaziz[a]

[a] Service de Réanimation Médicale, CHU Habib Bourguiba, route el Ain Km 1, 3029 Sfax, Tunisia
[b] Laboratoire de Microbiologie, CHU Habib Bourguiba, route el Ain Km 1, 3029 Sfax, Tunisia

Received 11 May 2006; accepted 8 June 2006

- Étude prospective
- MDR *P aeruginosa-A baumanii*
- 78 infections
- Pulmonaire 78,2%
- Dose moy: 5.5+/-1,1 MU/j
- Durée moy: 9,3+/-3,8j




- Evolution clinique favorable: 76,9%
- Altération de la fonction rénale: 7 cas

Int J AA 2006

# Toto-résistance

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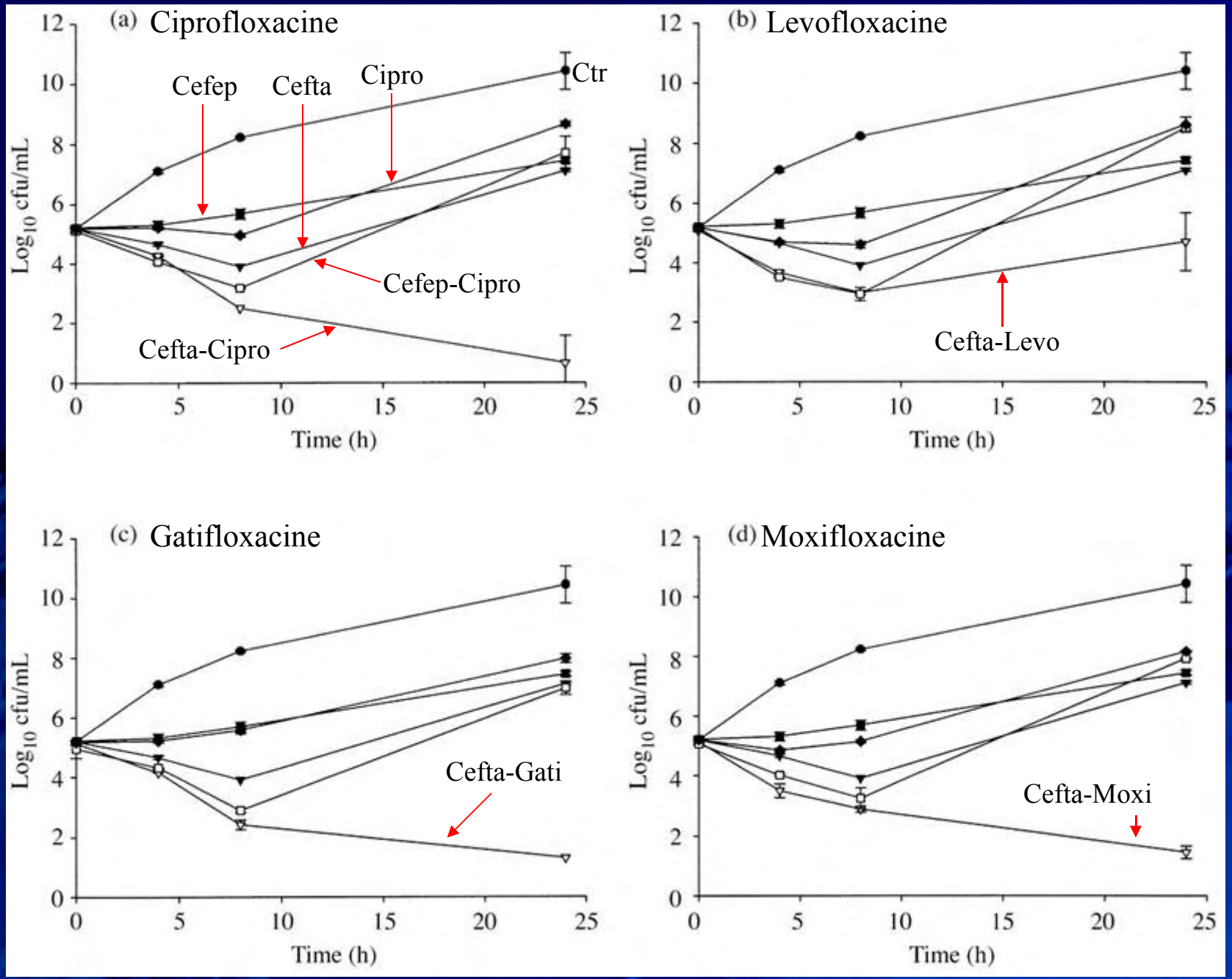


Fish et al, JAC 2002

# Souches multi-résistantes

- 7 isolats résistants à pip/merop/cefta/cefoperazone-sulb/aztreonam/amk/cipro
- Bithérapie :
  - AZT+AMK : inhib 5/7
- Trithérapie
  - Cefta+Pipe+Amk : inhib 7/7
  - Cefta+Azt+Amk : inhib 7/7

(Oie et al, JAC 2003)

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ELSEVIER

Antimicrobial susceptibility studies

# Postantibiotic effect of antimicrobial combinations on multidrug-resistant *Pseudomonas aeruginosa*

Evangelos J. Giamarellos-Bourboulis*, Nikolaos Kentepozidis, Anastasia Antonopoulou, Diamantis Plachouras, Thomas Tsaganos, Helen Giamarellou

