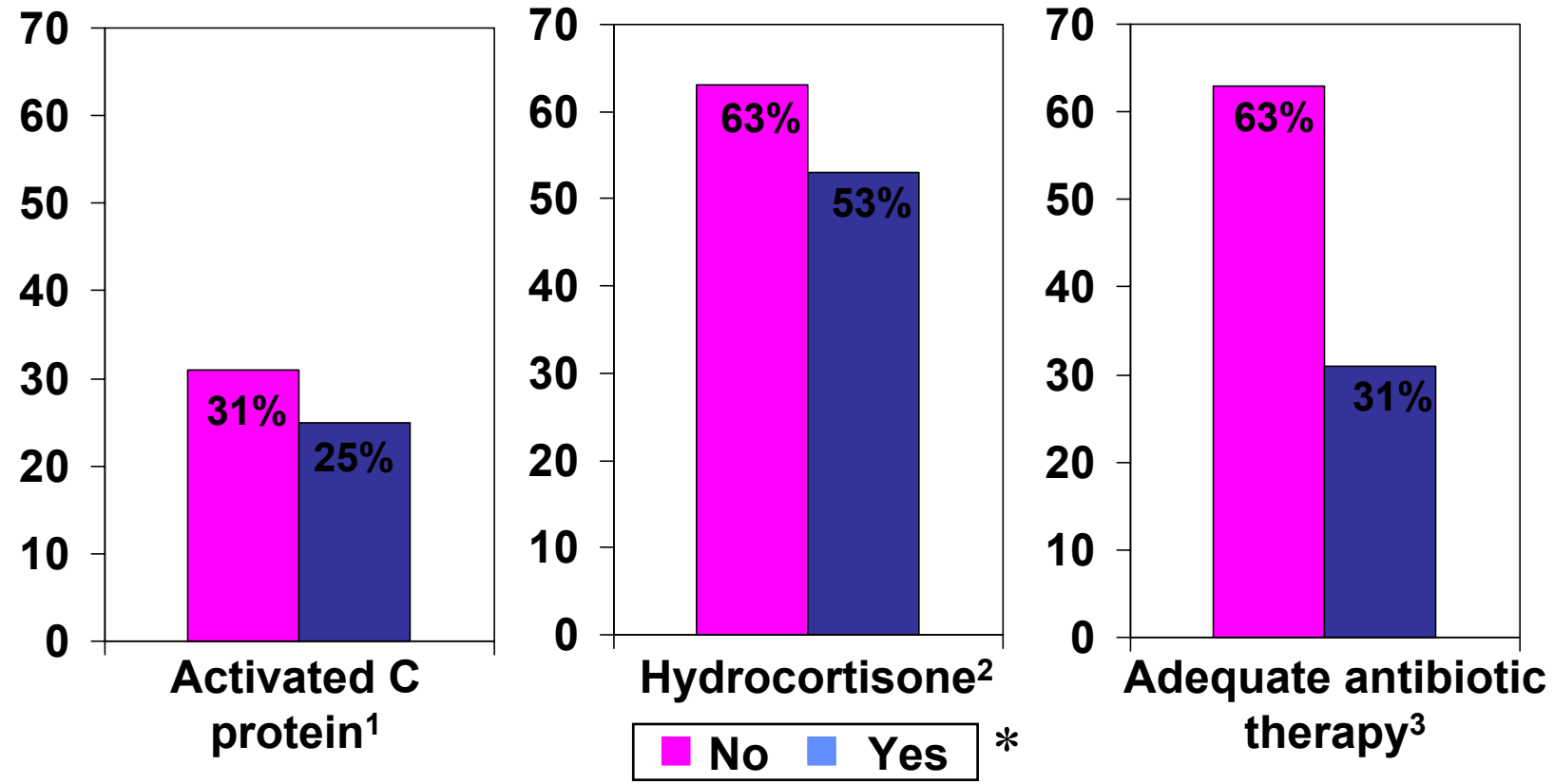
Problem primjene antibiotika u JIM

Uvjeti uspješne antimikrobne terapije

- Izbor antibiotika (monoterapija, kombinirana terapija)
- Pravovremeni početak liječenja
- Doziranje i način primjene
- FK/FD odnosi
  - Često promijenjena farmakokinetika kod bolesnika u JIM
  - Promjenjena farmakodinamika (porast MIK-a)
- Dostupnost žarišta u koje antibiotici slabo ulaze
- Smanjenje upalne mase (kirurško zbrinjavanje)
- Interakcije s drugim lijekovima
- Nuspojave
- Indukcija rezistencije

Treatment Can Affect Mortality in Patients With Sepsis: Three Interventions



es" indicates that patients received the specified treatment, "No" indicates that they did not.

Bernard GR et al. *N Engl J Med* 2001:344:699-709.

Surviving sepsis campaign

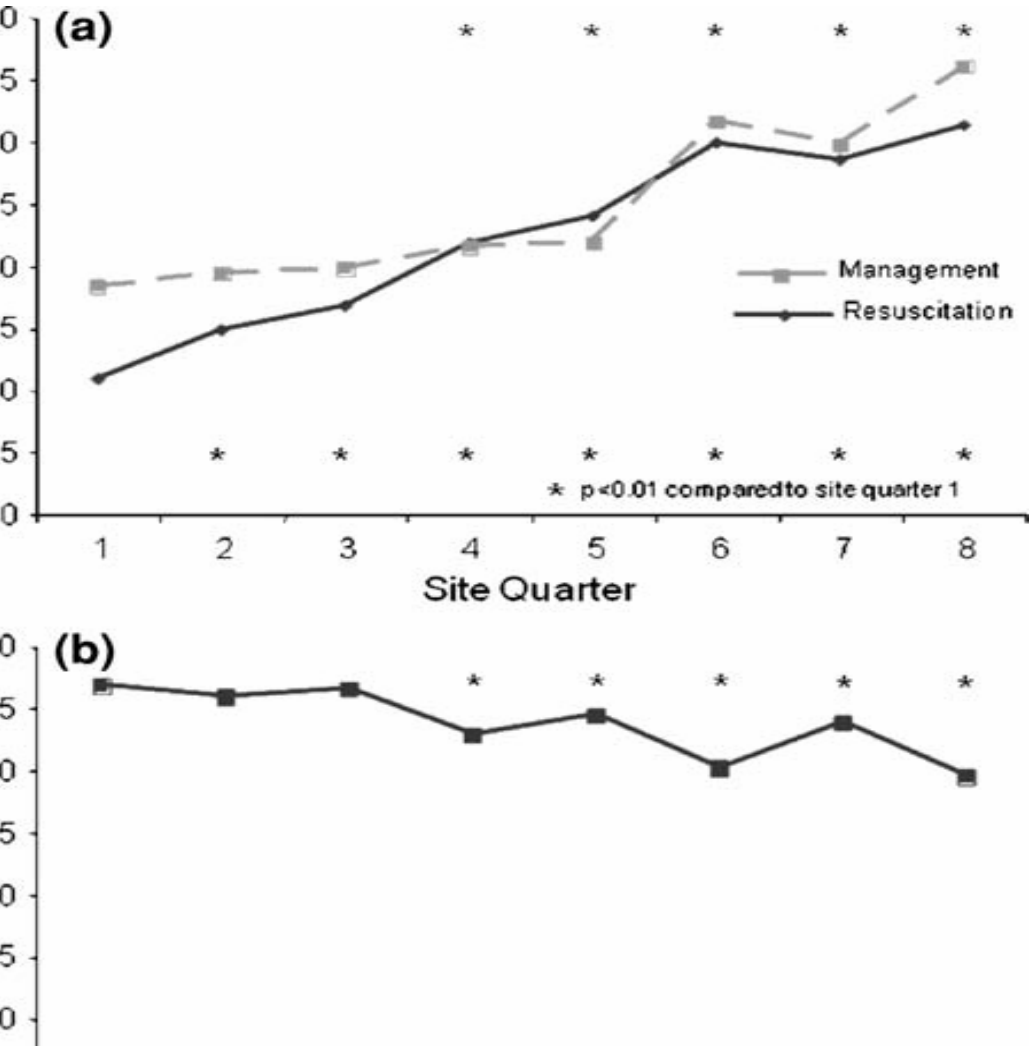


Fig. **Compliance and mortality change over time**: a) change in the percentage of patients compliant with all elements of the resuscitation bundle (dotted line) and the management bundle (solid line) **over 2 years** of data collection (*P\0.01 compared to first quarter). Note that both Y axes are truncated at 40% to emphasize relative change over time as opposed to absolute change;
b) Change in hospital mortality over time (*P\0.01 compared to first quarter)

ystematic review and Meta-analysis of the efficacy of appropriate empiric antibiotic therapy for Sepsis

- Septic shock was the only clinical variable significantly affecting results
  - OR 1.6 for inappropriate empirical treatment
- 34% mortality with inappropriate empirical treatment

Antibiotic treatment strategies in nosocomial infections

- Empirical antibiotic treatment:

