

Use of pharmacodynamics and Monte Carlo simulations to predict clinical cure of *Pseudomonas aeruginosa* infection



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Pseudomonas infections

Bacteremia

- **Incidence 1 per 1000 admissions** (Boffi E, CID 2001,33:1859)
- **Mostly nosocomial**

Pseudomonas infections

Bacteremia

- Incidence 1 per 1000 admissions (Boffi E, CID 2001,33:1859)
- Mostly nosocomial

Mortality (39%) (Kang CI, CID,2003:37:745)

- **Multivariate analysis 30-day mortality** (+/-;%)
 - **Septic shock** OR **45** (85/24)
 - **Pneumonia** OR **11** (77/31)
 - **Ineffective Abtic**
 - **Empirical** OR **4.6** (45/28)
 - **Definitive** OR **11.6** (75/30)

Pseudomonal bacteremia Mortality vs « good Rx »

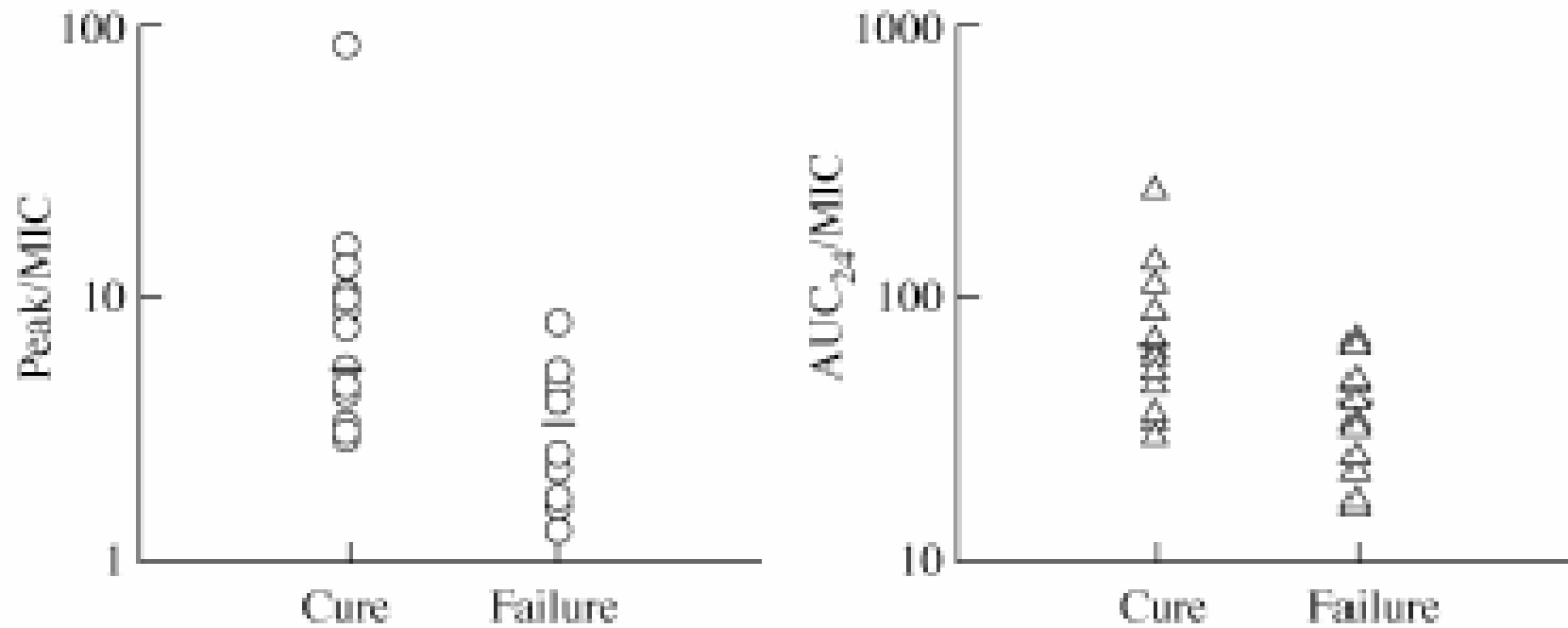
antimicrobial Rx		Mortality at day 30%
empirical	definitive	
inadapted	inadapted	75.5
inadapted	adapted	43.4
adapted	adapted	27.7

Pseudomonal infections

- **Clinical trial**
 - **Difficult**
 - **Multiple clinical situations**
 - **Unachievable number of patients**
- **Aim of this study**
 - **To explore the PK-PD characteristics of anti-pseudomonal regimens**
 - **By using « realistic-virtual » PK simulations**