PAE (mean ± SE) of ceftazidime, imipenem, or ciprofloxacin and of their interaction with amikacin on multidrug-resistant isolates of *P. aeruginosa* subjected to the synergistic effect of the tested interactions

| Antimicrobial or interaction | PAE (h) |
|---|---|
| Ceftazidime (9) | 0.60 ± 0.27 |
| Amikacin (9) | 0.64 ± 0.33 |
| Ceftazidime + amikacin (9) | 3.10 ± 0.71[a,b] |
| Imipenem (6) | 1.50 ± 0.53 |
| Amikacin (6) | 0.64 ± 0.33 |
| Imipenem + amikacin (6) | 4.38 ± 0.83[c,d] |
| Ciprofloxacin (5) | 1.00 ± 1.00 |
| Amikacin (5) | 0.64 ± 0.33 |
| Ciprofloxacin + amikacin (5) | 3.33 ± 2.83[e,f] |

ELSEVIER

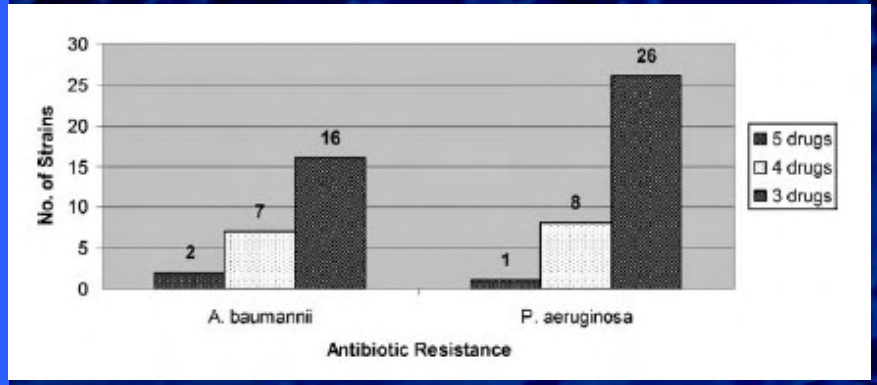
International Journal of Antimicrobial Agents 27 (2006) 224–228

