Treatment of multi-drug resistant *P. aeruginosa*

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Case report (1)

- 77-year old man
- 2/1/06 Coronarography
- Inguinal hematoma → surgical drainage

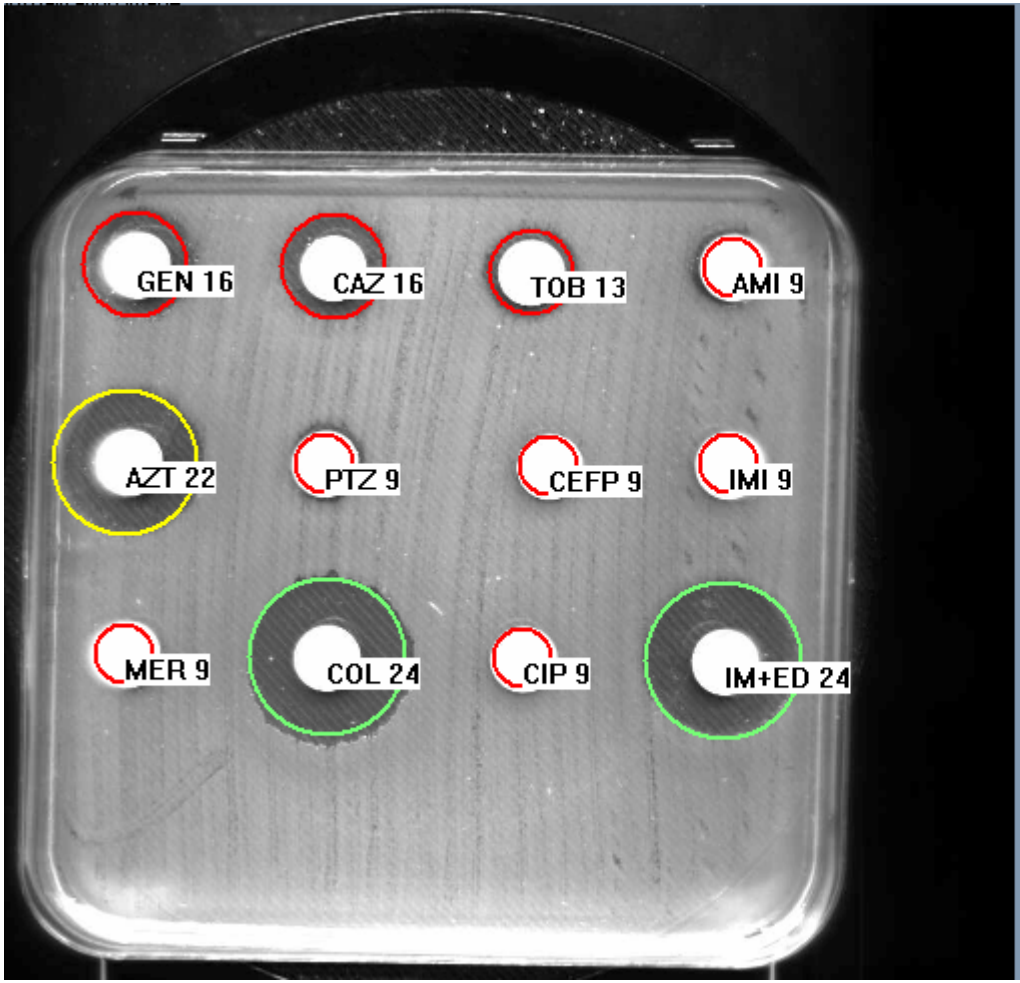
- Infection of the surgical wound by
  - MDR *P. aeruginosa* (sensitive to polymyxin and fosfomycin, resistant to all the other drugs)
  - *K. pneumoniae* (ampi-R)

- Local treatment, amoxicillin-clavulanic acid
- Discharge on 1/3/06 with local treatment

Case report (2)

- Admission at Erasme Hospital on 10/3/06
- 40.5°C, inguinal cellulitis +++
- CT scan: diffuse infiltration, hematoma
- Surgery: drainage of infected hematoma.
- In the following hours: development of septic shock

- Intra-operative swab:
  - Gram stain: gram + cocci, gram-negative bacilli (*Pseudomonas?*)
  - Culture:
    - MRSA
    - *P. aeruginosa* MBL-producteur (VIM-2)
      - aztreonam-I (CMI 32), pip-tazo R, ceftazidim-R, cefepime-R, ciprofloxacine-R, aminoside-R, fosfomycine-R
      - Colimycine S



ANTIBIOTIQUE	C.M.I	Resultat	DIAMETRE
AMI	> 64	Résistant	9
TOB	> 16	Résistant	13
GEN	> 8	Résistant	16
CIP	> 32	Résistant	9
AZT	> 8	Intermédiaire	22
CAZ	32	Résistant	16
CEFP	> 256	Résistant	9
MER	>= 0	Résistant	9
IMI	> 128	Résistant	9
PTZ	>= 12	Résistant	9
COL	1	Sensible	24
IM+ED	<= 0	Sensible	24

+ fosfomycin disk: R

E-test:
Aztreonam 32 µg/ml
Colimycine 2 µg/ml

Antimicrobial treatment ??

- **Antimicrobial treatment:**
  - Vancomycin, metronidazole
  - + aztreonam (2g loading dose then 6g CI),
    gentamicin (7mg/kg OD) then fosfomycin (8 g loading dose then 24g/d) then stop
    colistin (3 10^6 IU x 3 IV)
- **Evolution:**
  - D5: 2nd surgical procedure (drainage of deeper infected hematoma)
  - Culture: MRSA
- **Outcome:** favorable

MBL-producing *P. aeruginosa*

MBL-producing *P. aeruginosa*

- MBL enzymes have the property of hydrolyzing imipenem or meropenem and other broad-spectrum β-lactams but not the monobactams.