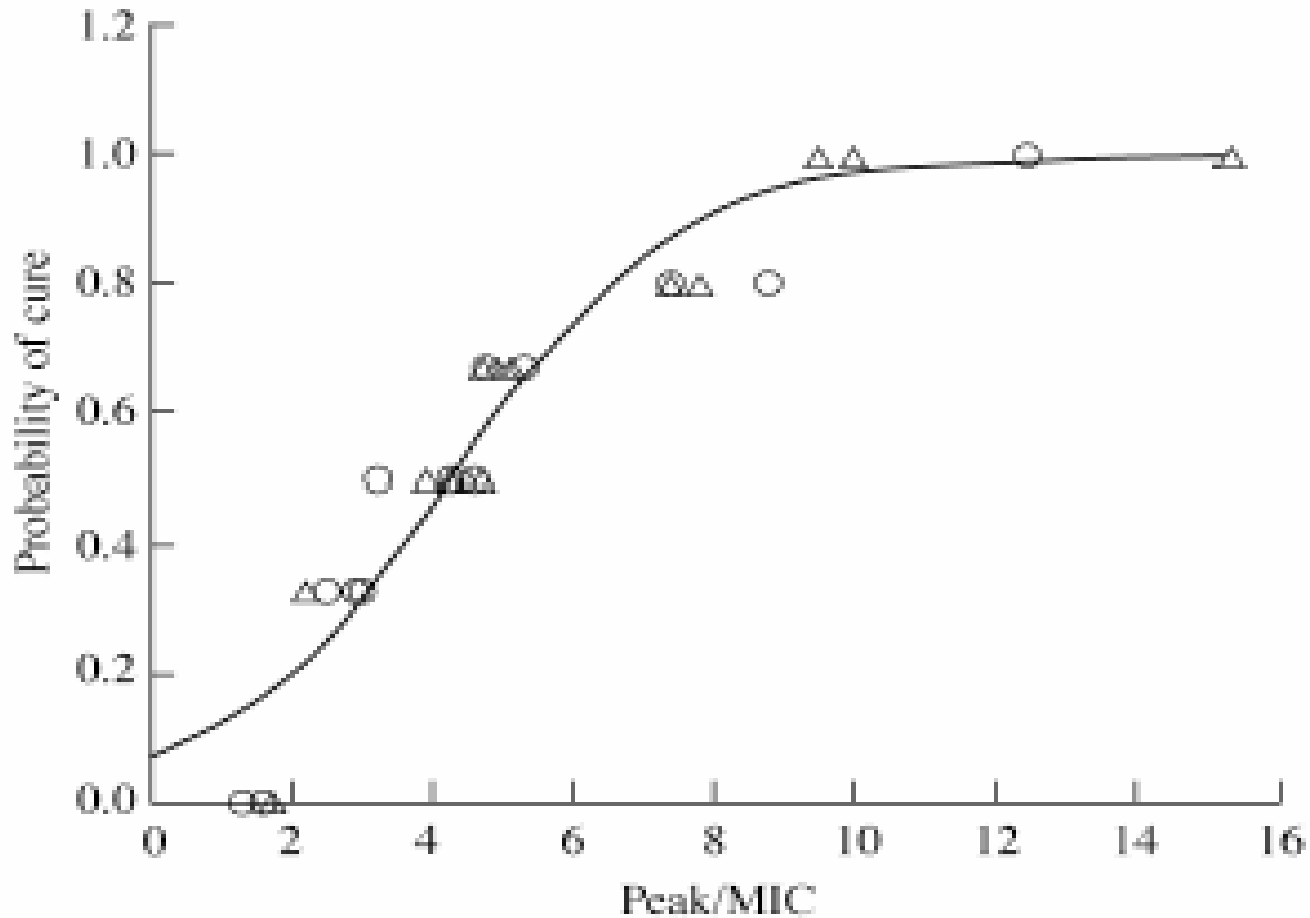
Pharmacodynamics of aminoglycosides, fluoroquinolone

Outcome of *Pseudomonas aeruginosa* bacteremia



Pharmacodynamics of aminoglycosides, fluoroquinolone

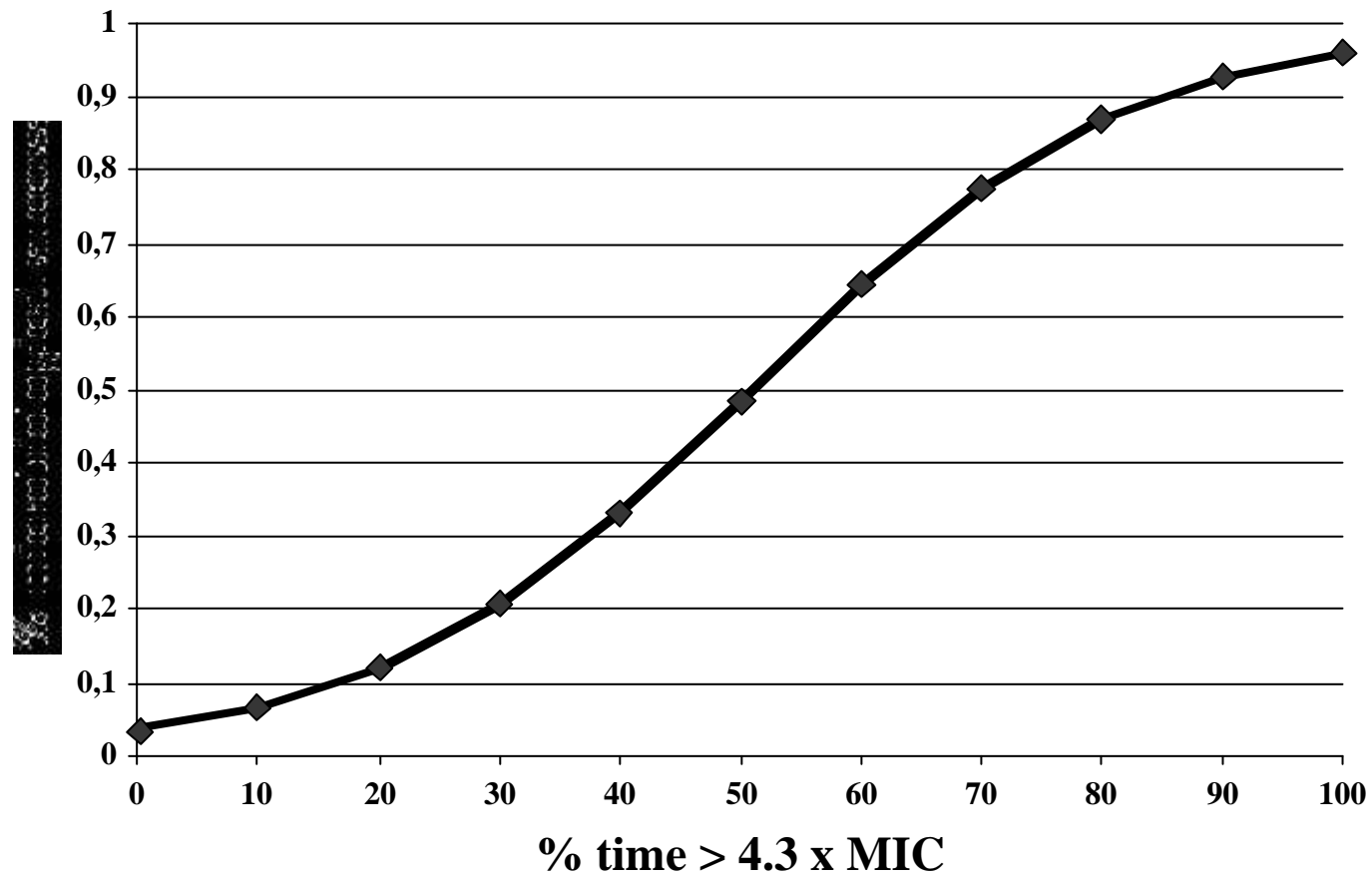
Outcome of *Pseudomonas aeruginosa* bacteremia