International Journal of Antimicrobial Agents

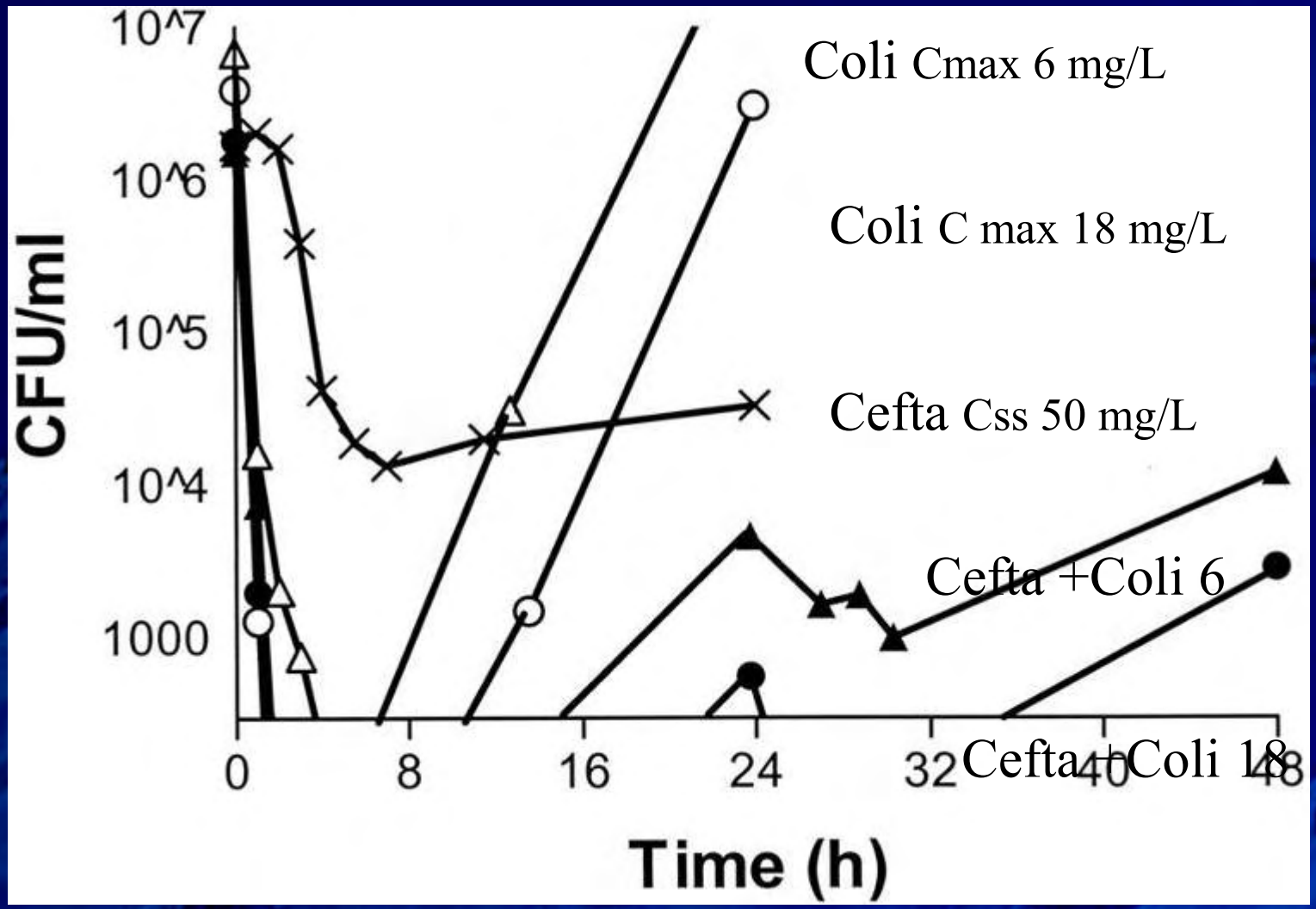
www.ischemo.org

# In vitro activities of non-traditional antimicrobials alone or in combination against multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolated from intensive care units

Funda Timurkaynak[a,*], Fusun Can[b], Özlem Kurt Azap[a], Müge Demirbilek[b], Hande Arslan[a], Sedef Özbalıkçı Karaman[a]




| Strain | Antibiotic combination of colistin + | FICI | Interpretation |
|---|---|---|---|
| 114 | Rifampicin | 0.5 | Synergistic |
| | Meropenem | 1.5 | Indifferent |
| | Doxycycline | 0.62 | Partially synergistic |
| | Azithromycin | 0.62 | Partially synergistic |
| 144 | Rifampicin | 1 | Additive |
| | Meropenem | 1.25 | Indifferent |
| | Doxycycline | 0.75 | Partially synergistic |
| | Azithromycin | 0.75 | Partially synergistic |
| 108 | Rifampicin | 0.31 | Synergistic |
| | Meropenem | 1 | Additive |
| | Doxycycline | 1 | Additive |
| | Azithromycin | 2 | Indifferent |
| 205 | Rifampicin | 0.51 | Partially synergistic |
| | Meropenem | 1 | Additive |
| | Doxycycline | 0.75 | Partially synergistic |
| | Azithromycin | N.D. | N.D. |
| 166 | Rifampicin | 0.62 | Partially synergistic |
| | Meropenem | 1.5 | Indifferent |
| | Doxycycline | 0.51 | Partially synergistic |
| | Azithromycin | 1 | Additive |




Gunderson et al, AAC 2003

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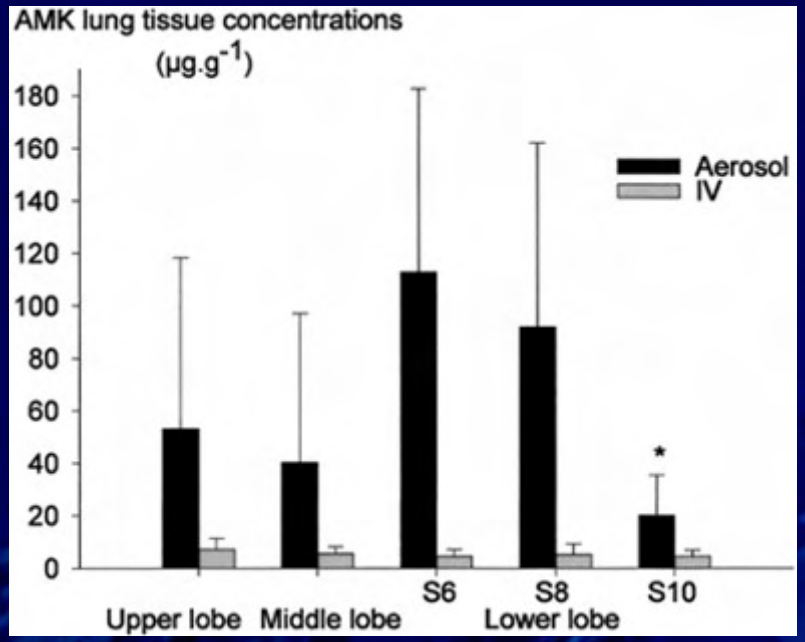