Mono-versus Combination therapy

- Local guidelines/Consensus recommendations

escalating strategy: initial narrow-spectrum coverage

deescalating strategy: initial broad-spectrum

Mono-versus Combination therapy

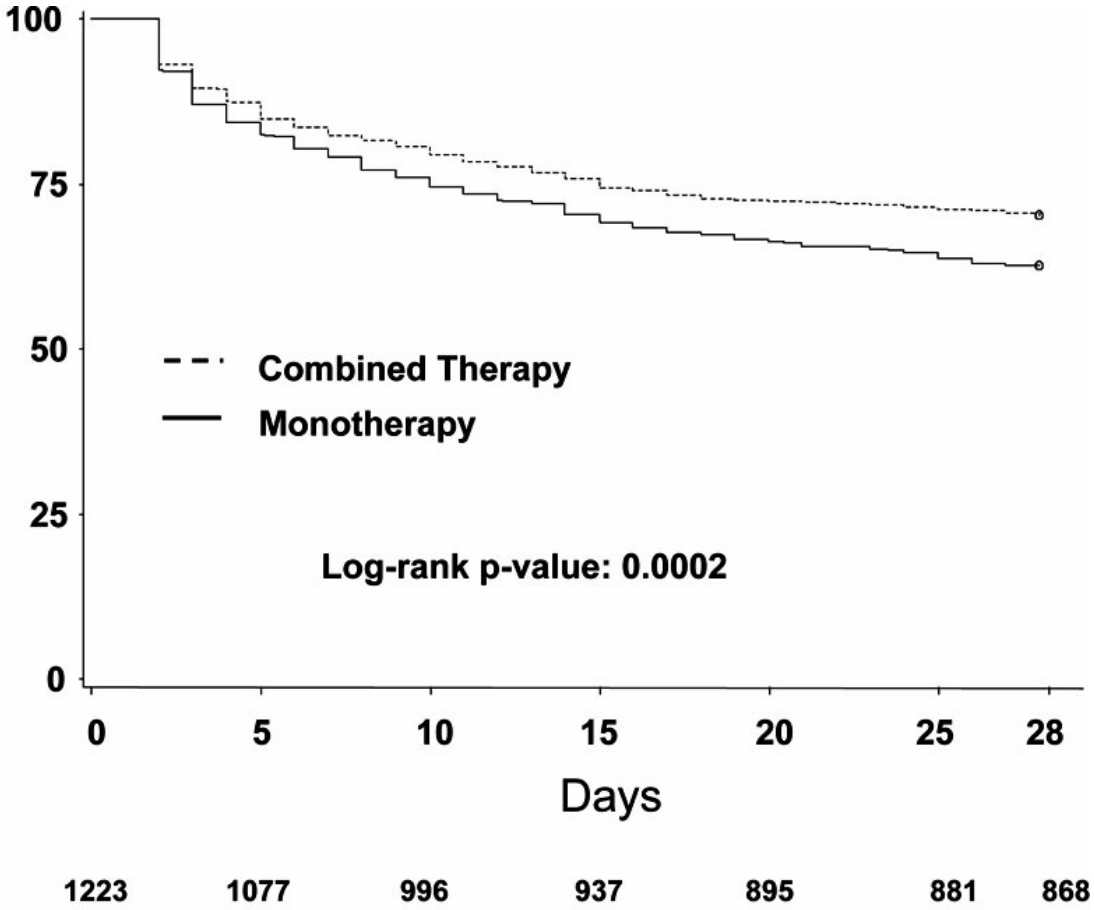


Figure: Adjusted Cox proportional hazards of mortality associated with combination antibiotic therapy of septic shock.

Mono-versus Combination therapy

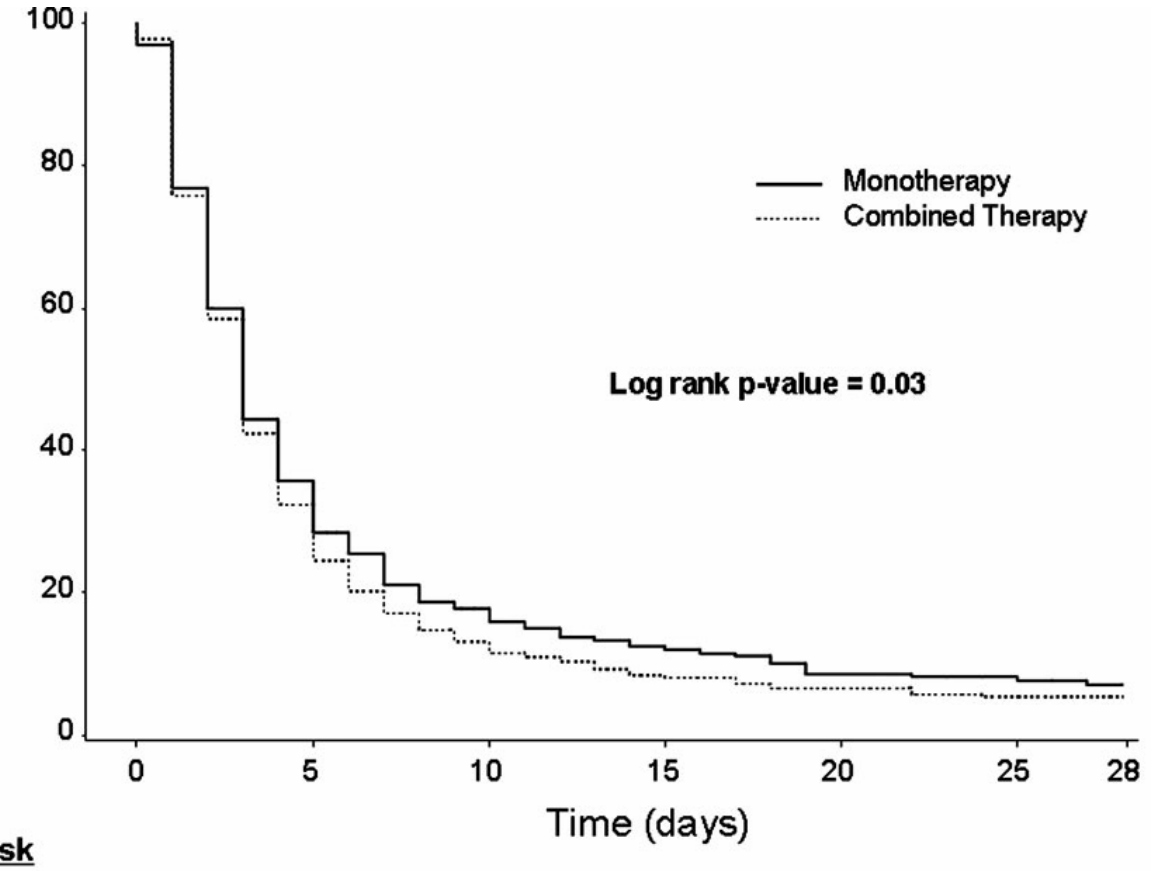
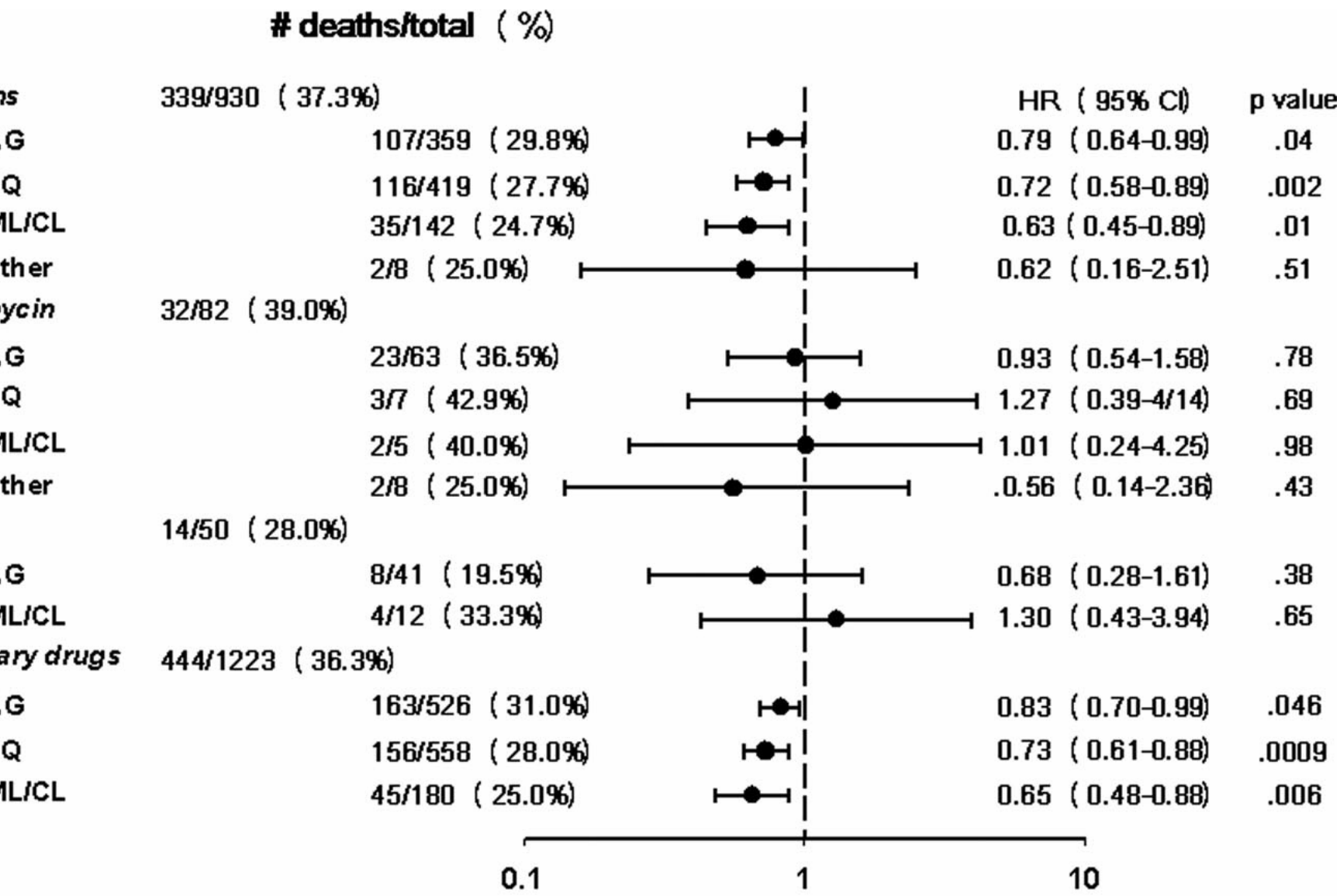


Figure : Log-rank assessment of persistence of pressor/inotrope dependence associated with combination therapy of septic shock. Combination therapy was associated with more rapid liberation from pressor/inotrope support.