- Many epidemiological studies
- Study on mechanism of resistance
- Few clinical studies

- No study focused on the clinical management of these infections and no treatment recommendations are available

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dki280
Advance Access publication 8 August 2005

Bacterial prostatitis due to *Pseudomonas aeruginosa* harbouring the *bla*$_{VIM-2}$ metallo-β-lactamase gene from Saudi Arabia

François Guerin[1], Corneliu Henegar[2], Gabriella Spiridon[2], Odile Launay[2], Dominique Salmon-Ceron[2] and Claire Poyart[1]*

- HIV-positive 46-year-old man coming from Saudi Arabia
- Abdominal mass due to *Cryptococcus neoformans*. Surgical resection
- 10 days after the procedure, prostatitis due to VIM-2 producing *P. aeruginosa*
  - R to most antipseudomonal agents, quinolones and aminoglycosides
  - Moderately susceptible to aztreonam (MIC 8 µg/ml) and sensitive to colistin and fosfomycin
- In vitro synergy between aztreonam and fosfomycin
- Cure with aztreonam (6g/d) and fosfomycin (12g/d) given during 21 days

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2006, p. 388–390 Vol. 50, No. 1
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.1.388–390.2006

Bloodstream Infections with Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa*: Epidemiology, Microbiology, and Clinical Outcomes

Alexandre R. Marra,[1]* Carlos Alberto P. Pereira,[1] Ana Cristina Gales,[1,2] Liana C. Menezes,[2] Ruy Guilherme R. Cal,[3] José Marconi A. de Souza,[3] Michael B. Edmond,[4] Cynthia Faro,[2] and Sérgio B. Wey[1]

- 7 pts with bloodstream infections
- Site of infection
  - Gastrointestinal: 3
  - Catheter 2
  - Respiratory 2
- Treatment: monotherapy with colistin (dose?)
- Outcome: 6/7 death (1 not related to infection)

Experience at Erasme Hospital

- Erasme University Hospital,
- Study period: January 2003 to November 2005
- All patients with infection due to MBL-producing *P. aeruginosa*

- Only *P. aeruginosa* with positive PCR for detection of *bla* VIM and *bla* IMP genes.

Patients

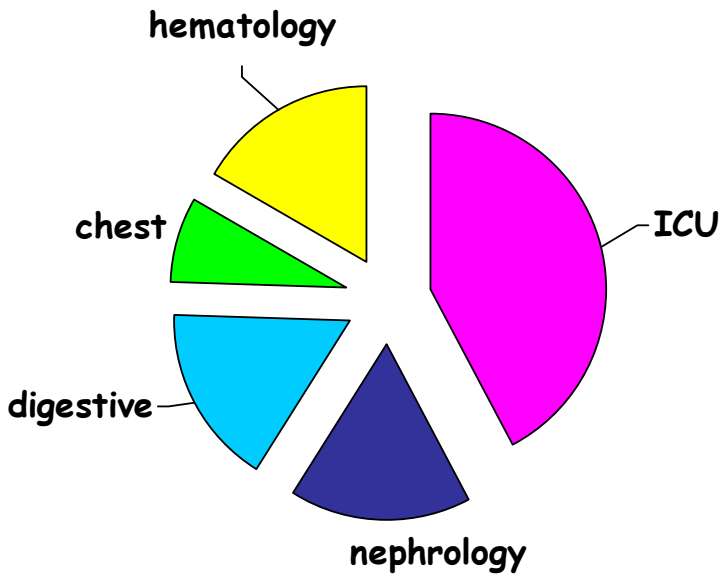
- 15 episodes in 14 patients

- 11 M 3F
- median age 60y (30-81y)

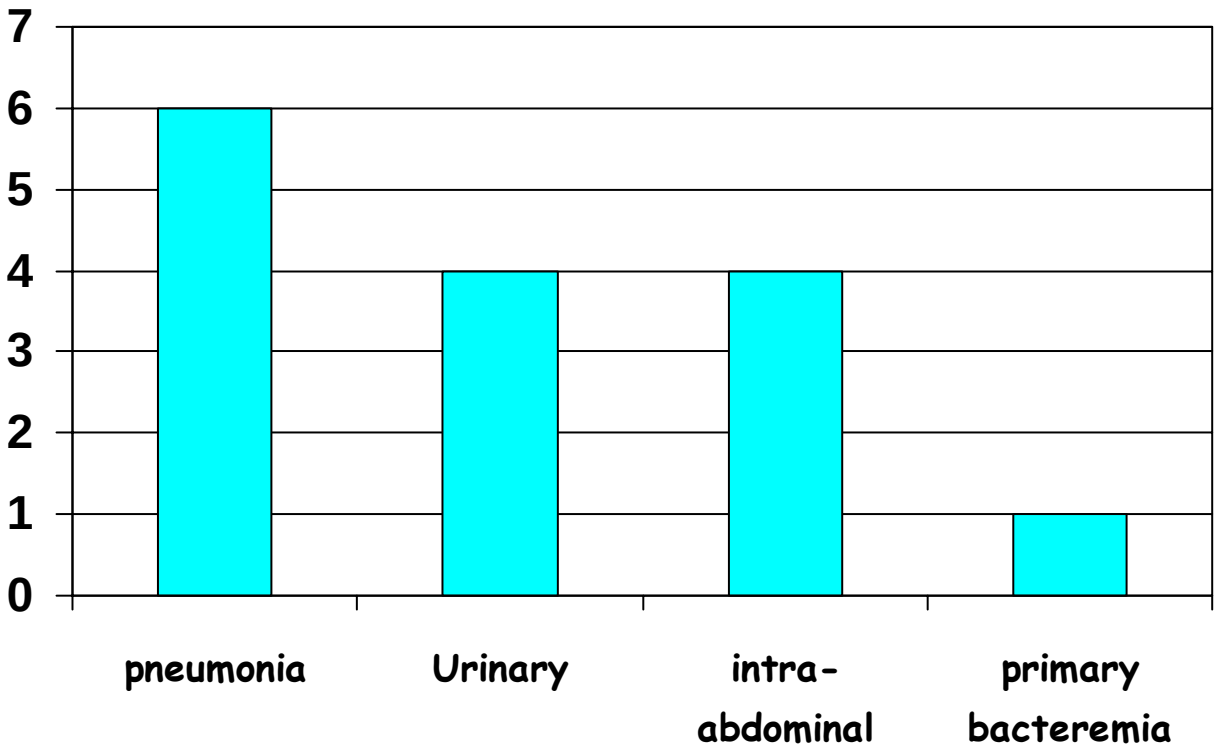
- Chronic underlying conditions:
  13/14 pts