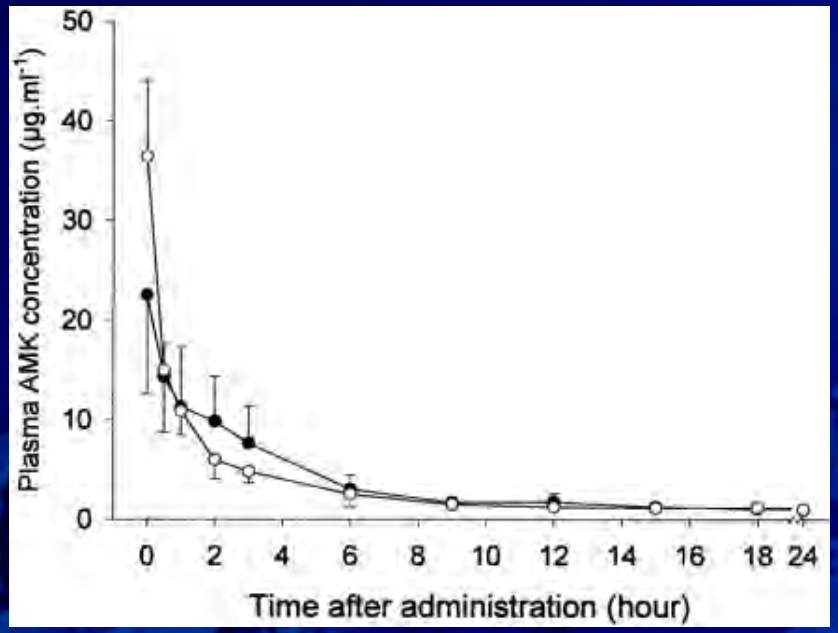


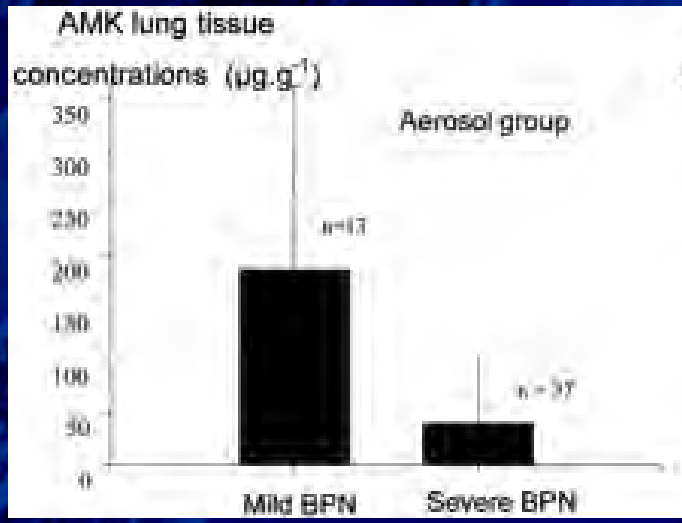


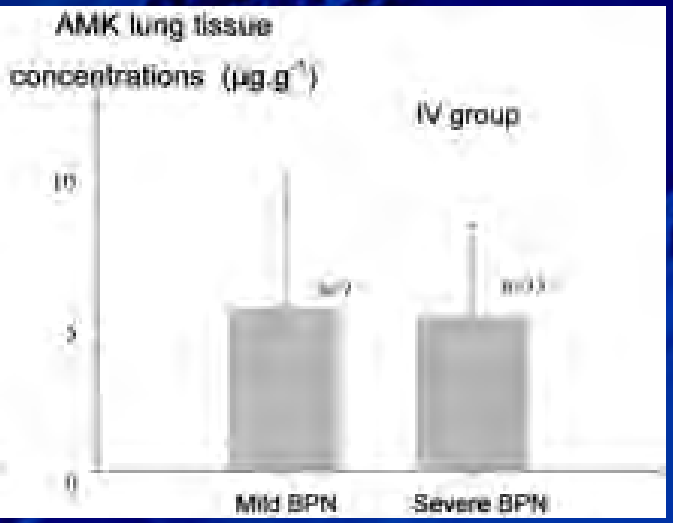


(Goldstein et al, AJRCCM 2002)

Nebulized Colistin in the Treatment of Pneumonia Due to Multidrug-Resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

**Andrea L. H. Kwa,[1] ChinSiew Loh,[1] Jenny G. H. Low,[2] Asok Kurup,[2] and Vincent H. Tam[3]**

[1]Department of Pharmacy and [2]Department of Internal Medicine, Division of Infectious Diseases, Singapore General Hospital, Singapore; and [3]University of Houston College of Pharmacy, Houston, Texas

- **21 patients avec un *Pseudomonas* MDR**
- **Nébulisation par polymyxin E**
- **Réponse clinique 57,1%**
- **Réponse microbiologique 85,7%**

CID 2005

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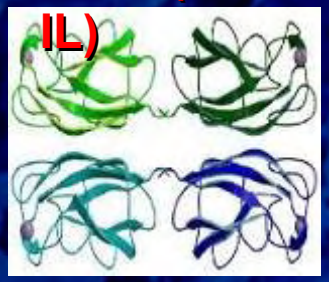
# Les lectines de *P. aeruginosa*

LecA (PA-IL)



(Cioci et al., 2003)