Zbog čega je bolja kombinirana terapija?

- Predmnijevani patogen osjetljiv je na barem 1 komponentu terapije
- Prevencija nastanka rezistentnih superinfekcija
- Potencijalno imunomodulatorno djelovanje drugog antibiotika
- Aditivno ili sinergističko djelovanje kombiniranih antimikrobnih lijekova


deaths/total (%)
ns
339/930 (37.3%)
HR (95% CI)
p value
G
107/359 (29.8%)
0.79 (0.64-0.99)
.04
Q
116/419 (27.7%)
0.72 (0.58-0.89)
.002
ML/CL
35/142 (24.7%)
0.63 (0.45-0.89)
.01
ther
2/8 (25.0%)
0.62 (0.16-2.51)
.51
ycin
32/82 (39.0%)
G
23/63 (36.5%)
0.93 (0.54-1.58)
.78
Q
3/7 (42.9%)
1.27 (0.39-4/14)
.69
ML/CL
2/5 (40.0%)
1.01 (0.24-4.25)
.98
ther
2/8 (25.0%)
.0.56 (0.14-2.36)
.43
14/50 (28.0%)
G
8/41 (19.5%)
0.68 (0.28-1.61)
.38
ML/CL
4/12 (33.3%)
1.30 (0.43-3.94)
.65
ary drugs
444/1223 (36.3%)
G
163/526 (31.0%)
0.83 (0.70-0.99)
.046
Q
156/558 (28.0%)
0.73 (0.61-0.88)
.0009
ML/CL
45/180 (25.0%)
0.65 (0.48-0.88)
.006
0.1
1
10

propriateness of various antibiotic combinations against m-negative pathogens in the study cohort[a]

tibiotic	% Susceptible to at least one antibiotic plus:		
	None	Ciprofloxacin	Gentamicin
pime	83.4	86.4	89.9
enem or meropenem	89.7	92.4	94.2
racillin-tazobactam	79.6	87.0	91.4

ek S.T. et al. Empiric Combination Antibiotic Therapy Is Associated with

Tablica 1. Čimbenici koji utječu na ishod antimikrobnog liječenja u JIM

1. osjetljivost izolata na primjenjeni antibiotik
2. vrijeme proteklo od početka bolesti do primjene odgovarajućeg antibiotika
3. monoterapija ili kombinirana terapija
4. **ostvarenje optimalnih farmakokinetičkih vrijednosti**
   na mjestu upale
   doza
   interval primjene
   način primjene
   penetracija u razna tkiva i prostore
5. trajanje antimikrobnog liječenja
6. pojava nuspojava
7. pojava rezistencije i superinfekcija

Parametri koji ulaze u analizu tih odnosa:

maksimalna koncentracija lijeka

minimalna koncentracija lijeka

AUC

MIK

trajanje koncentracija iznad vrijednosti MIK-a

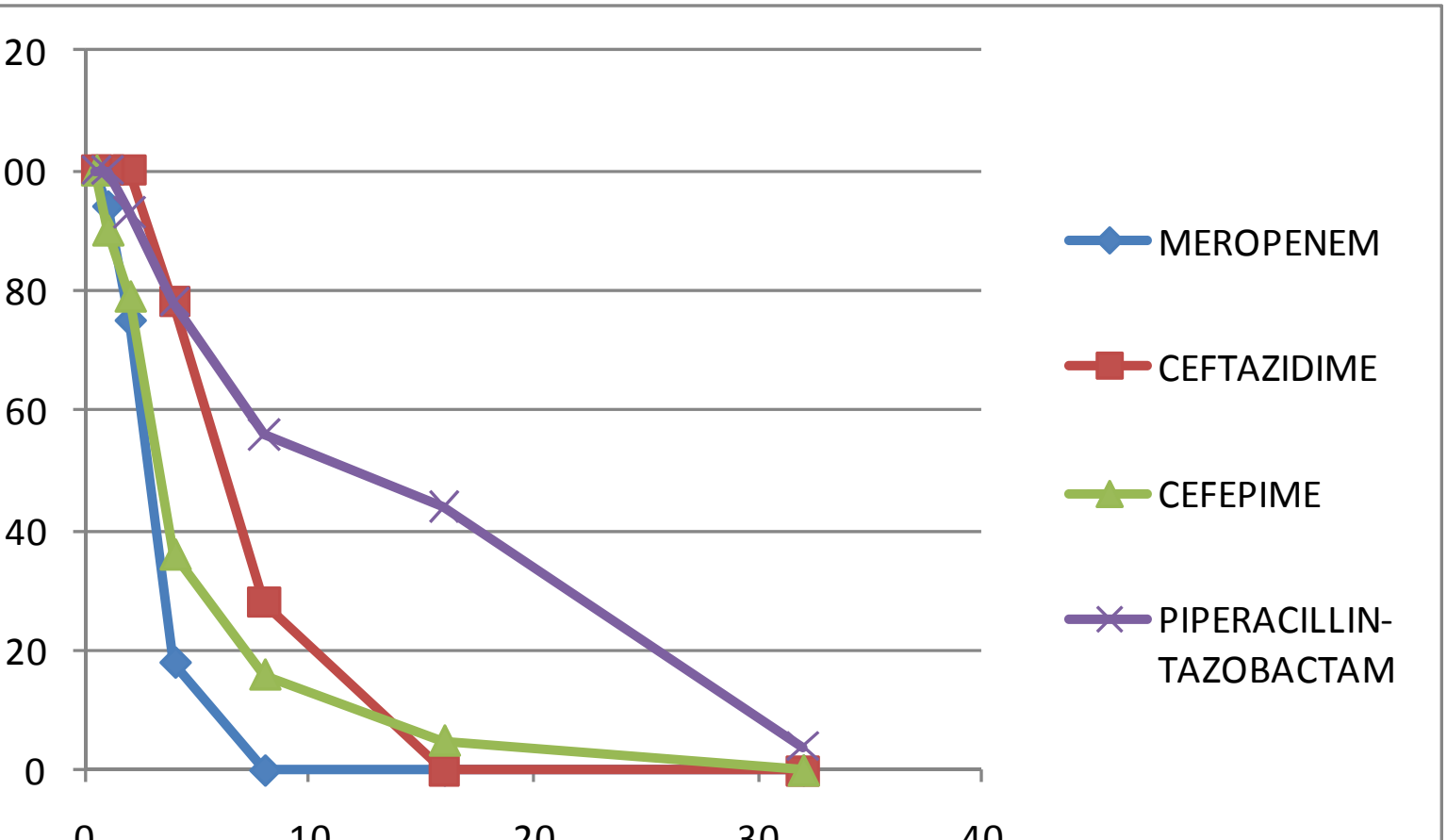
postantibiotski učinak

quate concentrations of the four drugs, with regard to renal dysfunction

	Meropenem (n=16)	Ceftazidime (n=18)	Cefepim (n=19)	Piperacillin-tazobactam (n=27)
4 x MIC (%)	57 (25-100)	45 (8-100)	34 (10-100)	33 (0-100)
quate PK,)	12 (75)	5 (28)	3 (16)	12 (44)
< 50 min (%)	5/6 (83)	3/9 (33)	2/12 (17)	10/14 (71)
> 50mL/min	7/10 (70)	2/9 (22)	1/7 (14)	2/13 (15) *

ta are expressed as counts (percentage) or median (range).
Cl, creatinine clearance; MIC, minimal inhibitory concentration; PK, pharmacokinetic.

Probability of target T > 4 x MIC attainment for various MICs



Recommended doses of piperacillin-tazobactam, cefepime and ceftazidime provided serum drug concentrations during the first 24 hours of treatment that were insufficient to cover *P. aeruginosa* and other less susceptible bacteria in patients suffering from severe sepsis and septic shock.

Recommended doses of **meropenem** resulted in adequate concentrations to cover *P. aeruginosa* and other less susceptible bacteria in 75% of patients.

Therapeutic drug monitoring is necessary to optimize β-lactam concentrations as no clinical or biological variable can predict β-lactam concentrations in this population.

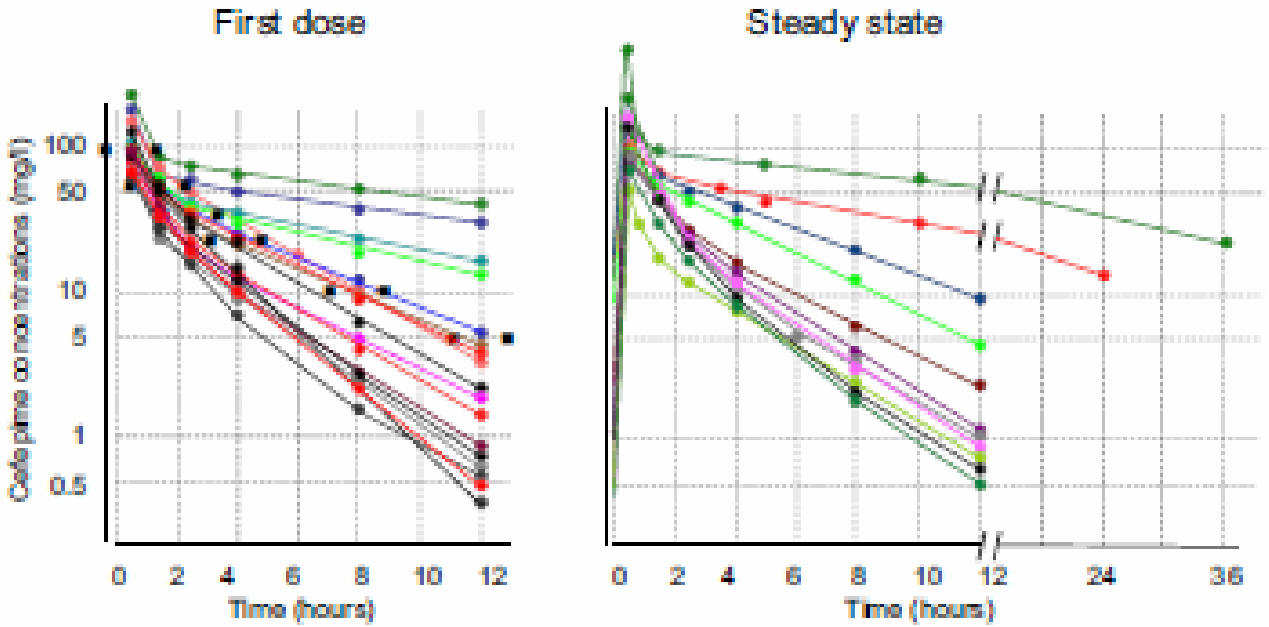


Figure 1 Pharmacokinetic profile of cefepime. Concentration of cefepime versus time determined in the plasmas of 21 consecutive patients as determined at the first dose (left panel; 17 individual PK profiles) or at steady state (right panel; 11 individual PK profiles). Colors identify individual patients.