Zelenitsky SA, JAC 2003,52:668

Open triangle= aminoglycosides
Circle= ciprofloxacin

Pharmacodynamics of b-lactam (cefepime) Outcome of Gram negative bacteremia

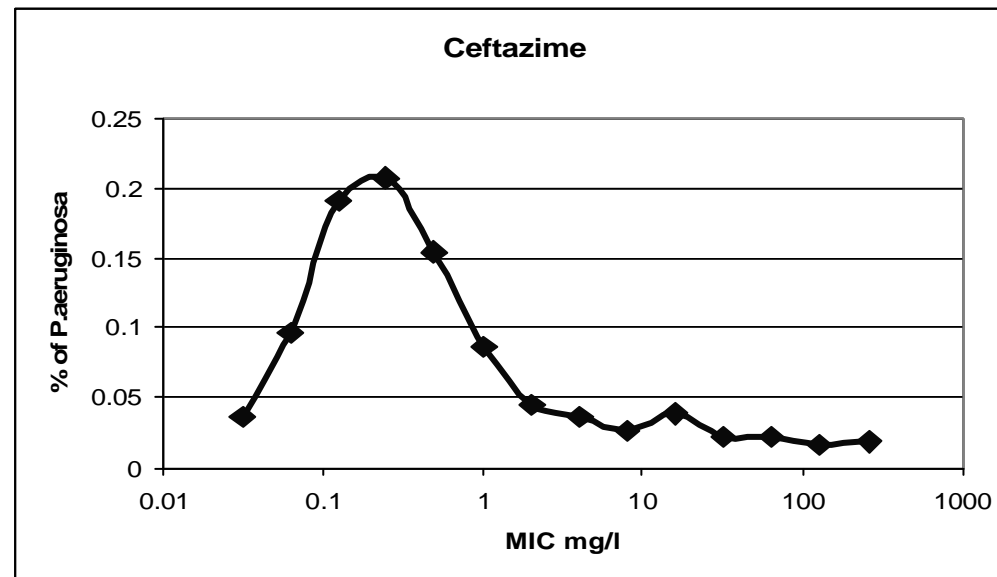


Method

- **Patients**
 - **CHU Dijon**
 - **400 pts from medical wards**
 - **Age, sex, weight, creatinemia => creatinin clearance**
(Cockcroft DW, Nephron 1976;16:31, Levey AS, Ann Intern Med 1999;130:46)

Method ^{1a}

- *Pseudomonas aeruginosa*
 - 300 « non-urinary » strains
 - In vitro testing: CA-SFM recommendations



Method 2

- **Treatment**
 - **Published or local PK-models**
 - Piperacillin-tazobactam, imipenem, ceftazidime, cefepime, aztreonam
 - Ciprofloxacin
 - Amikacin, tobramycin
- **Simulations**
 - Monte Carlo
 - $N \Rightarrow$ asymptotic situation

Method

% of patients attaining the PK-PD target

Target attainment rate TAR

PK-PD target (unbound fraction)

- **b-lactam**
 - $T > MIC > 70\%$
 - $AUC/MIC > 125$
 - $C_{min}/MIC > 4$
- **Fluoroquinolone, aminoglycosides**
 - $C_{max}/MIC > 10$
 - $AUC/MIC > 125$

Results

Patients

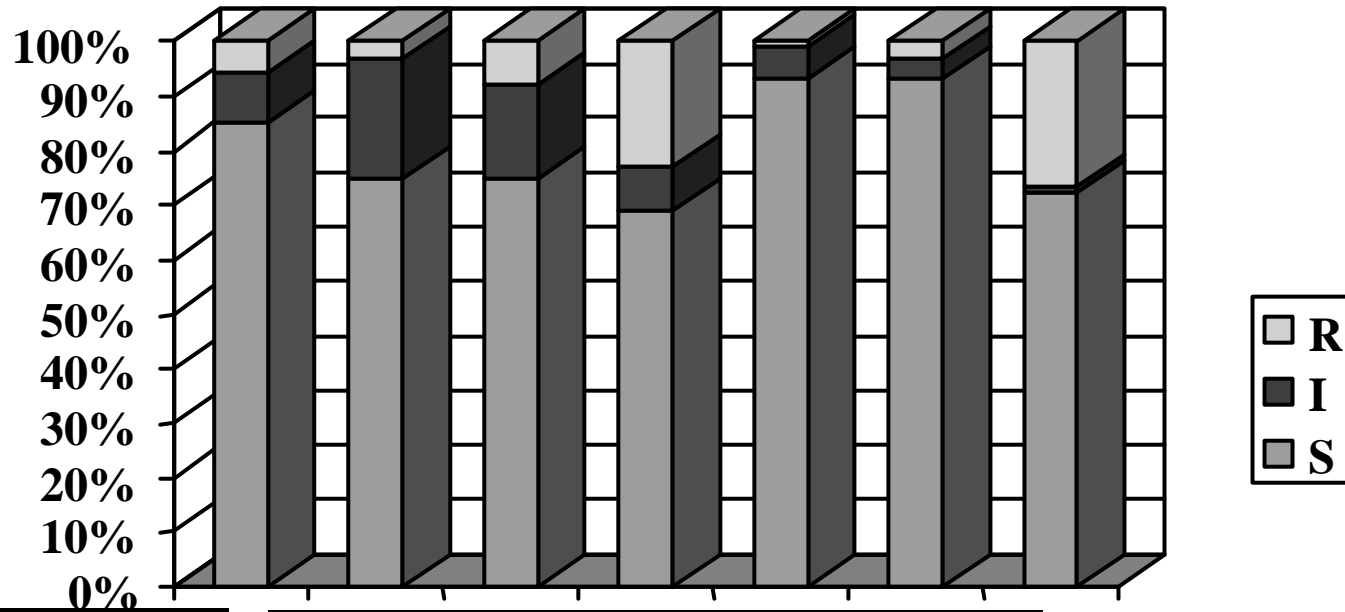
- **Age:** 62 [20-95] y.
- **Sex:** f/m 4/6
- **Weight:** 65 ± 15 kg
- **Creatinemia** 73 ± 30 mmol

Results

antimicrobials - PK

		VD	t1/2	%bound
		l	h	
Pipera-taz		16±4	1.4±0.2	16
Ceftazidime	(β)	20±5	3±1.3	17
Cefepime		29±6.7	4.3±1.8	19
Imipenem	(β)	27±6.1	2.6±0.4	9
Aztreonam		19.5±4.5	3.2±0.9	56
Ciprofloxacin		117±27	6.4±3.4	40
Amikacin		33±7.4	7.3±3	10
Tobramycin		20±5	6.3±2.6	1

Pseudomonas aeruginosa in vitro susceptibility



PKPD simulations of b-lactam

Ceftazidime

- 1gr x 3
- 2gr x 3
- 4gr cont.