**D-galactose**

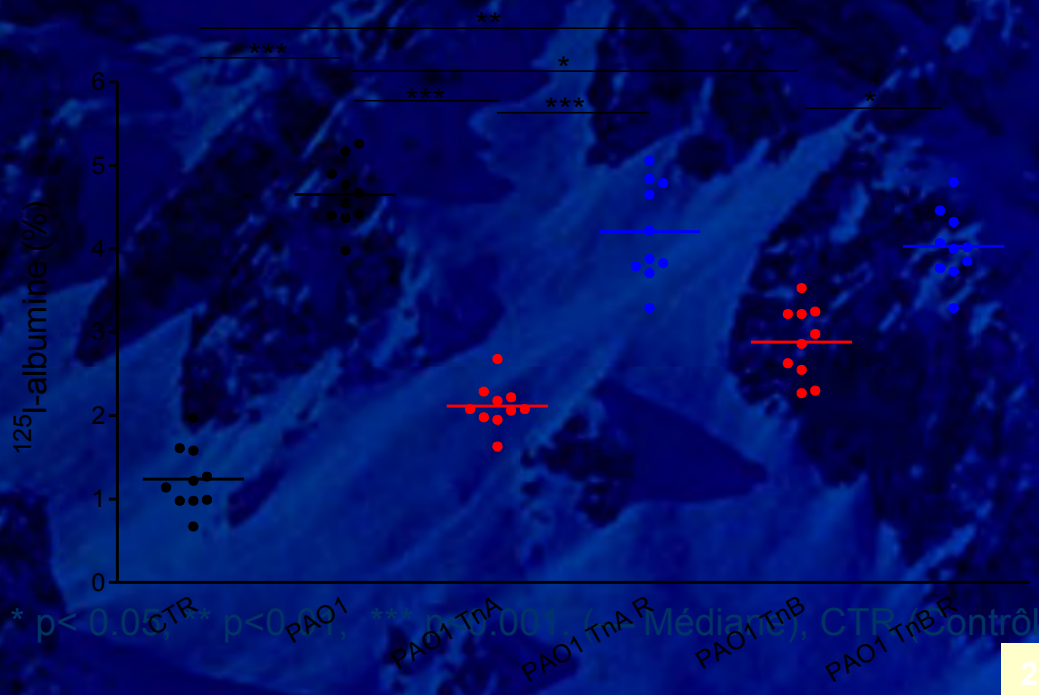
LecB (PA-IIL)

(Loris et al., 2003)

**L-fucose**

# Perméabilité de la barrière alvéolo-capillaire

**16H après infection**




n = 10/groupe. * p< 0.05; ** p<0.01; *** p<0.001 (— Médiane); CTR (Contrôle)