Ischemic cardiomyopathy	7
Corticosteroids	7
Chronic pulmonary obstructive diseases	4
Solid or hematological tumor	4
Liver cirrhosis	3
Solid organ transplantation	2
Diabetes mellitus	2
Neutropenia	2

Departments when infection developed



Types of infection



Positive blood cultures: 10/15 episodes (66%)

2 ventilator-associated pneumonia

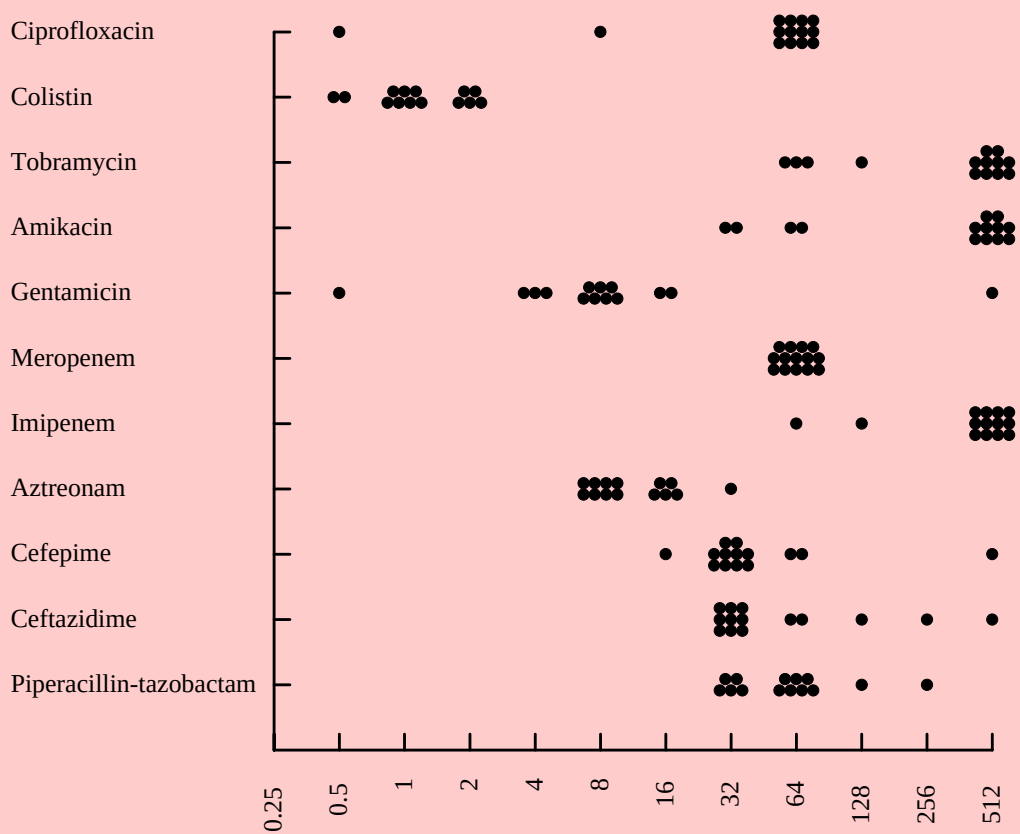
Infection of renal graft: 3
Acute pyelonephritis: 1

Intra-abdominal abscess: 3
CAPD peritonitis: 1

Clinical manifestations

- Non-urinary tract infections:
  - Severe sepsis or septic shock: 8/11pts
  - Admission to ICU
    - 6 pts developed infection when hospitalized in ICU
    - 3 pts admitted into ICU for treatment of MBL P. aeruginosa infection
- Urinary tract infections:
  - Severe sepsis or septic shock: 0/4
  - Signs of sepsis: 4/4
  - No pt in USI

In vitro sensitivity



Antimicrobial treatment

- Empirical treatment:
  - 5 episodes: known colonization by MBL-producing *P. aeruginosa*