Cefepime

- 2gr x 2
- 2gr x 3
- 4gr cont.

Imipenem

- 1gr x 3

Aztreonam

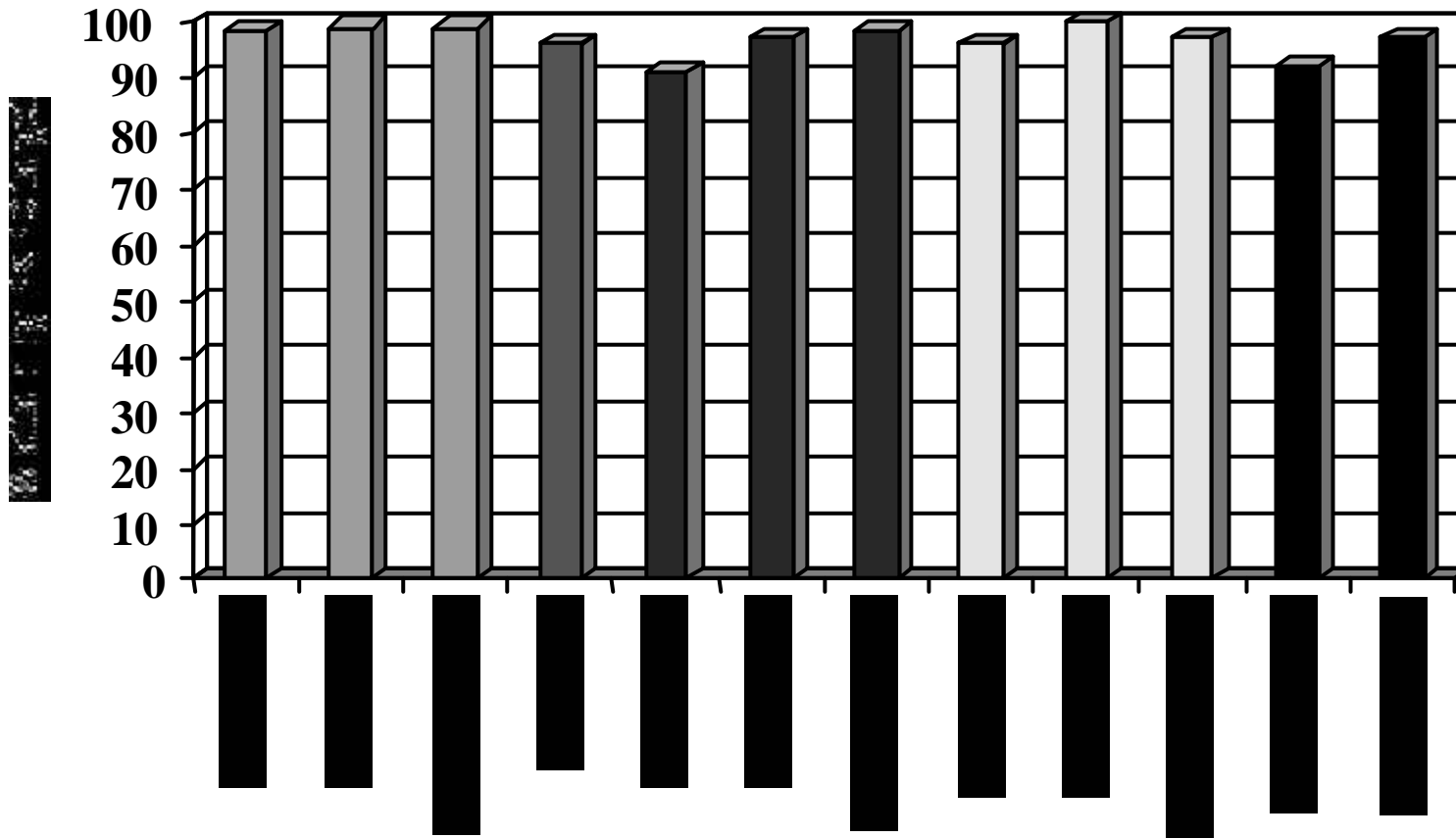
- 1gr x 3
- 2gr x 3
- 6gr cont.