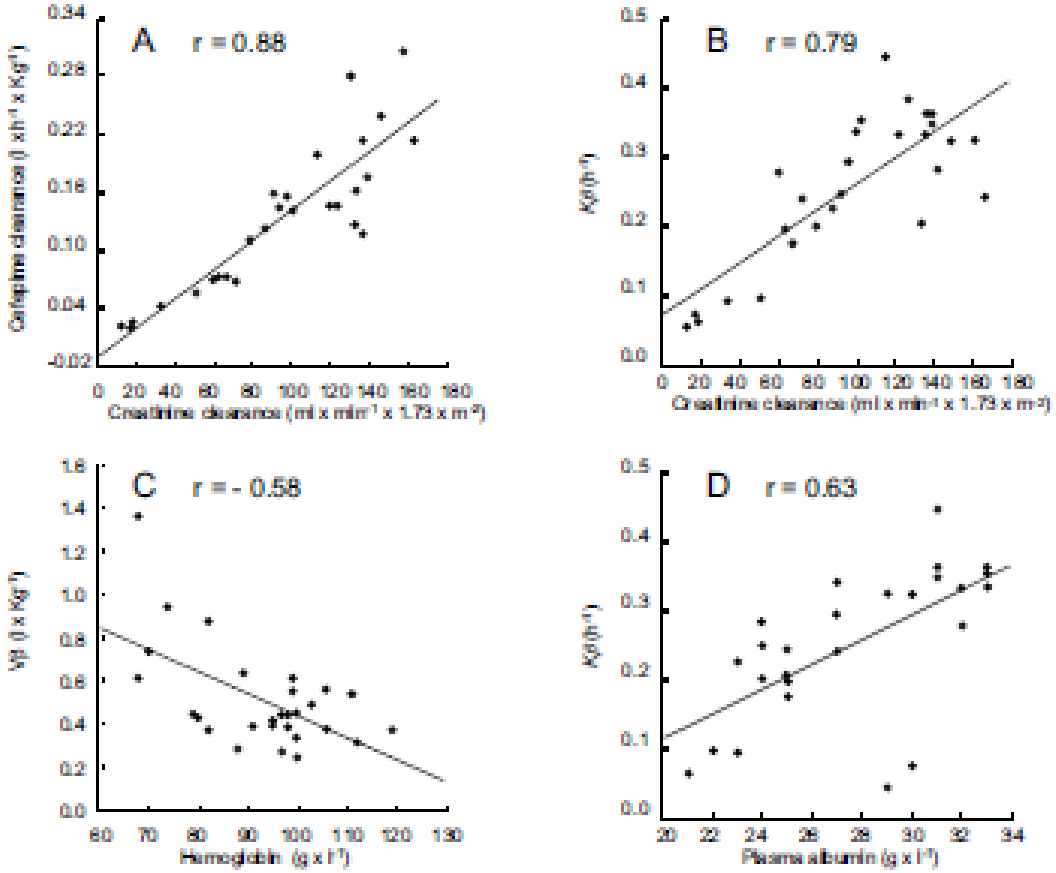
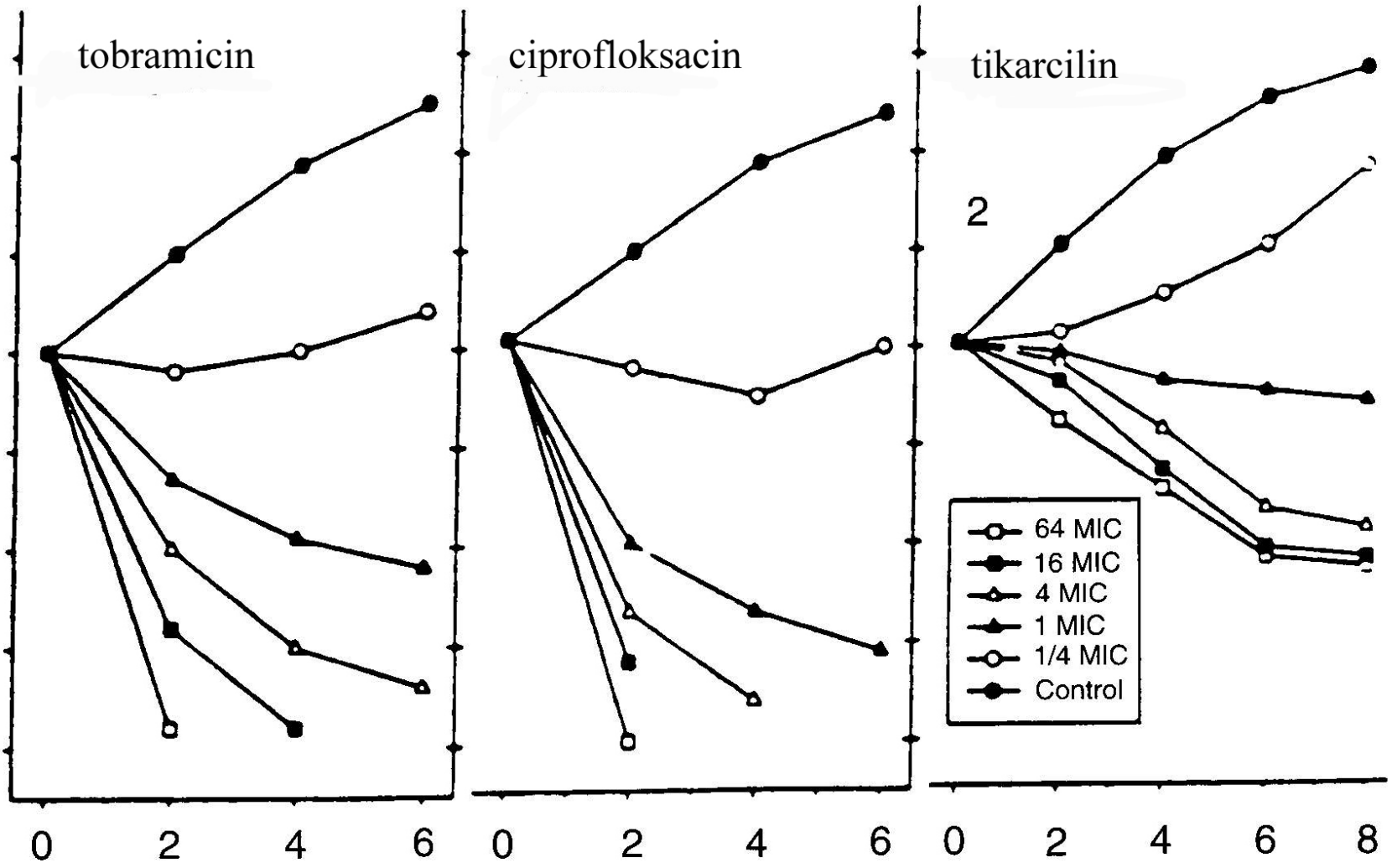
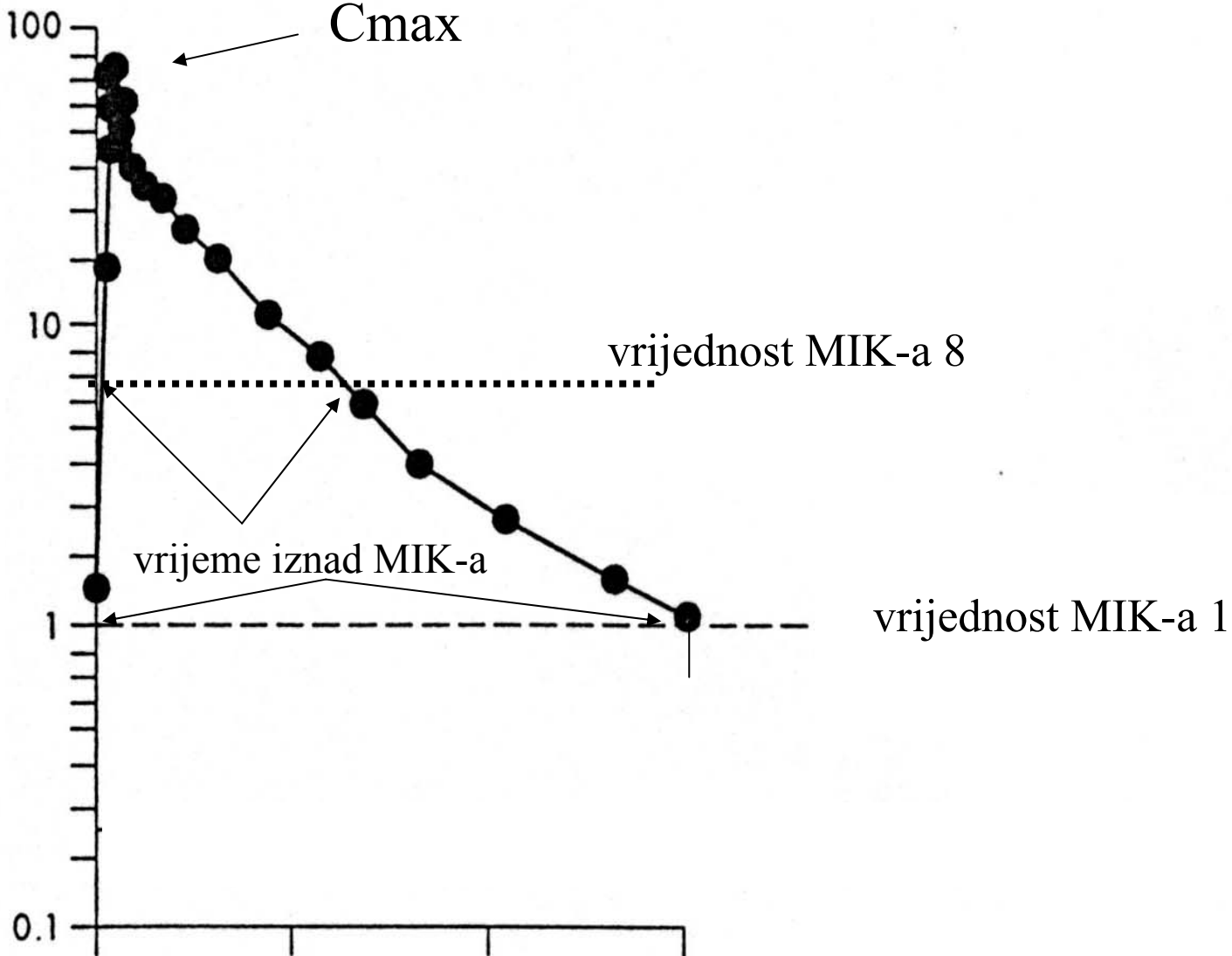