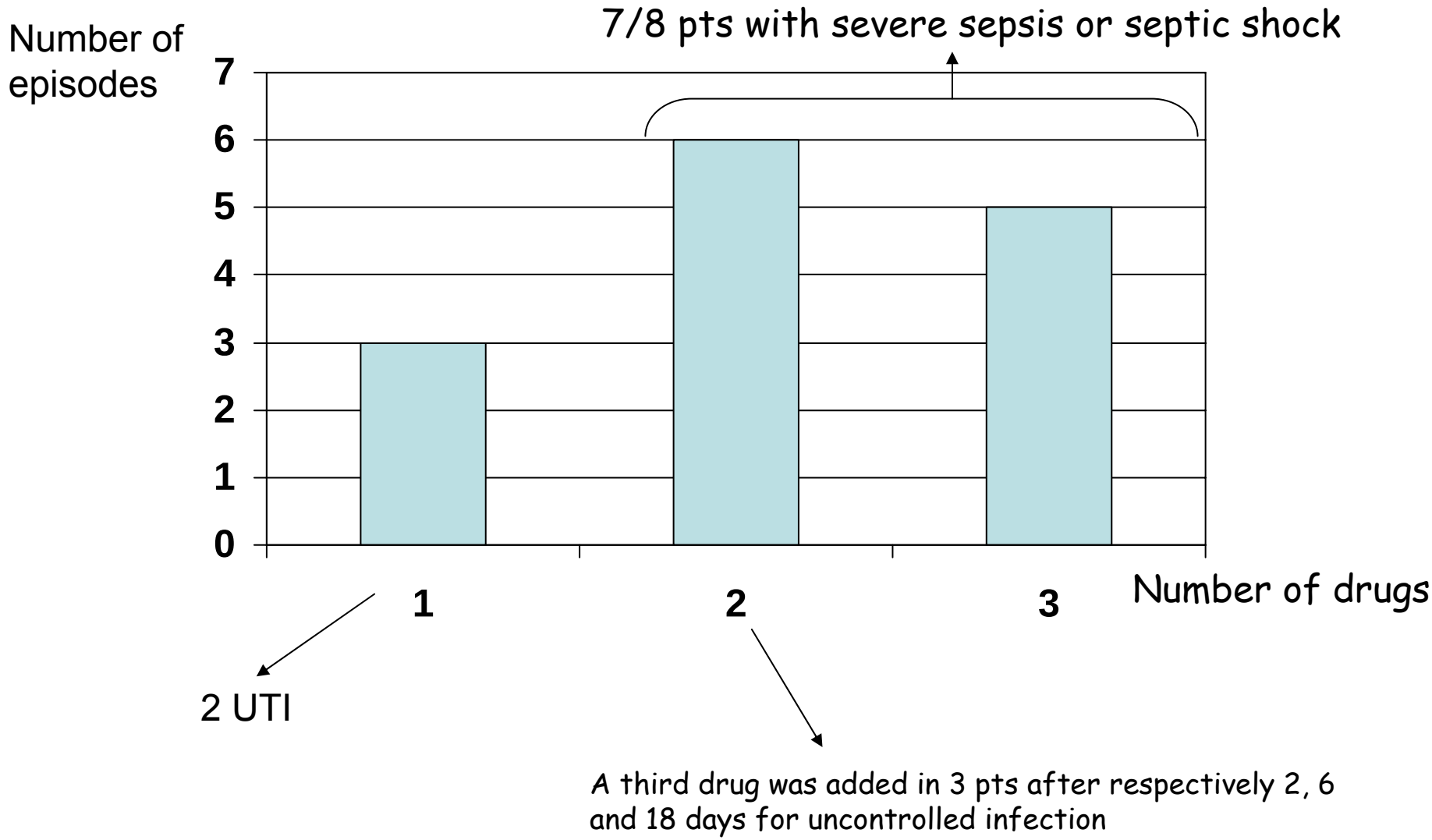
    → Appropriate empirical treatment: **5/5**
  - 10 episodes: no previous detection of MBL-producing *P. aeruginosa*

    → Appropriate empirical treatment : **0/10**

    (meropenem 5; cefepime 3; quinolone 2)

- After identification
  - 1 death before identification
  - Median delay: 3 days (1-6d)

Appropriate antimicrobial treatment

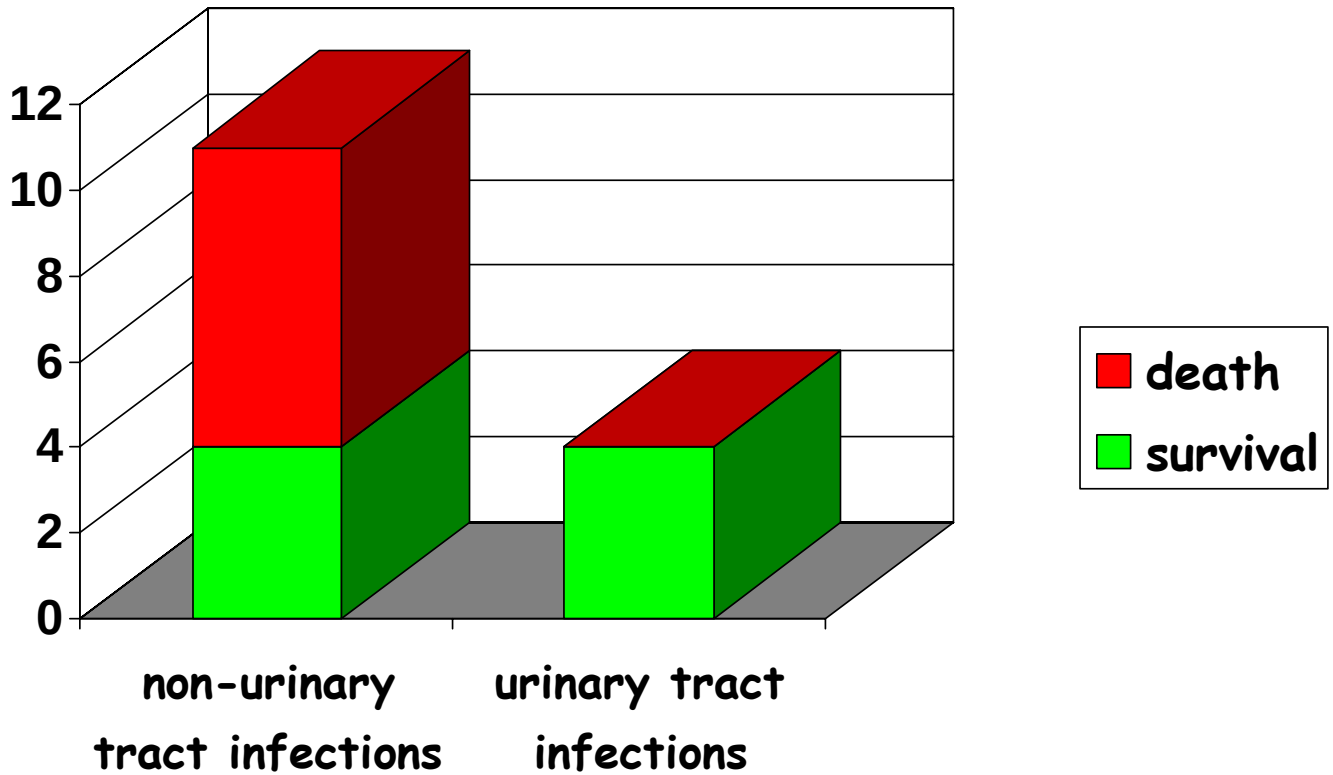


Source control

- 4 patients:
  - 1 pt with pancreatic abscesses: endoscopic (1) and surgical treatment (2)
  - 2 kidney transplant recipients: removal of kidney graft
  - 1 liver transplant recipient: re-transplantation for infected graft