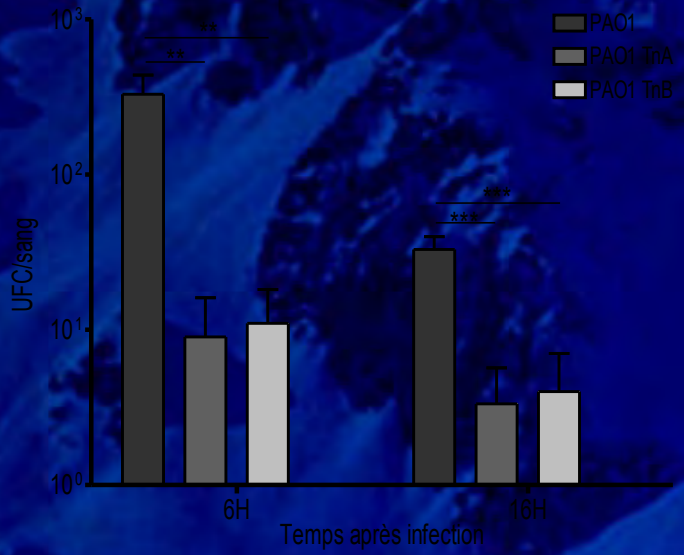
2b

Chemani et al, Soumis

# Bactériémie

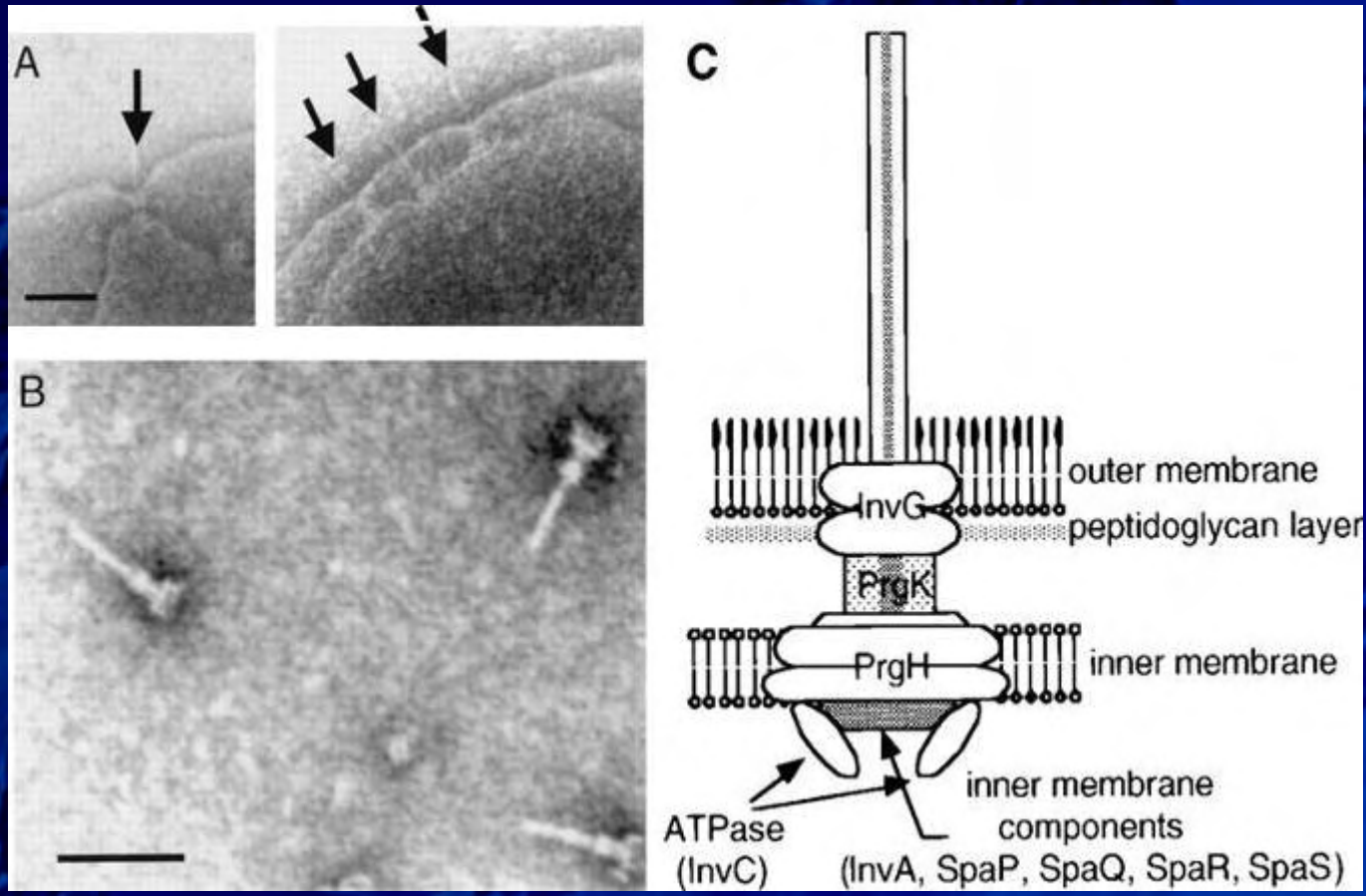
**Hémocultures qualitatives**

| Souches | 6H | 16H |
|---|---|---|
| PAO1 | 9/10 | 10/10 |
| PAO1 TnA | 2/10 | 2/10 |
| PAO1 TnB | 3/10 | 2/10 |