Figure 2 Significant correlations between physiological and pharmacokinetic parameters. Cefepime elimination closely correlated with creatinine clearance (panels **A** and **B**), as abundantly described [15-20]. In addition, more intricate parameters also showed independent negative and positive correlations with drug elimination, as for in-


tobramicin
ciprofloksacin
tikarcilin
2
64 MIC
16 MIC
4 MIC
1 MIC
1/4 MIC
Control
0
2
4
6
0
2
4
6
0
2
4
6
8

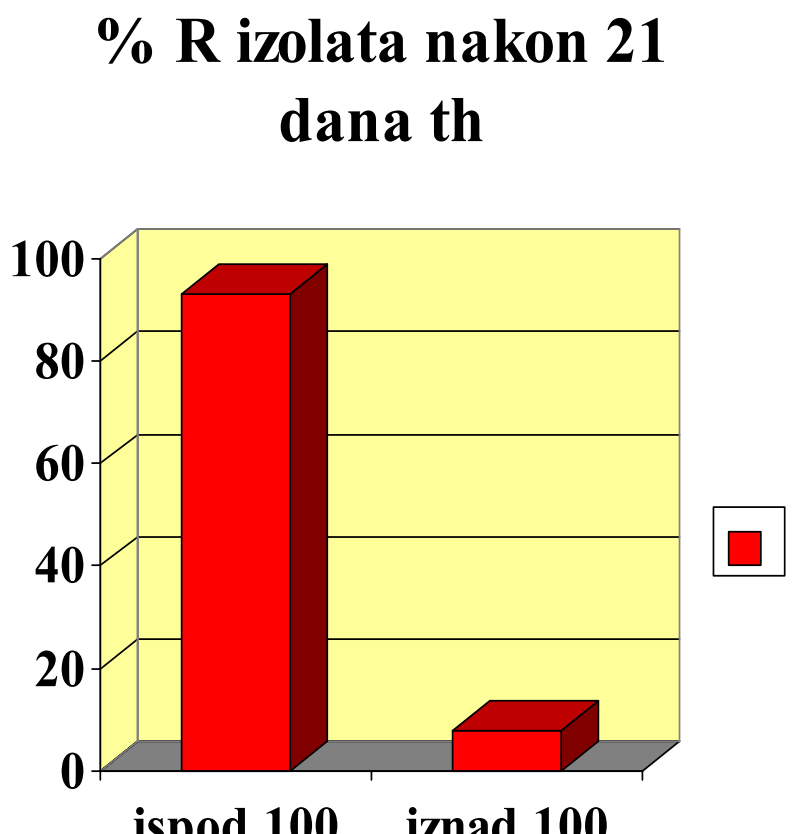

Cmax
100
10
1
0.1
vrijednost MIK-a 8
vrijeme iznad MIK-a
vrijednost MIK-a 1

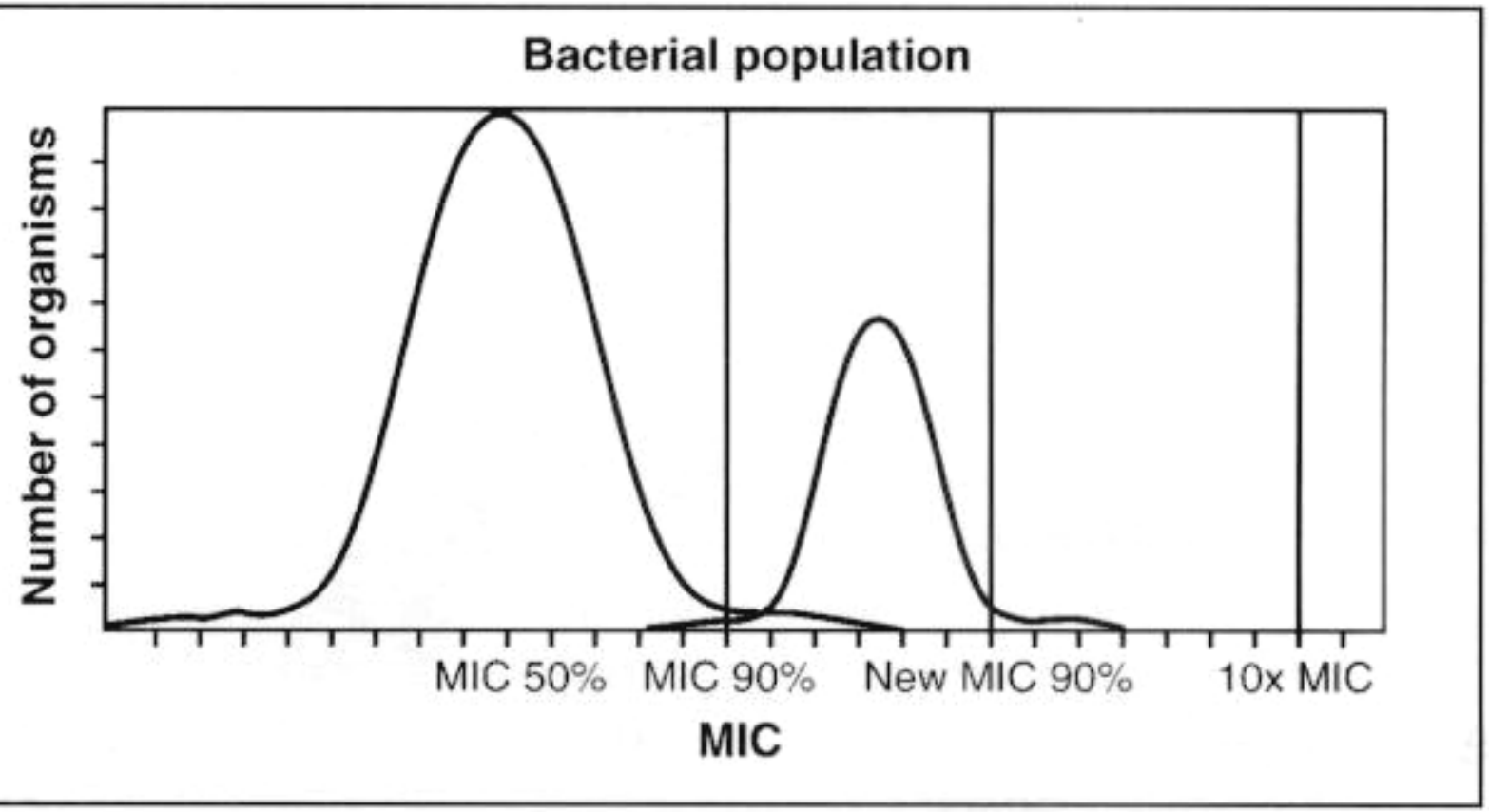
Utjecaj niskih doza na razvoj rezistencije kod bolesnika s bolničkim pneumonijama