Clinical evaluation

Median delay of death associated with infection
4 days



2/7 deaths unrelated to infection

1 relapse
2 months later

Non urinary-tract infections

	Site of infection	Blood cultures	Severity	Delay of appropriate treatment	Traitement of documented infection	Source control	Death associated with infection
2003	abdominal	+	septic shock	4	PIP/TZ + COLI	Laparotomy (2), endoscopy (1)	+
2003	abdominal	+	sepsis	2	PIP/TZ + AMIKA then COLI	Removal of peritoneal catheter and of kidney graft	-
2004	pulmonary	+	septic shock	1	PIP/TZ + AZT	no	+
2004	pulmonary	+	severe sepsis	0	PIP/TZ + AZT + COLI	no	+
2004	pulmonary	-	Severe sepsis	0	AZT + CIPRO + adjunction of COLI after 48h	no	-
2004	abdominal	+	septic shock	none	-	Laparotomy, second liver transplantation	+
2004	pulmonary	-	sepsis	6	COLI	no	+
2005	pulmonary	+	sepsis	1	PIP/TZ + AZT + COLI	no	-
2005	pulmonary	+	septic shock	0	PIP/TZ +COLI +AMIK; adjunction of AZT (CI) after 6 days, shift AMIK to GENTA	no	-
2005	abdominal	+	Septic shock	3	COLI +GENTA +AZT (CI)	no	-
2005	Primary bacteremia	+	Severe sepsis	4	COLI+GENTA+AZT	no	-

5/7

0/4

Side effects of treatment

- Transient decrease in renal function
- 1 polynevritis

Conclusions (1)

- Initial presentation:
  - severe with severe sepsis and septic shock (72%) in non urinary tract infection
- Empirical treatment inadequate in 100% if colonization by MBL *P. aeruginosa* is not detected
- Aztreonam, gentamicine, piperacilline-tazobactam: the most in vitro effective drugs but with high MIC's
- Colistin effective on all strains.

Conclusions (2)

- Improvement of survival
  - Improvement of adequate empirical treatment: role of surveillance cultures?
  - Antimicrobial treatment:
    - At least 3 in vitro effective drug
    - High doses:
      - Continuous infusion of aztreonam
      - Gentamicin once a day
      - High doses of colistin (9 10^6 IU/d)
- Larger studies are needed to confirm these preliminary data

Therapeutic options

Colistin

Continuous infusion of β-lactames

Fosfomycin

(Rifampicin)

BUT absence of clinical studies evaluating such therapeutic options

Colistin (Colomycin®)

- Cationic polypeptide antibiotic of the polymyxin family
- 5 polymyxin: A-E (only B and E in clinical practice)

- Discovered in 1949, synthesized by *Bacillus colistinus*.
- Used therapeutically during the 1950s. Gradually abandoned in the early 1980s because of the reported high incidence of nephrotoxicity

- IV use of colistin: mainly restricted for the treatment of lung infections due to MDR gram-negative bacilli in cystic fibrosis patients

Falagas CID 2005; 40: 1333-41;
Li Int J Antimicrob Agents 2005; 25: 11-25

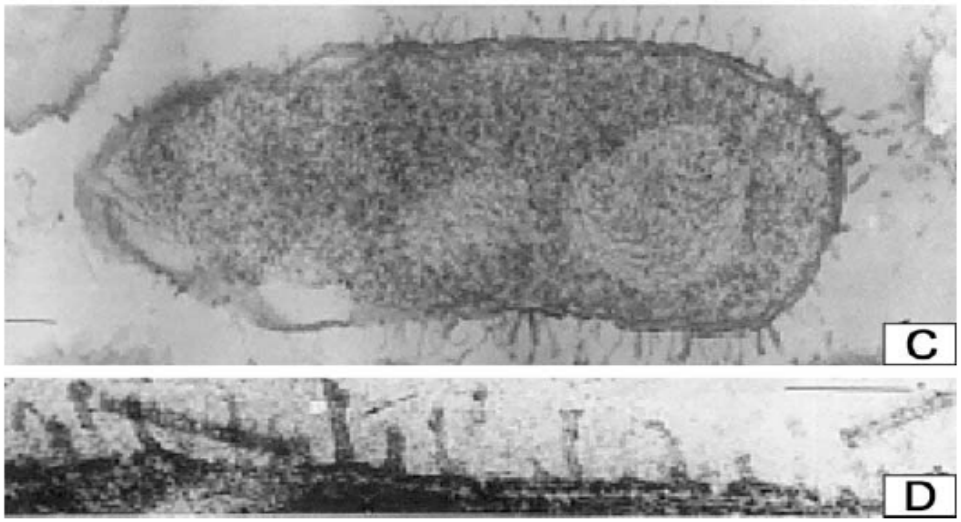
Different preparations

2 forms of Polymyxin E (colistin) commercially available:

- **colistine sulfate**:
  - given orally (bowel decontamination) or
  - topically (bacterial skin infections)

- **colistimethate sodium**: IV, aerosol:
  - less toxic and less potent than colistin sulfate
  - hydrolyzes and forms a complex mixture of partially sulfomethylated derivatives and colistin

Mechanism of action



- Target of activity: **bacterial cell membrane**

- Binds with the LPS molecules in the outer membrane of the gram-negative bacteria
  → displaces Mg and Ca, which normally stabilize the LPS molecules
  → local disturbance of the outer membrane
  → increase in the permeability of the cell envelope, leakage of cell contents
  → cell death