Piperacillin-taz

- 4gr x 3
- 4gr x 4

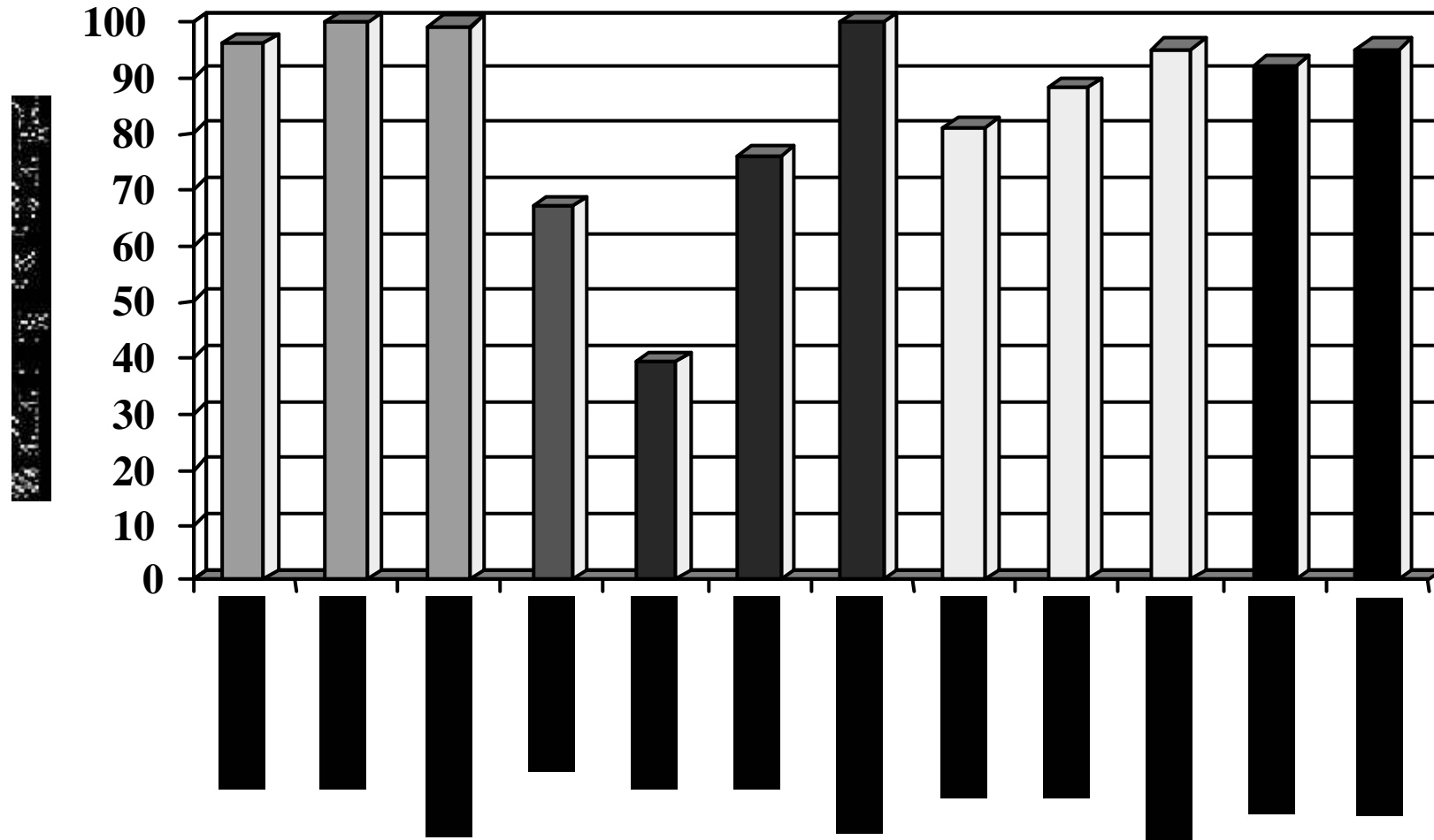
PKPD simulations of b-lactam for TAR for susceptible strains (T>MIC)

T>MIC 70%



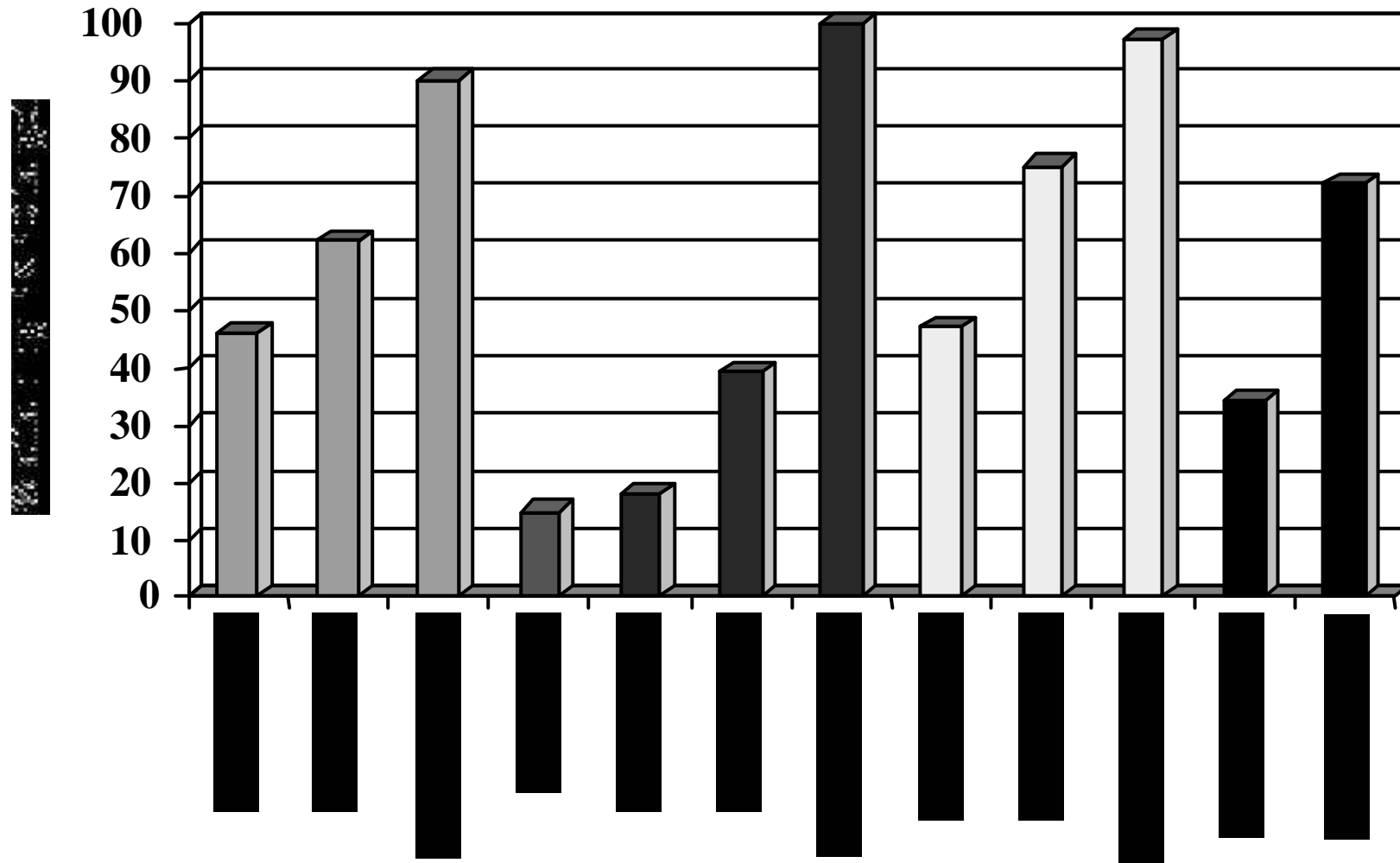
PKPD simulations of b-lactam for TAR for susceptible strains (AUC/MIC)