kinoloni

UIC= AUC/MIC90

aćen razvoj
rezistencije kod
7 bolesnika



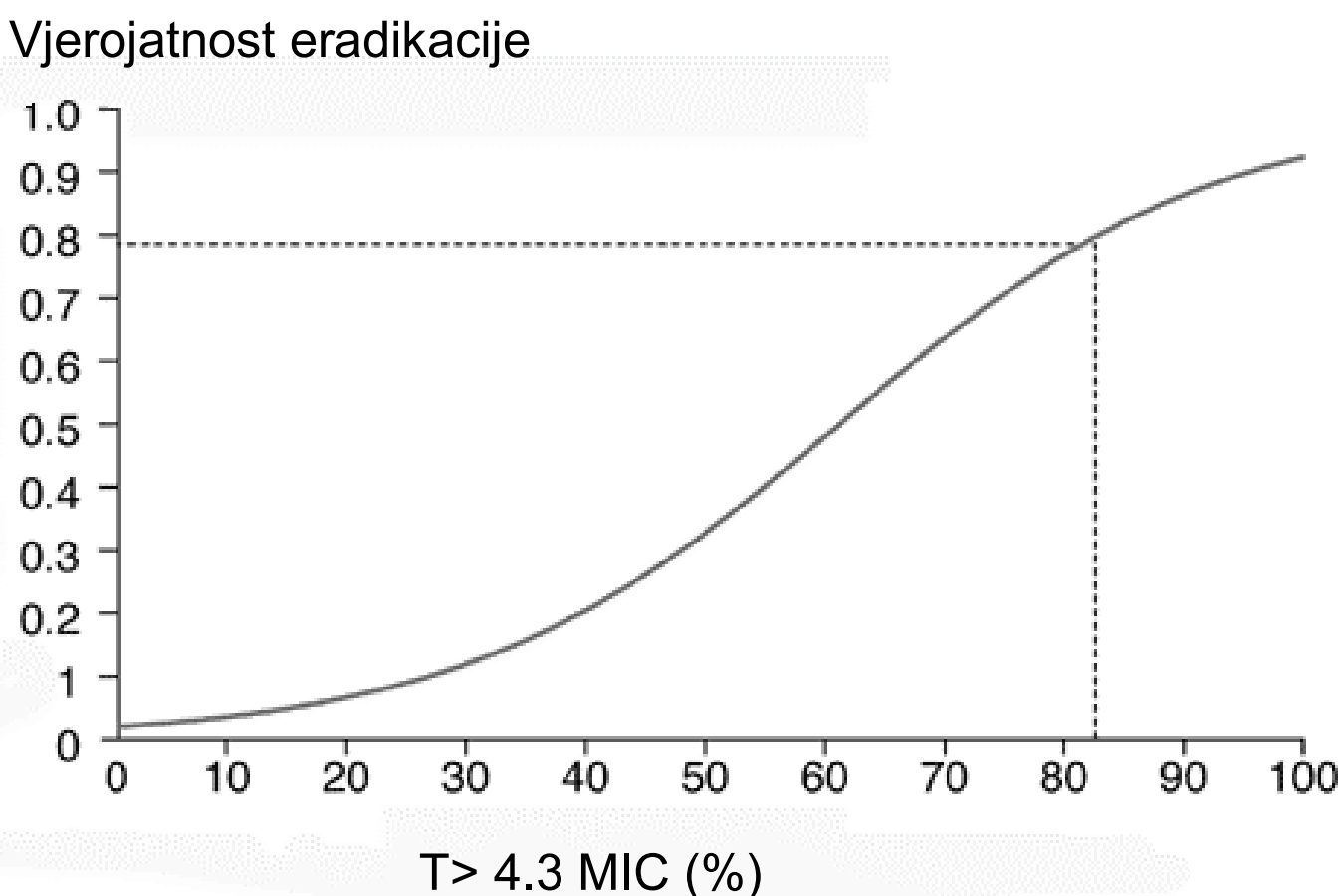


Replication of a population of resistant organisms, resulting in an

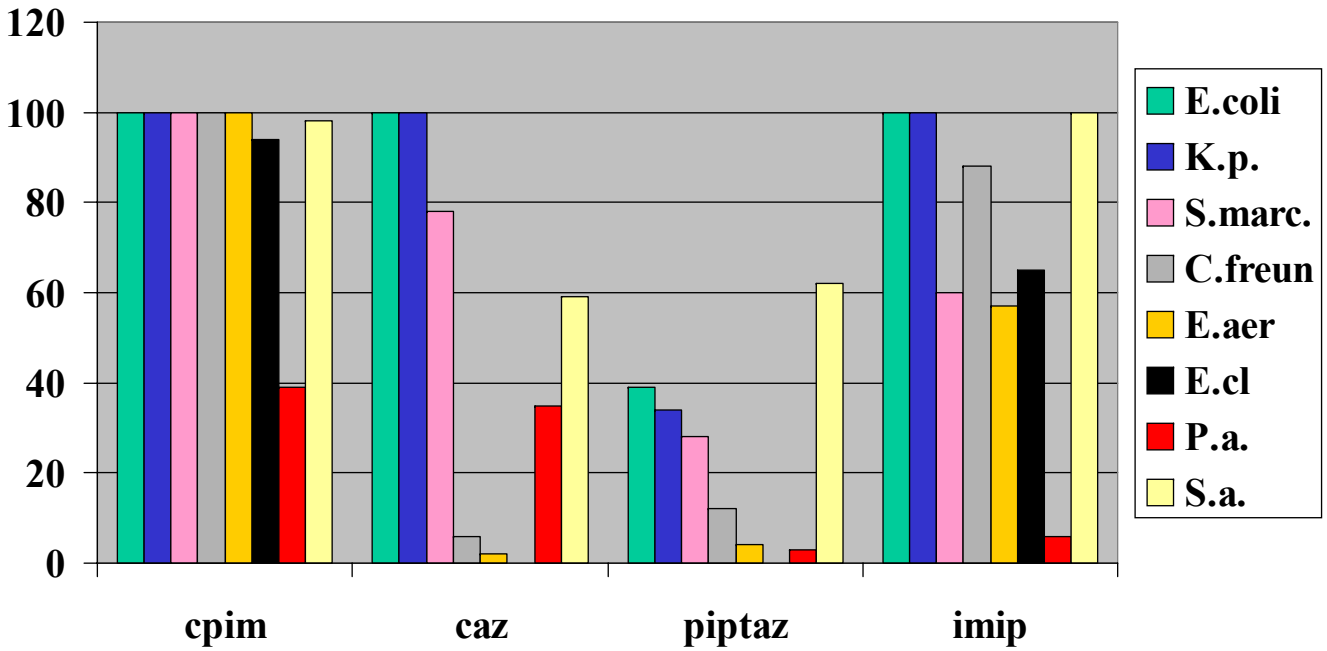
Ciljne vrijednosti AUIC u liječenju pneumonije uzrokovane *S.aureusom* vankomicinom (Moise PA i sur,2000)

Klinički uspjeh	
AUIC <= **345**	21%
AUIC > **345**	78%
Eradikacija	
AUIC< **866**	39%
AUIC >= **866**	91%

Vjerojatnost eradikacije *P. aeruginosa* kod primjene beta-laktamskog antibiotika