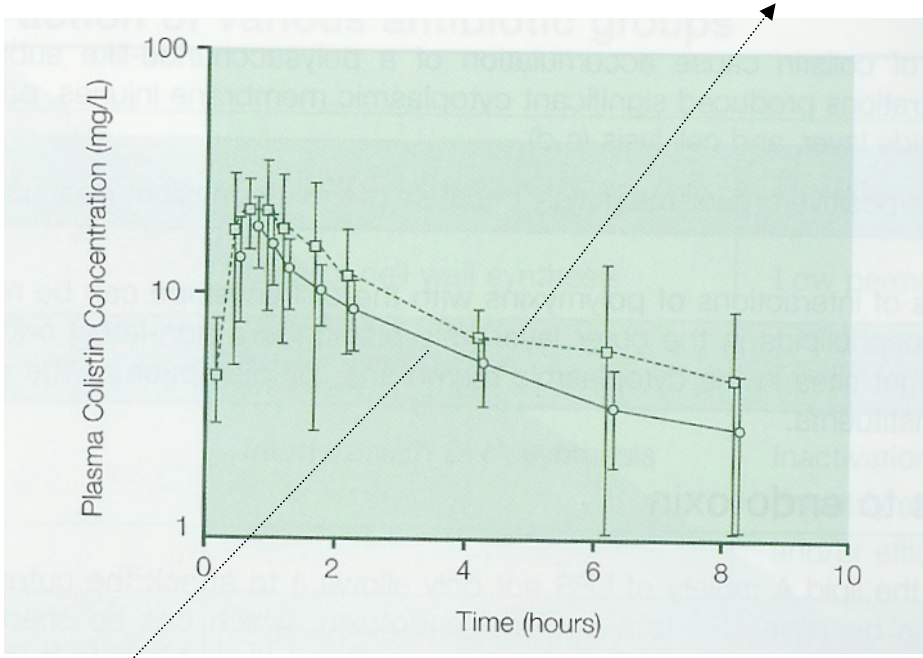
- The killing process is not dependent upon bacterial metabolic activity → slow development of resistance

PK/PD properties

- Mean half-life
  - 2h for colistimethate sodium
  - 6h for colistin sulfate
- Vd: 0. 34 ± 0.09 l/kg
- Renal excretion (glomerular filtration)
- Concentration-dependent activity
- Poorly distributed to the pleural cavity, lung parenchyma, bones, CSF (? 25% of the serum concentration)

Jimenez-Mejias Eur J Clin Microbiol Infect Dis 2002; 21: 212-14

Steady state



1st dose 0.9 10^6 IV

Reed J Clin Pharmacol 2001; 41, 645-654

Doses

Usual doses: 1-2 10^6 IU (or 80-160mg) x 3 IV/j

Recommended doses: 3 10^6 IU x 3 IV/j

Intrathecal administration: 3-20 mg/j (250.000 IU/d)

Spectrum of activity

- Excellent and rapid bacterial activity against most gram-negative bacilli
  except
  P. mallei, B. cepacia, Proteus sp, Providentia, Serratia, Brucella and some strains of S. maltophilia
- Not active against gram-positive and gram-negative cocci, gram-positive aerobic bacilli, all anaerobes, fungi and parasites

- Breakpoint: S if ≤ 4 mg/L, R if > 8 mg/L
- Few experimental and clinical studies showing synergistic activity of colistin with other antimicrobial agents:
  - Anti-pseudomonal β-lactams
  - Rifampin-colistin
- <u>Development of resistance</u>
  - Alteration in the cell-membrane lipid and cation structure
    - Low in *P. aeruginosa* (cystic fibrosis patients):
      - 81% of CF pts treated chronically with inhaled colistin are still susceptible to colistin (Li AAC 2001; 45, 781-785)
    - High in *A. baumannii* (up to 30% *Acinetobacter* in Greece)

Clinical use

Author	Micro-organisms	Types of infection/number of pts	Design of the study	Good clinical response	Toxicity
Levin CID 1999	*P. aeruginosa, A. baumannii*	60 pts, various types of infection 3-4 10^6 IU/d	Observational	58% (25% pneumonia)	Renal failure 32%
Garnacho-Montero CID 2003	*A. baumannii*	35 pts VAP colistin 3-4 10^6 IU/d imipenem 3g/d	Prospective, comparative groups Imipenem-colistin	57% in both groups	Renal failure Coli 5/21 and Imip 6/14 No neuromuscuar toxicity
Markou Critical care 2003	*P. aeruginosa, A. baumannii*	24 pts (ICU), various types of infection 3 10^6 IU x 3/d	Observational	73%	Renal failure 14.3%
Linden CID 2003	*P. aeruginosa*	23 ICU pts, pneumonia, IAI Dose? 3-4 10^6 IU/d	Observational	61%	Diffuse weakness: 1 pt
Kidd ESCMID 2004	*P. aeruginosa, A. baumannii*	51 pts, various types of infection 4-6 M IU/d	Retrospective	49%	Renal failure 23%
Kasiakou AAC 2005	*A. baumannii, P. aeruginosa*	Various types of infections, 4-6 10^6 IU/d	Retrospective	67%	Renal failure 8%

Toxicity in old series

- Nephrotoxicity: 20%
  - Acute tubular necrosis

- Neurotoxicity: 7%
  - Facial and peripheral paresthesia, dizziness, weakness, vertigo, visual disturbance, confusion, ataxia, neuromuscular blockade leading to respiratory failure and apnea

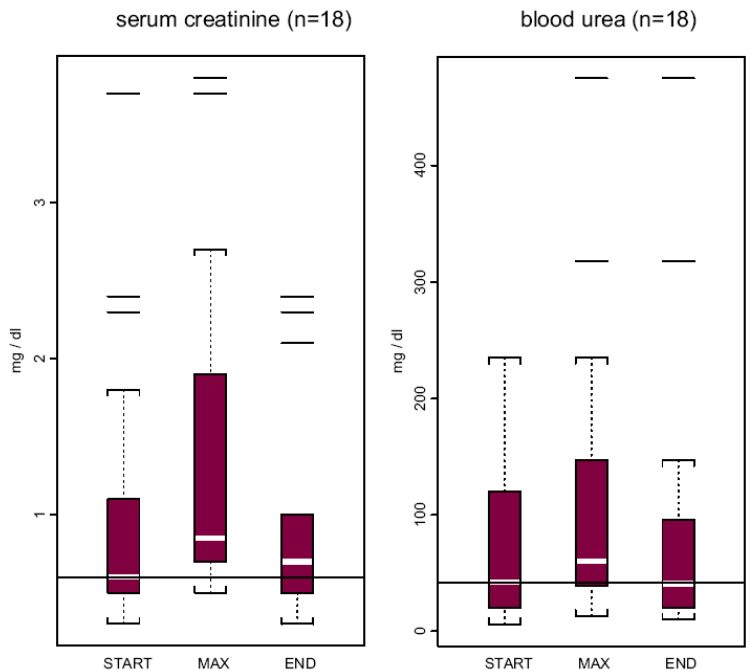
Both are dose-dependent and usually reversible early after discontinuation of the drug