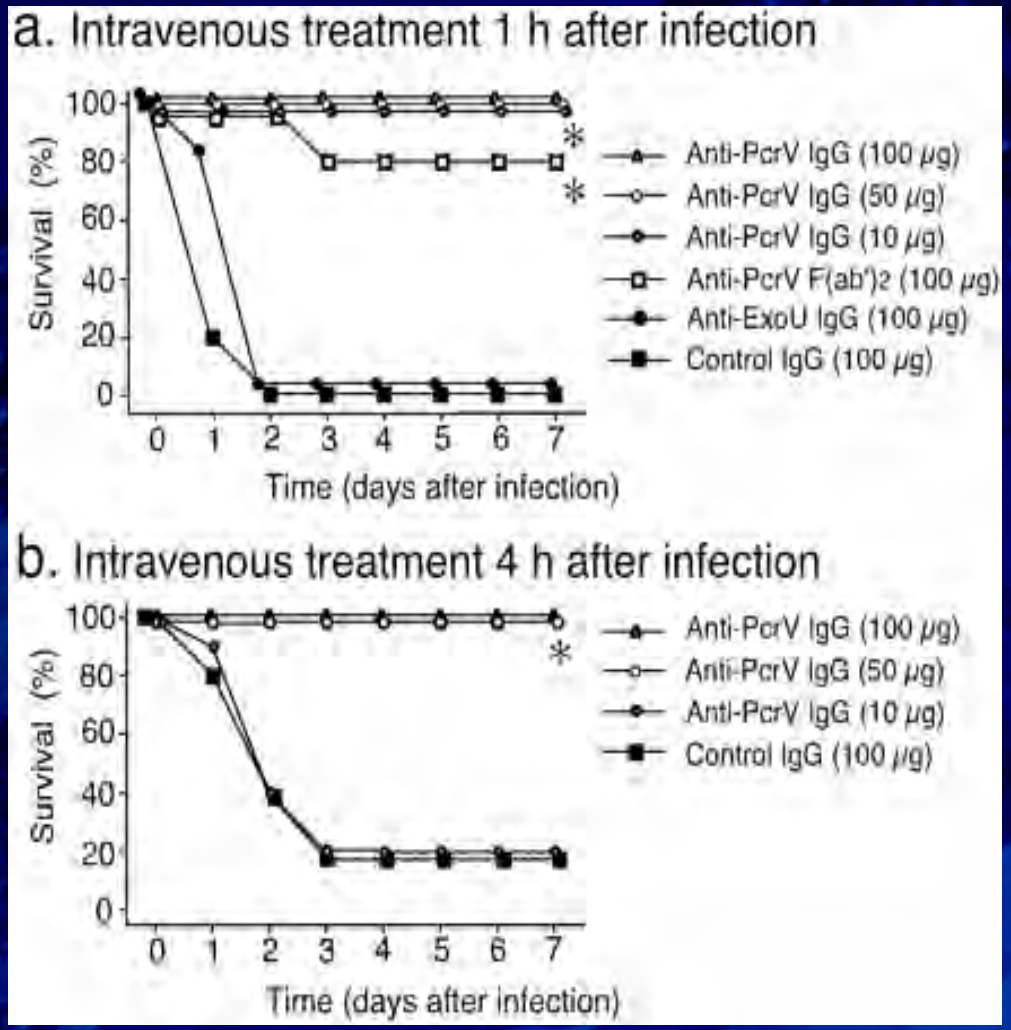

Chemani et al, Soumis

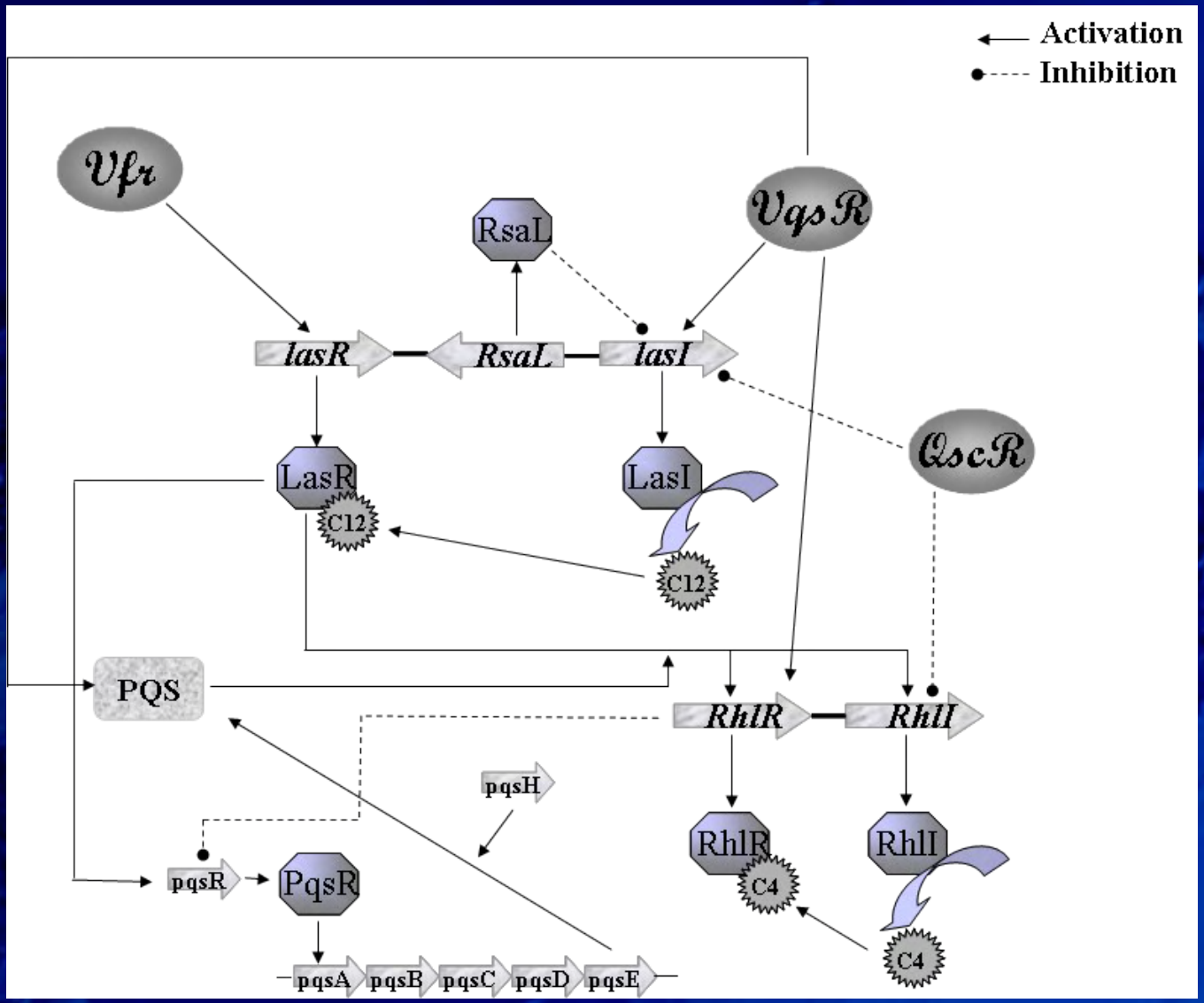
# TTSS: a needle




Kubori *et al.* Science 1998,**280**,602

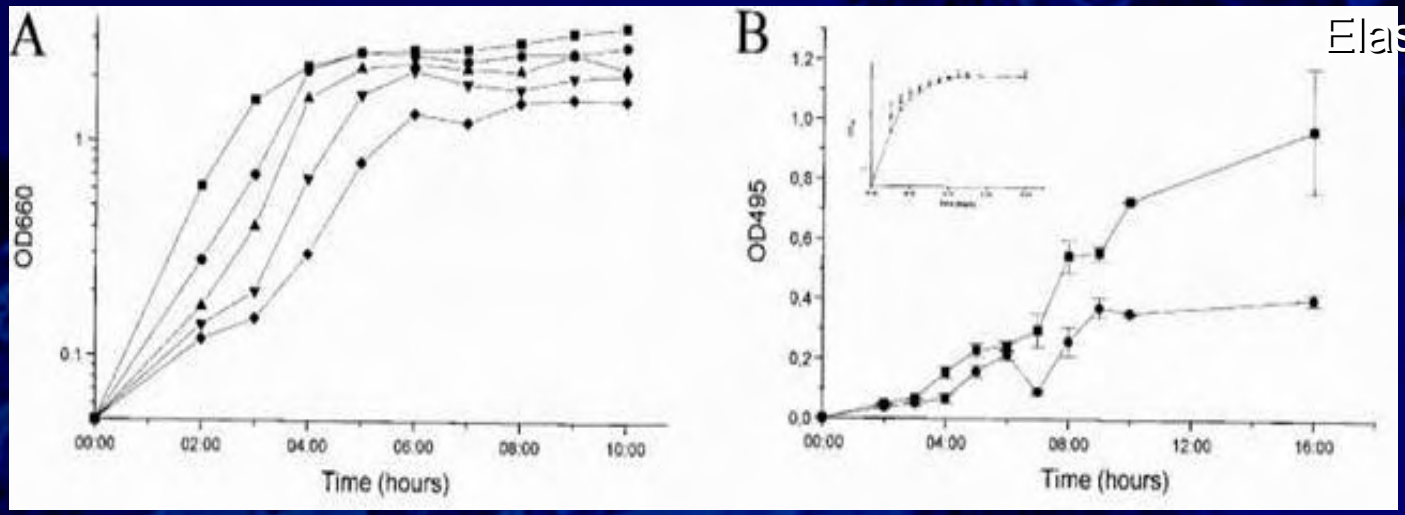
Shime et al, J Immunol 2001





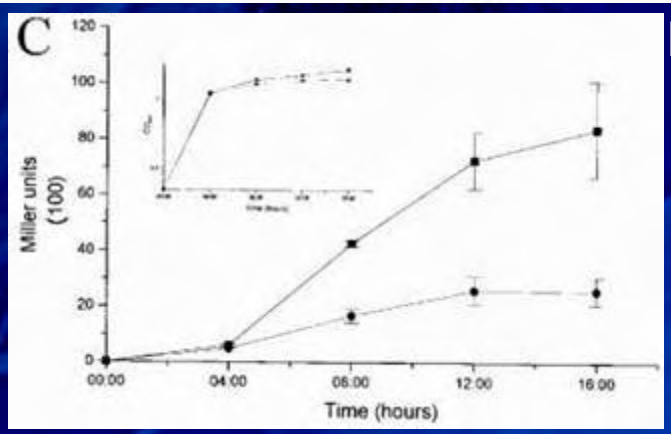

Le Berre et al, MMI 2006

# Inhibition du QS par les macrolides




Elastase

Ni bactéricide
Ni bactériostatique



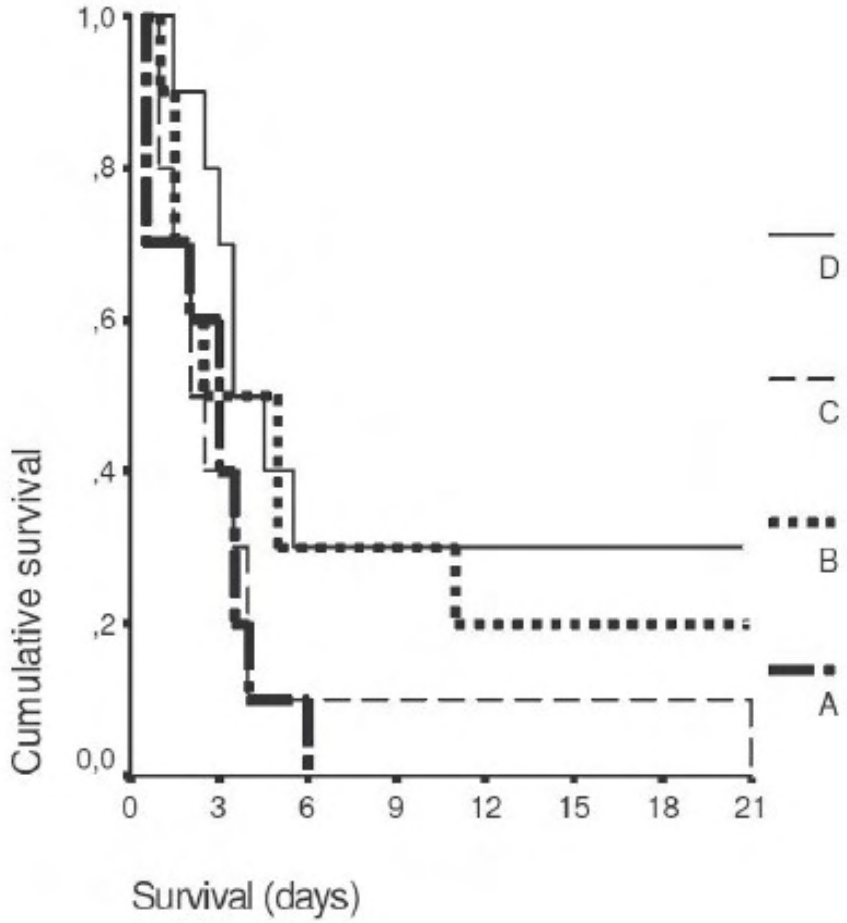

Rhamnolipide

Inhibition du QS

Tateda K et al. AAC 2001

**Clarithromycin is an effective immunomodulator when administered late in experimental pyelonephritis by multidrug-resistant *Pseudomonas aeruginosa***

Evangelos J Giamarellos-Bourboulis*, Anastasia Antonopoulou, Maria Raftogiannis, Pantelis Koutoukas, Thomas Tsaganos, Vassiliki Tziortzioti, Charalambos Panagou, Theodoros Adamis and Helen Giamarellou




Amk + clarithro

Amk

Clarithro

Ctr

BMC Inf Dis 2006