AUC/MIC 125



PKPD simulations of b-lactam for TAR for susceptible strains (C_{min}/MIC)

C_{min}/MIC 4



PKPD simulations of fluoroquinolone and aminoglycosides

Amikacin

- **15 mg/kg**
 - **Qd**
 - **Adapted interval**

Tobramycin

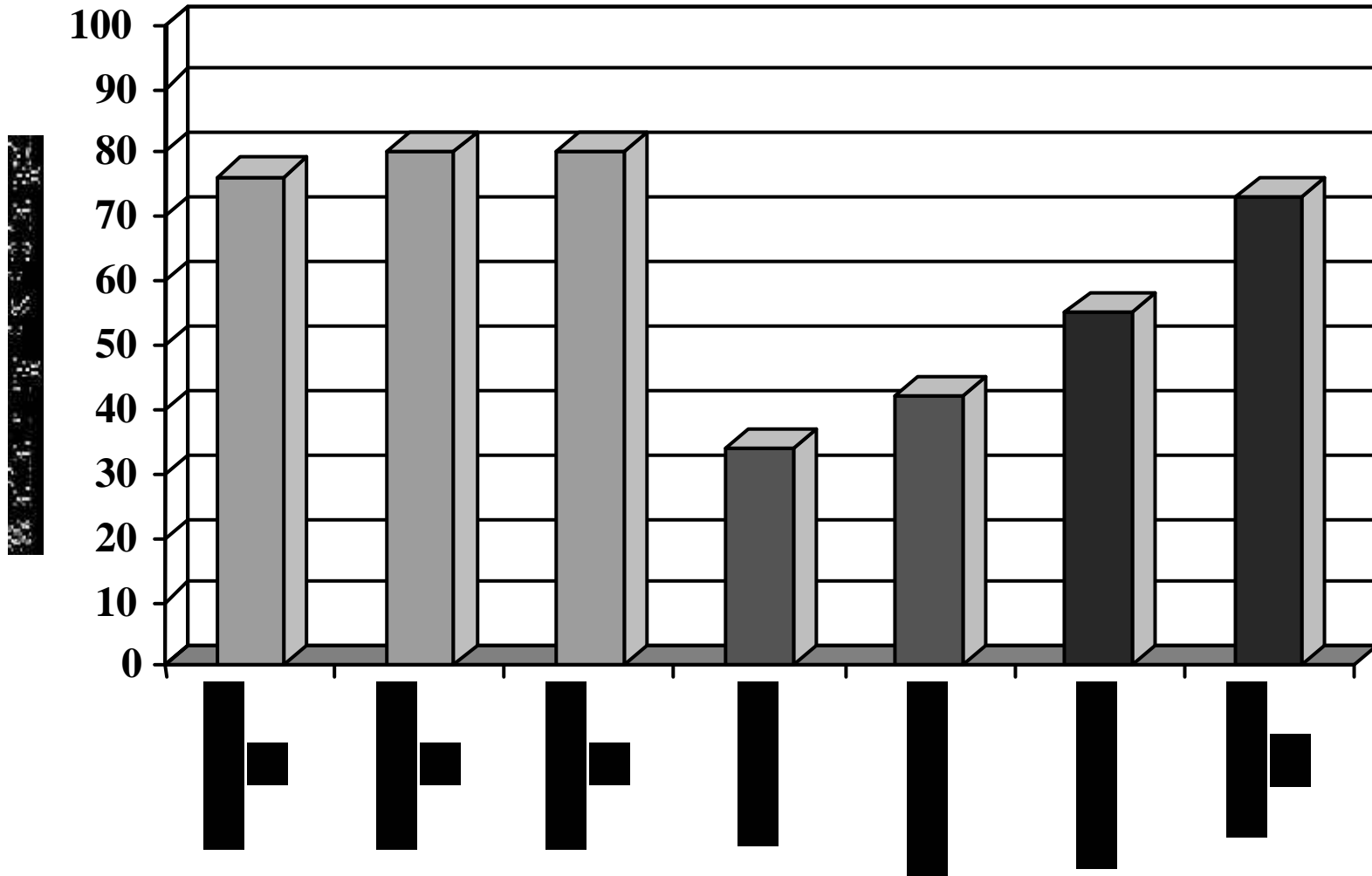
- **10 mg/kg**
 - **Qd**
 - **Adapted interval**