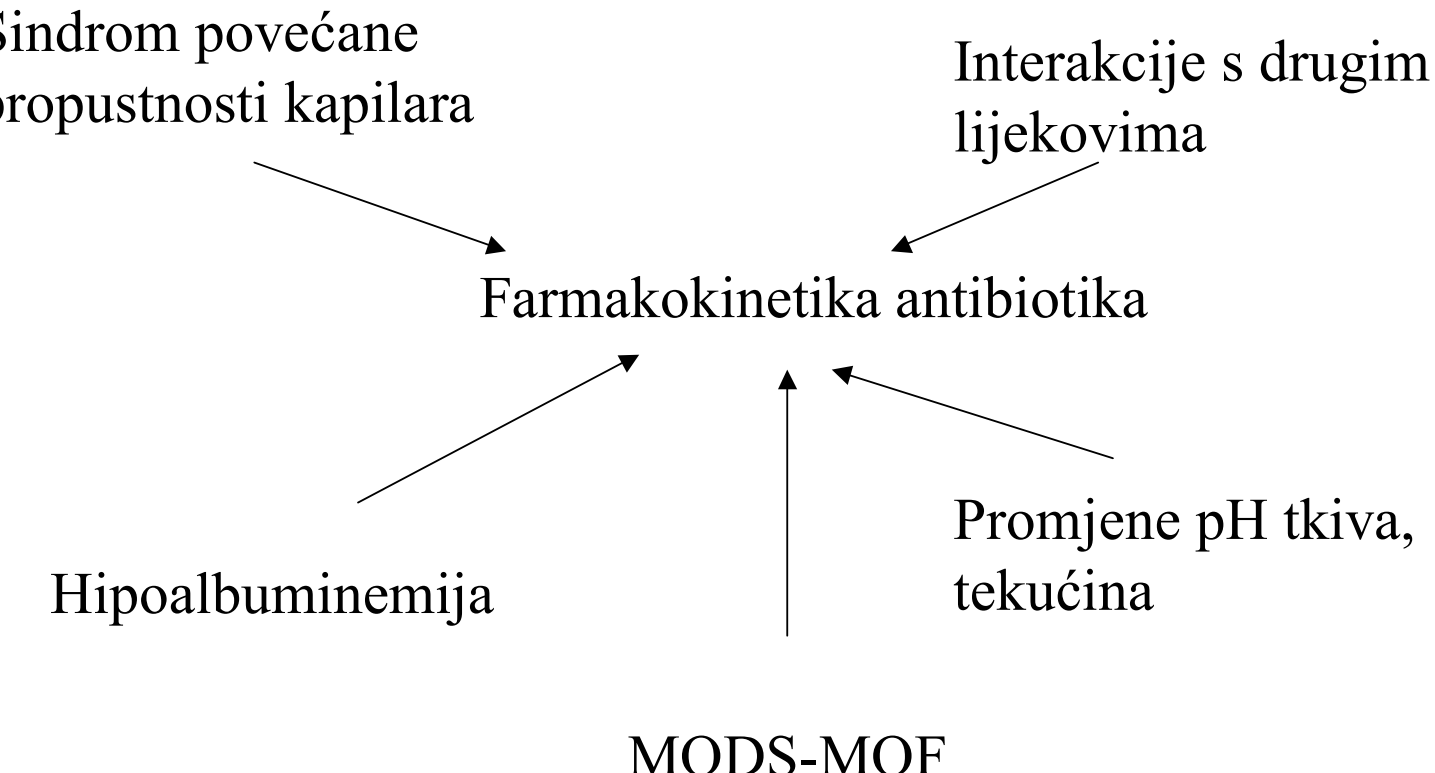


Simulirane vrijednosti T>MIC kod primjene beta-laktamskih antibiotika

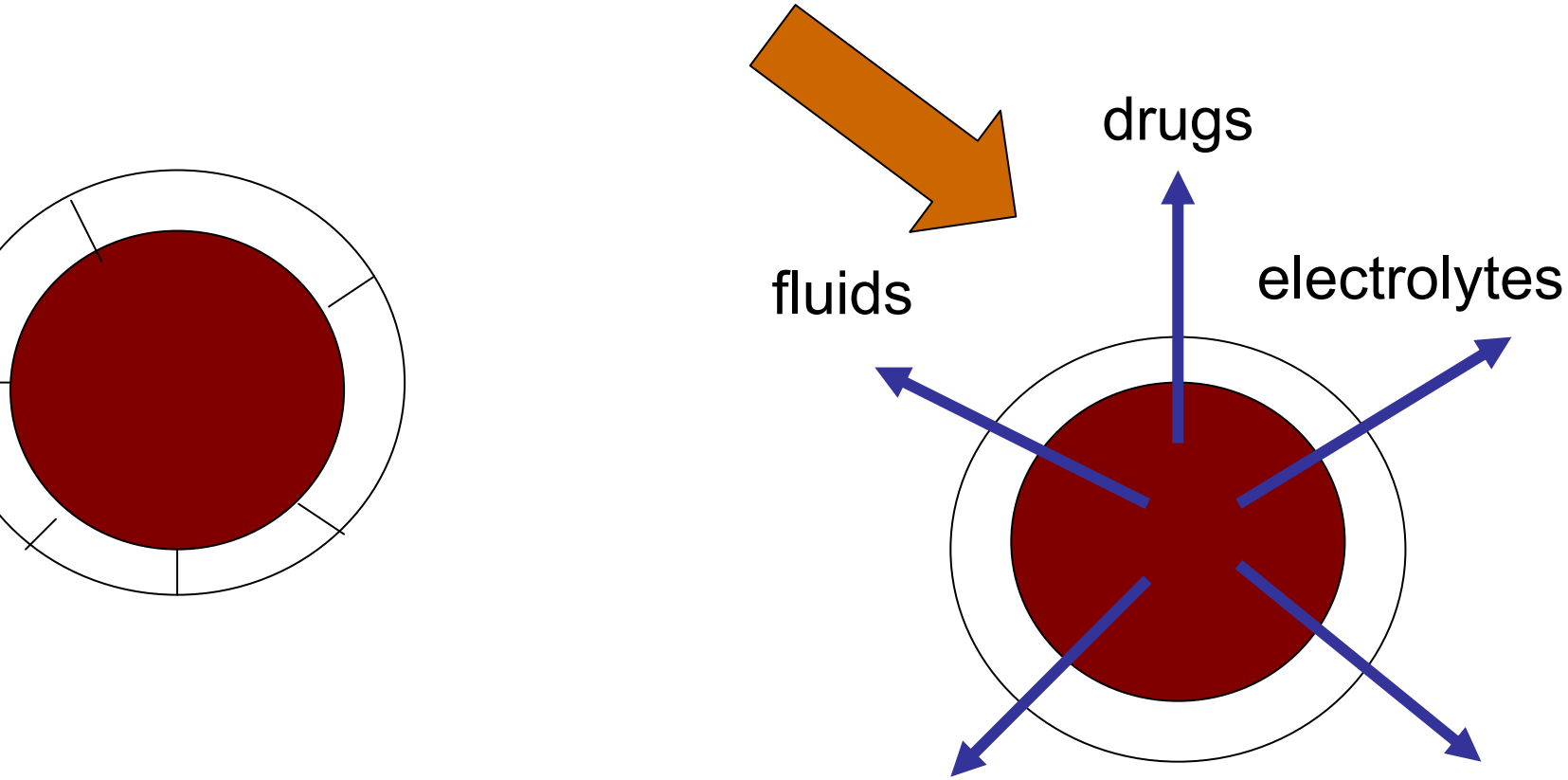


Cefepim 2 x 2g ; ceftazidim 3 x 2 g; piperacilin/tazobaktam 3 x

Čimbenici koji utječu na farmakokinetiku antibiotika u JIM



Capillary leak syndrome



Piperacillin pharmacokinetics in septic shock patients

ssue	shock	volunteers
lasma	265+-54	695 +-132
uscle	27 +-5	216 +-20
ubcutis	13 +-6	118 +-19
D	40.7 +-8.7	9.6 +-1.8

Pharmacokinetic of BL ATB in septic patients

ftriaxone 2g iv (12 pts)

clirens 100% (41 +-12 ml/min ⇧

Vd 90% (20 +-2.2 L)

t 1/2 ⇧ 6.4 +-1.1

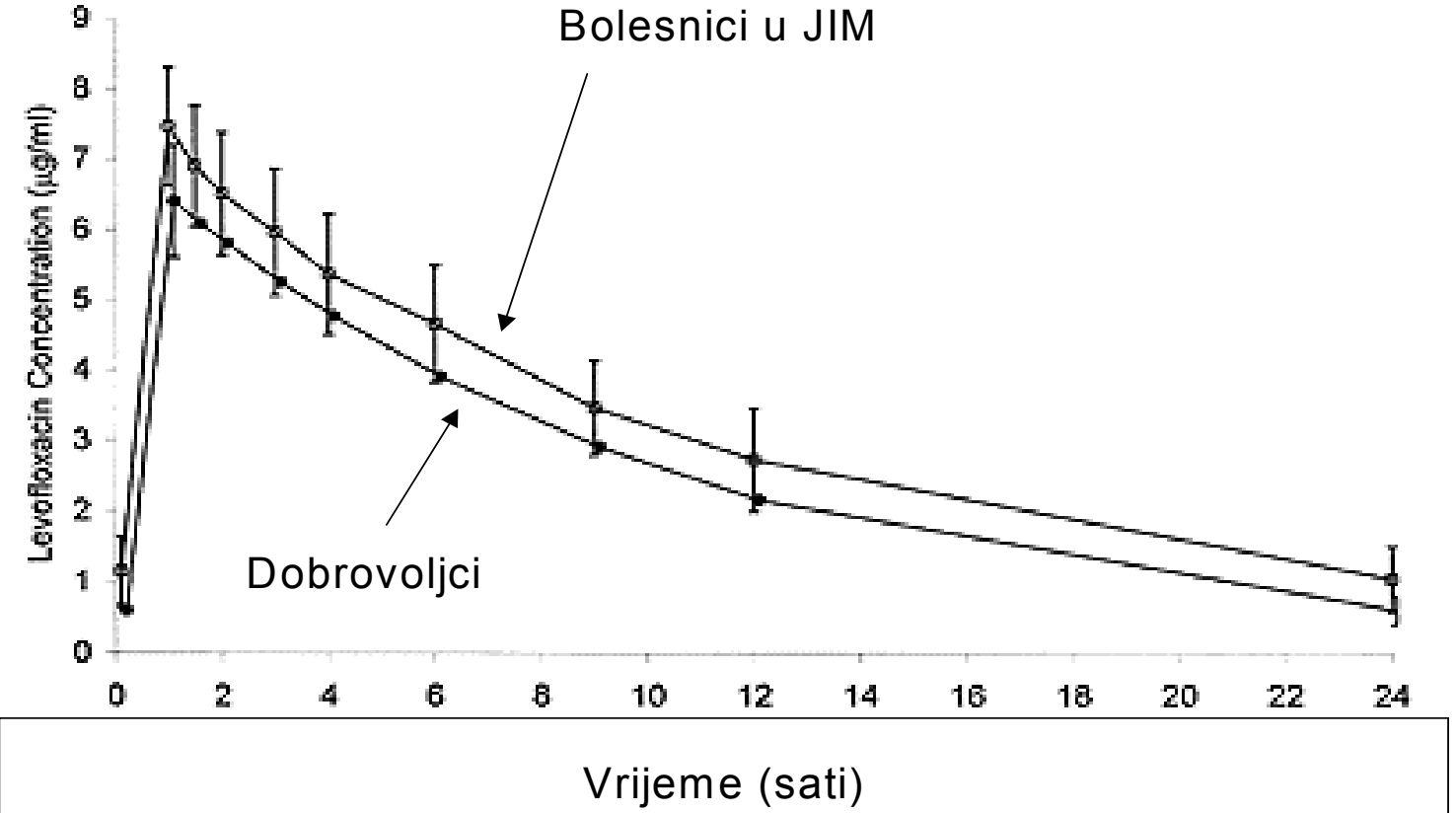
3/9 patients substantially ⇒ suboptimal plasma conc.