- Allergic reactions: 2%

Toxicity in recent series

- Nephrotoxicity: less frequently reported
  - 2 recent studies with 9 10^6 IU/d: 18.6% et 14.3%
  - 1 study with ICU and non-ICU pts (4.5 10^6 for a mean duration of 21 days): 8%
  - Comparison Imipenem-cilastatine and colistin in VAP: more frequent if treated with imipenem-cilastatin
- Not highly nephrotoxic when given without other nephrotoxic drugs

Colistin: prolonged treatment



19 pts
4 weeks of colistin
4.4 ± 2.2 10^6 IU/d

Falagas Crit Care 2006; 10 R 27
Falagas BMC Infectious Dis 2005; 5, 1

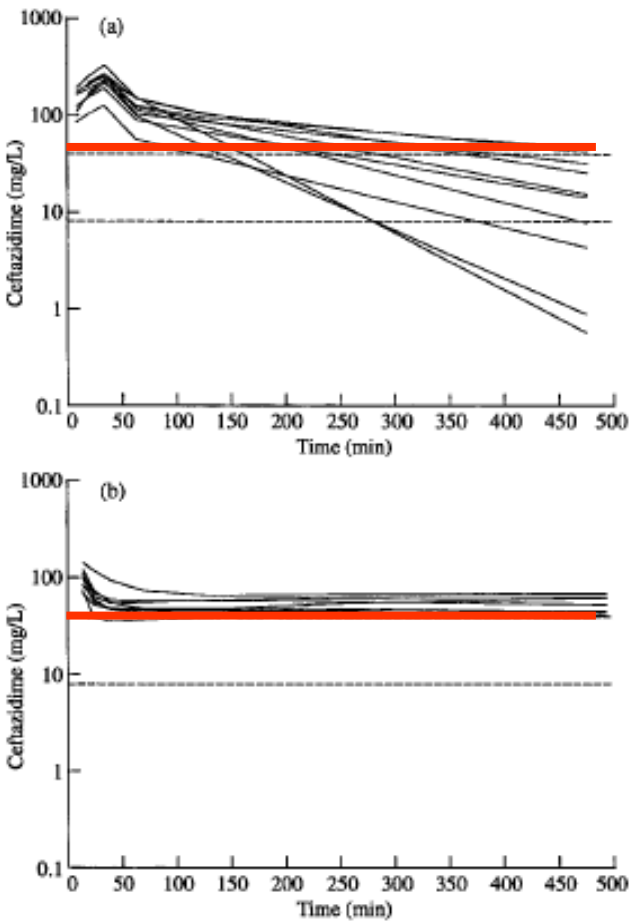
Continuous infusion of β-lactams

- In order to potentiate or rescue the activity of these agents against resistant strains by the optimization of their pharmacodynamic parameters

To increase Time above MIC

Continuous infusion ofceftazidime

40 µg/ml



40 µg/ml

Figure. Ceftazidime serum concentrations *vs* time (logarithmic scale) for the bolus group (a) and continuous infusion group (b) over 8 h. Broken lines are at 8 mg/L (high MIC for *P. aeruginosa*) and five times that, i.e. 40 mg/L.