Ciprofloxacin

- **400mg x 2**
- **400mg x 3**
- **400mg x 4**

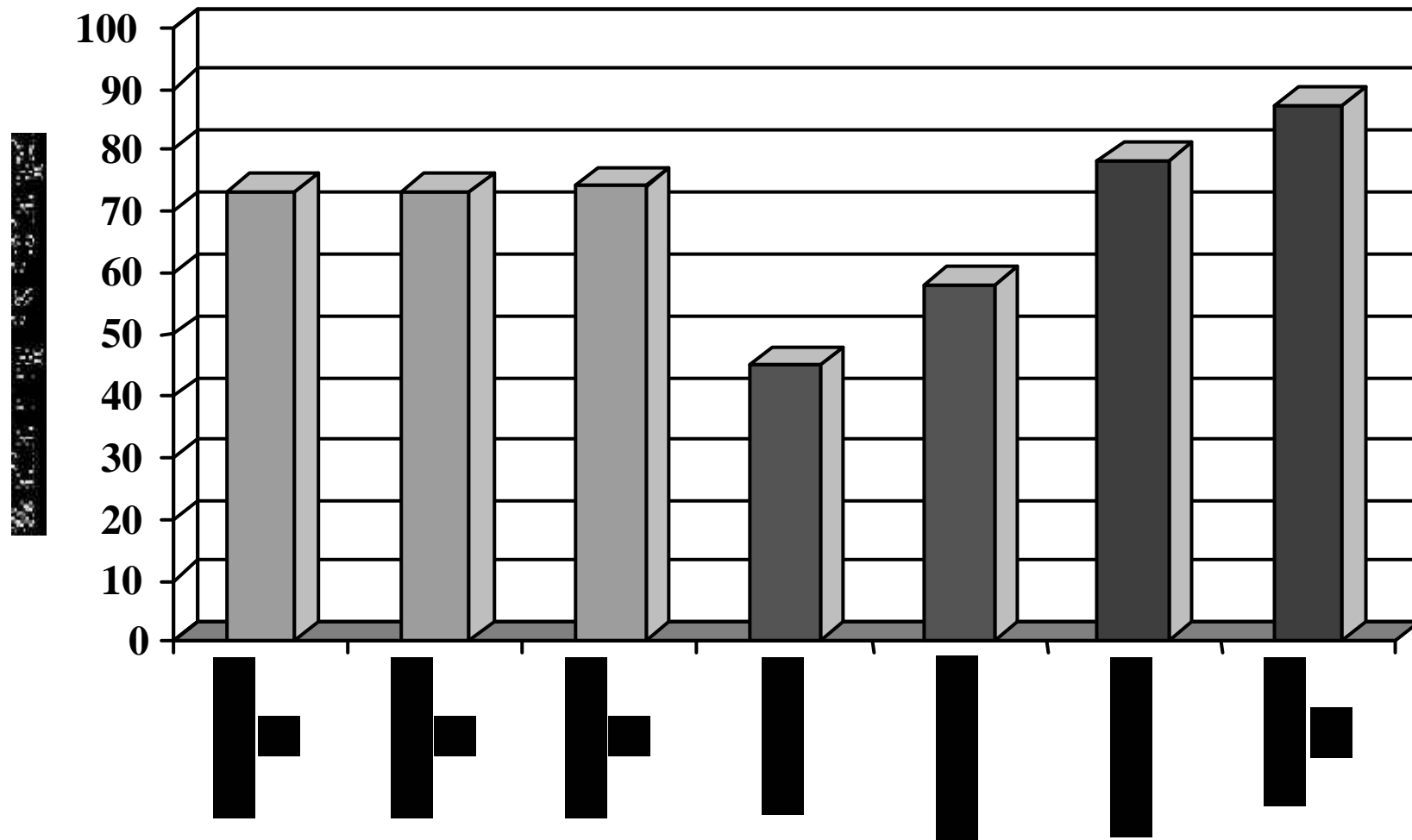
**PKPD simulations of fluoroquinolone and aminoglycosides for
TAR for susceptible strains (AUC/MIC)**

AUC/MIC 125



PKPD simulations of fluoroquinolone and aminoglycosides for TAR for susceptible strains (C_{max}/MIC)