Cefpirome 2 x 2 g iv

- Vd (median 26L) ⇧
- t 1/2 (median 2.5 h) ⇧

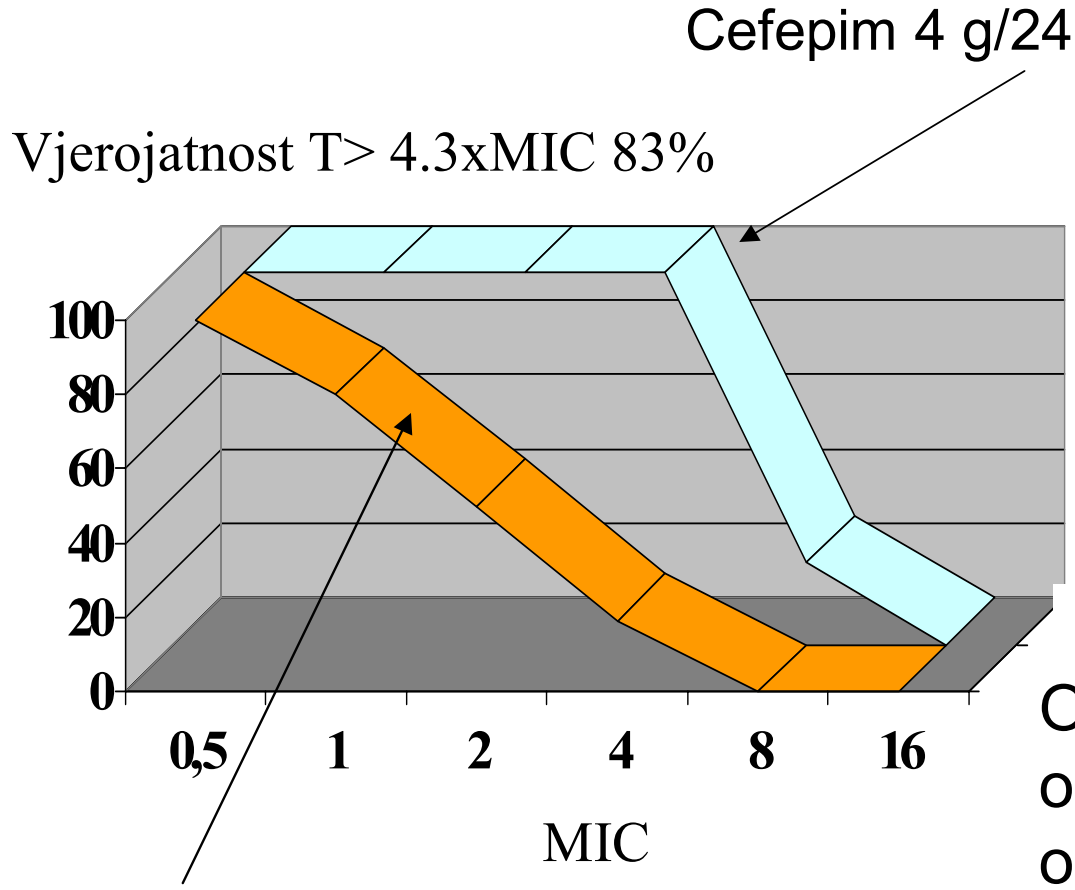
time>MIC >60% achieved only in 5/10 patients

Farmakokinetika levofloksacina kod bolesnika liječenih u JIM

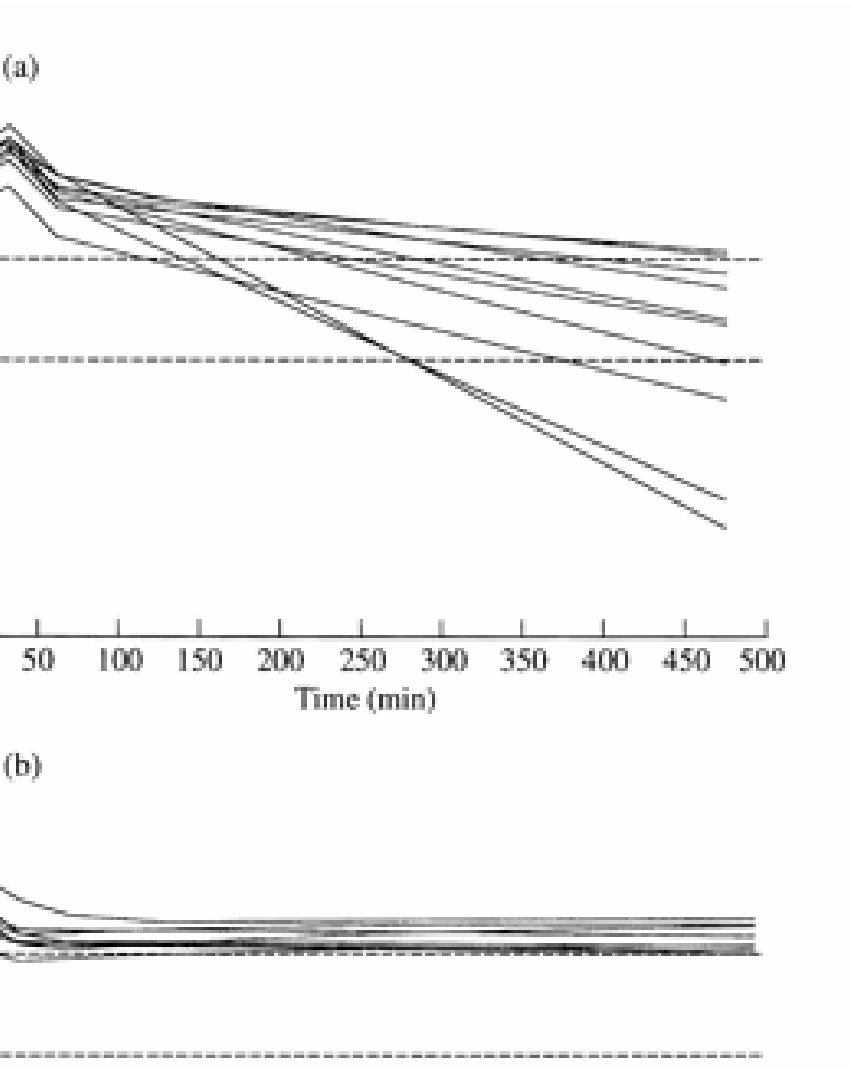


Postupci za postizanje optimalnih FK/FD odnosa

- Primjena jednom dnevno
  - aminoglikozidi
- Primjena viših doza
  - kinoloni
- Kontinuirana primjena:
  - cefepim, ceftazidim
  - meropenem, imipenem (3h)
  - piperacilin, piperacilin-tazobaktam
  - vankomicin



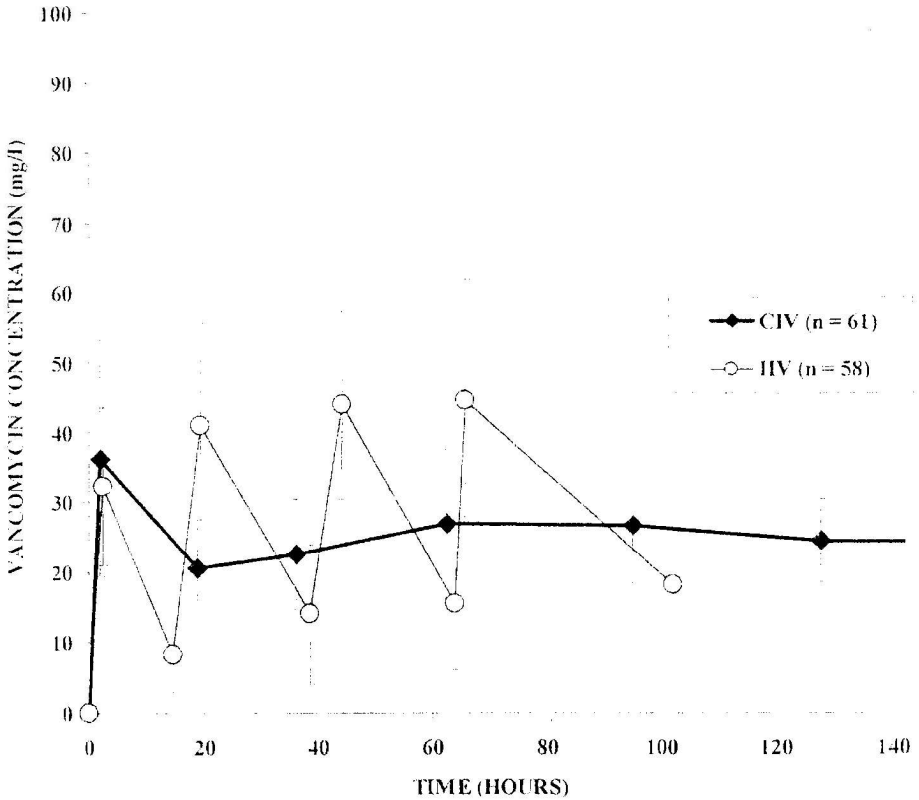
Ovisnost postizanja optimalnog FK/FD odnosa o načinu primjene antibiotika i MIC, kod bolesnika s



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.

Lipman J, JAC 1999

Primjena vankomicina u kontinuiranoj infuziji



anges in serum vancomycin concentrations over time in the two treatment groups. The AUC_{24h} was 577 ± 120 in the CIV group and liter/h in the HV group. The AUC and the daily dose given over 10 days of treatment have less variability between patients with

Kontinuirana infuzija:

- Manje interindividualne varijacije
- Smanjuje potrebe za kontrolom koncentracija
- Brže postizanje odgovarajućih koncentracija
- jeftinija

Utjecaj podešavanja FK/FD vrijednosti na ishod liječenja

Aminoglilozidi

– Cmax:MIC >= 8

Kinoloni

– Cmax:MIC >=10

Betalaktamski atb

– Cmax:MIC 4 mg/L i T>MIC 70%

Table 7
Patients eligible for the study

Period of study:	October 2000–April 2001
Patients included	680
Evaluated for PK/PD	223 (32.8%)
Dose or interval adjusted	84 (37.7%)
Adjustment failed	6 (5 ciprofloxacin; 1 amikacin)

Table 8
Outcome of dose adjustment based on optimising PK/PD indices

	Length hospitalisation(days)[a]	Failure	Mortality
PK/PD analysed	11 (7–16)	39/223 (17.5%)	11 (4.9%)
PK/PD not analysed	16 (9–23)	147/457 (31.9%)	46 (10.1%)

Zaključci

- Liječenje teških infekcija ostaje veliki problem
- Manjak novih aktivnih antibiotika
- Potrebno je poduzeti sve mjere da se osigura optimalno liječenje
  - Deeskalacija
  - Pravovremena primjena
  - Smanjiti rizik nepovoljnih FK/FD odnosa

A new paradigm for treating infections: "go hard and go home"

oman J, Boots R. Crit Care Resusc. 2009 Dec;11(4):276-81.