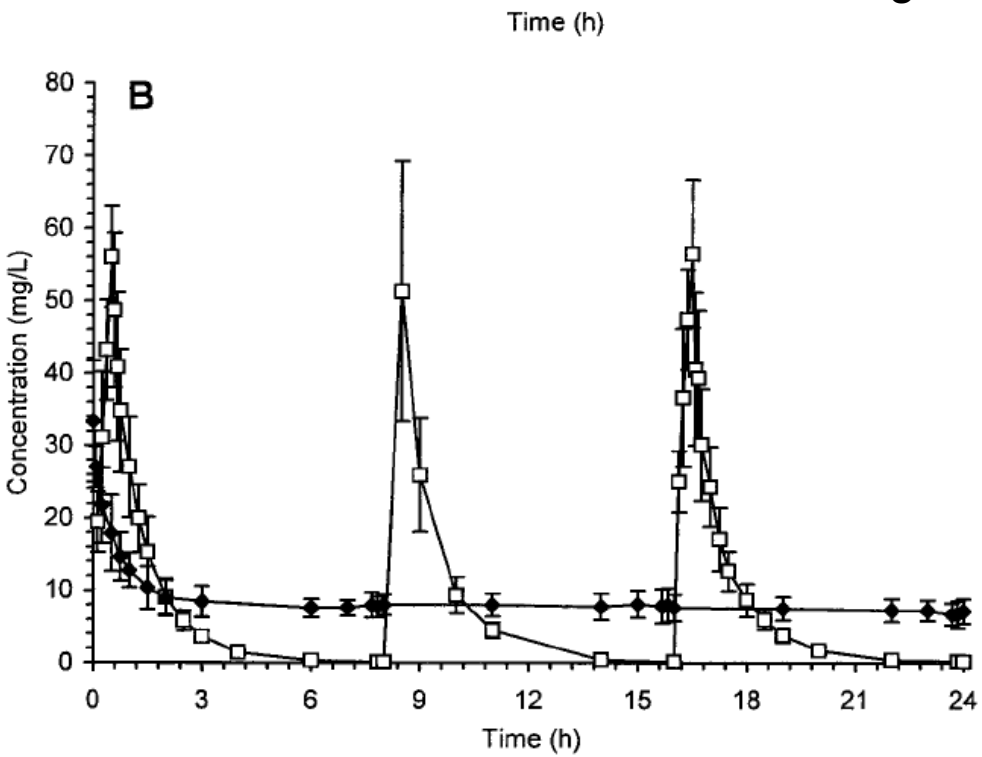
1g puis 6g CI

1g puis 2g x 3 IV

Lipman JAC 1999; 43, 309-311

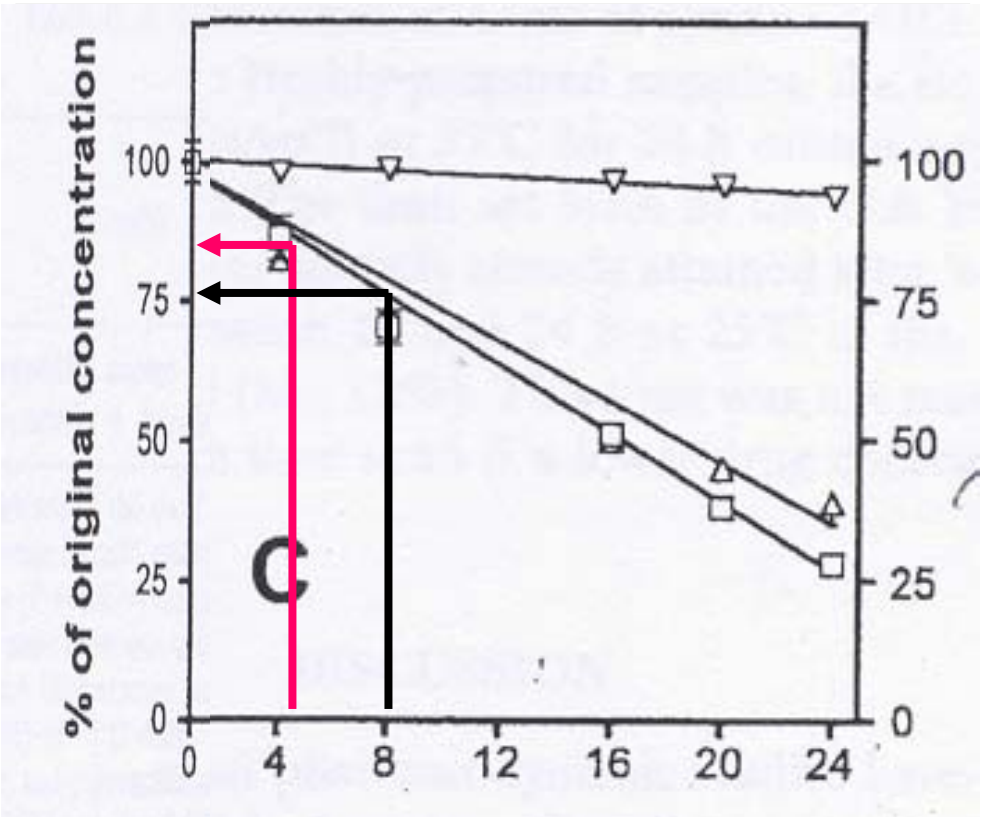
Meropenem

CI: 500 mg loading dose then 3g/d
IA: 1g x 3 IV



Krueger AAC 2005; 49, 1881

Stability of carbapenems at 37°C



Faropénem

Meropenem
Imipenem

→ 3-hour infusions

Cefepime continuous infusion

Cefepime 2 gr bolus + 4 gr continuous infusion

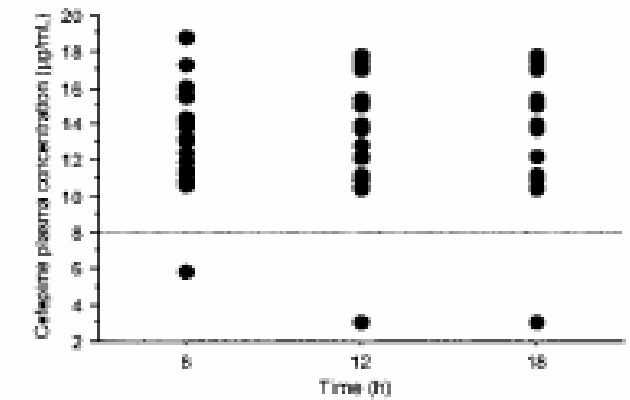


Figure 1. Cefepime plasma concentrations over 18 hrs.

Plasma concentration
Steady-state after
48 h of therapy

Boselli et al. CCM 2003;31:2102

Serum concentration of β-lactams given as CI

Drug	Dose	Serum concentration at steady state
Ceftazidime	1g then 6g/day	40 µg/ml
Cefepime	2g then 4g	10-18 µg/ml
Meropenem	500mg then 3g/d	8 µg/ml
Atreonam	6g/d	40 µg/ml

Fosfomycine (Fosfocine®)

- Bactericidal antibiotic. Interferes with the first step in the synthesis of bacterial cell wall

- Active in vitro against a wide range of gram-positive and gram-negative bacteria
  - Cocci + : *S. pneumoniae*, enterocoque, MRSA, MSSA
  - BGN:
    - Sensibles: *Citrobacter, Enterobacter* (10-30% R), *E. coli*, *HI, Klebsiella, Proteus P. aeruginosa* (30-70% R), *Serratia, Salmonella, ….*
    - Résistants: *Acinetobacter, Burkholderia, M. morganii, Stenotrophomonas*

- Breakpoint: S ≤ 32, R > 32 µg/ml

- In vitro synergy with β-lactams and many other drugs

- Bacterial resistance: chromosomal or by plasmid. When used as monotherapy: rapid emergence of resistance

Pharmacokinetics

- Presentation
  - Orally:trometamol or calcium salt
  - IM or IV: disodium salt
- PK:
  - 3g fosfomycin orally → peak concentration 22-32 µg/ml (bioavailability 30-40%)
  - 3g IV: peak serum concentration 220µg/ml
- Widely distributed in body fluids, including the CSF
- Plasma half-life: 2 hours
- Excreted unchanged in the urine, by glomerular filtration, within 24 hours

Fosfomycin (Fosfocine®)

- Doses:
  - Loading dose: 12g then 16-24g/24h
    (given in 4h → C° max 123µg/ml, 24 à h8)

- 1g of fosfomycin 14,4 MEq Na → 24g=345mEq

- 40€/4g not reimbursed

Conclusions