C_{max}/MIC 10

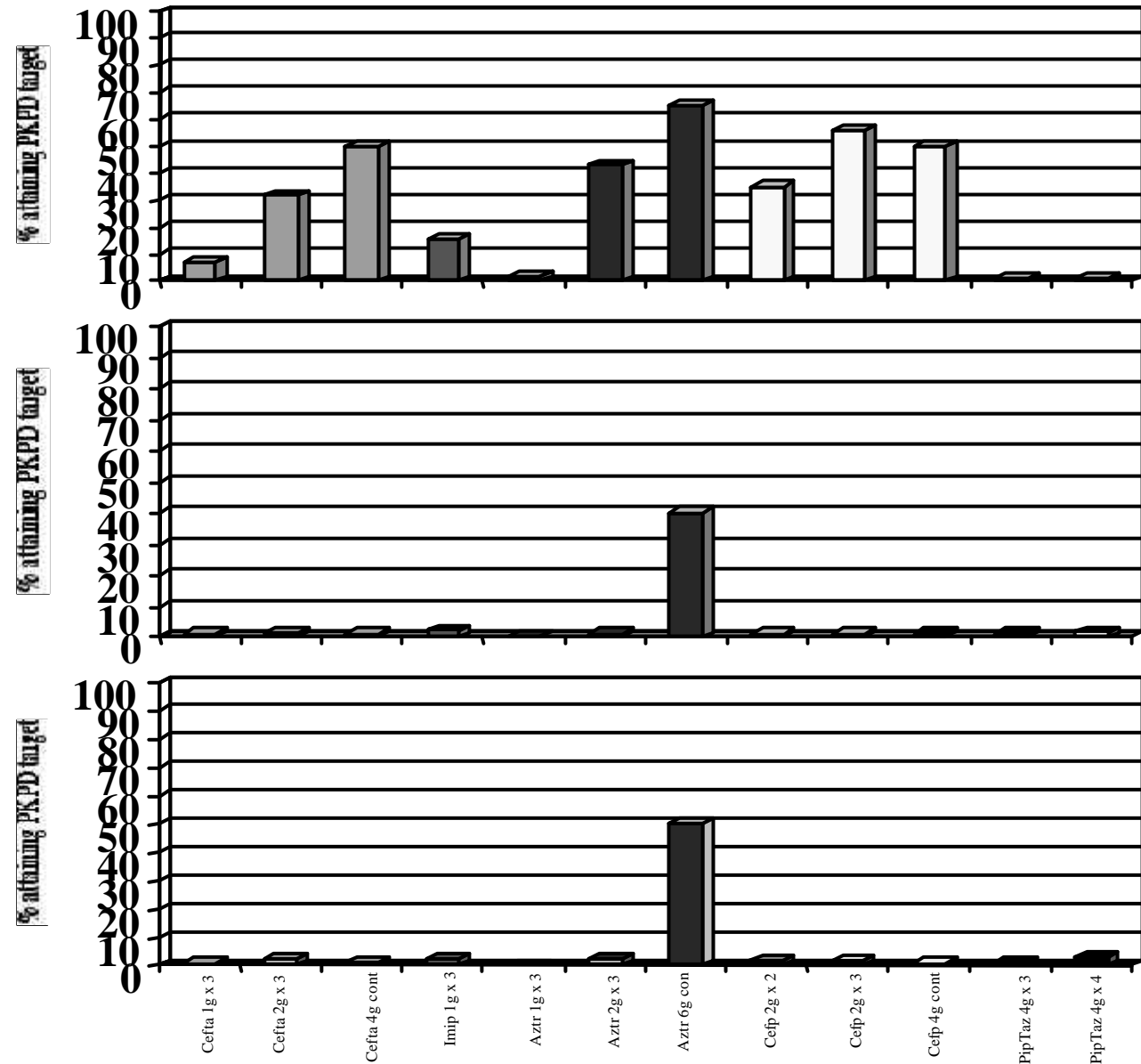


TAR for β -lactam and « I » strains

$T_{MIC} > 70\%$

$AUC/MIC > 125$

$C_{min}/MIC > 4$

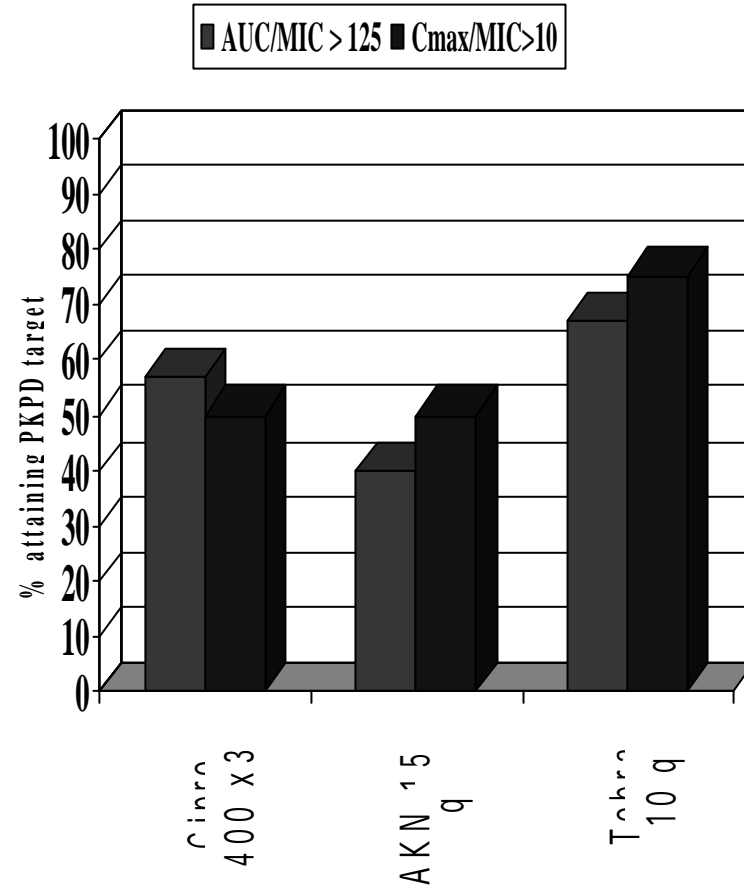
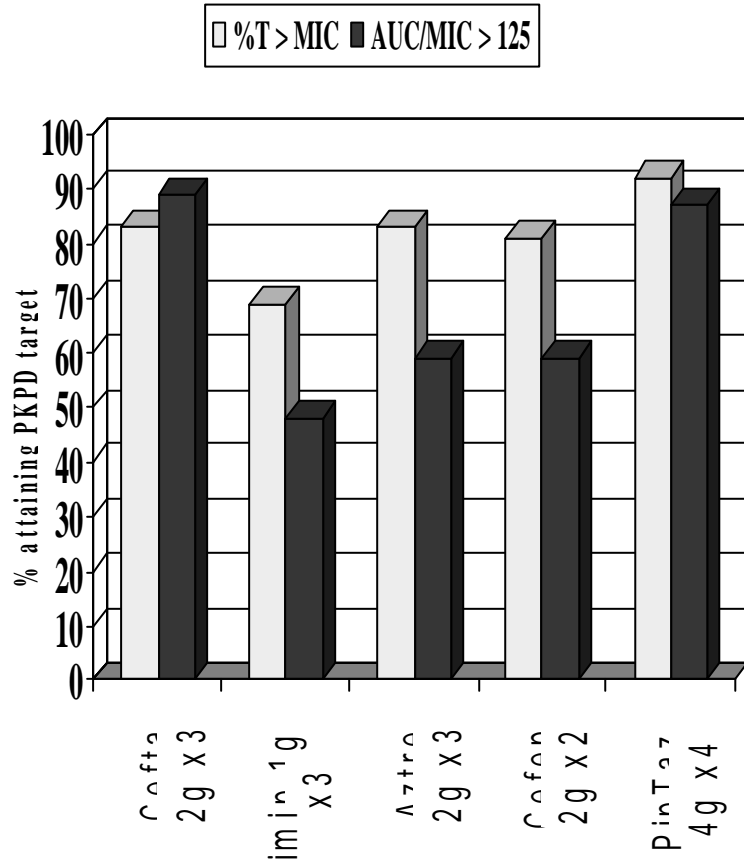


Pseudomonal infections

Presumptive treatment: « TAR for vs all strains »

b-lactam

Cipro, amikacin, tobra



Conclusions ₁

For Pseudomonas aeruginosa infections in Dijon (Fr)

PK-PD target not reached even for susceptible strains-infections with :

- **Ciprofloxacin regimens in > 40%**
- **Amikacin regimens in > 50%**

Not anticipated from in vitro data

Conclusions ₂

For Pseudomonas aeruginosa infections in Dijon (Fr)

- **PK-PD target reached for most strains S(+I)-strains-infections with**
- **b-lactam regimens, except imipenem,**
- **Cefta = pipe-taz = aztreonam = cefepime > imipenem**
- **Problem for true allergic patient**

Conclusions ³

**For Pseudomonas aeruginosa infections in Dijon (Fr)
PK-PD simulations can guide the antimicrobial
strategies :**

- **In our hospital, decrease the exposition of:**
 - **fluoroquinolones and**
 - **aminoglycosides and**
 - **Imipenem**
- **For patients:**
 - **individualized « PK-PD adapted » regimen**

!! The end !!