Le rino-sino-otiti Opinioni a confronto: Il parere del farmacologo

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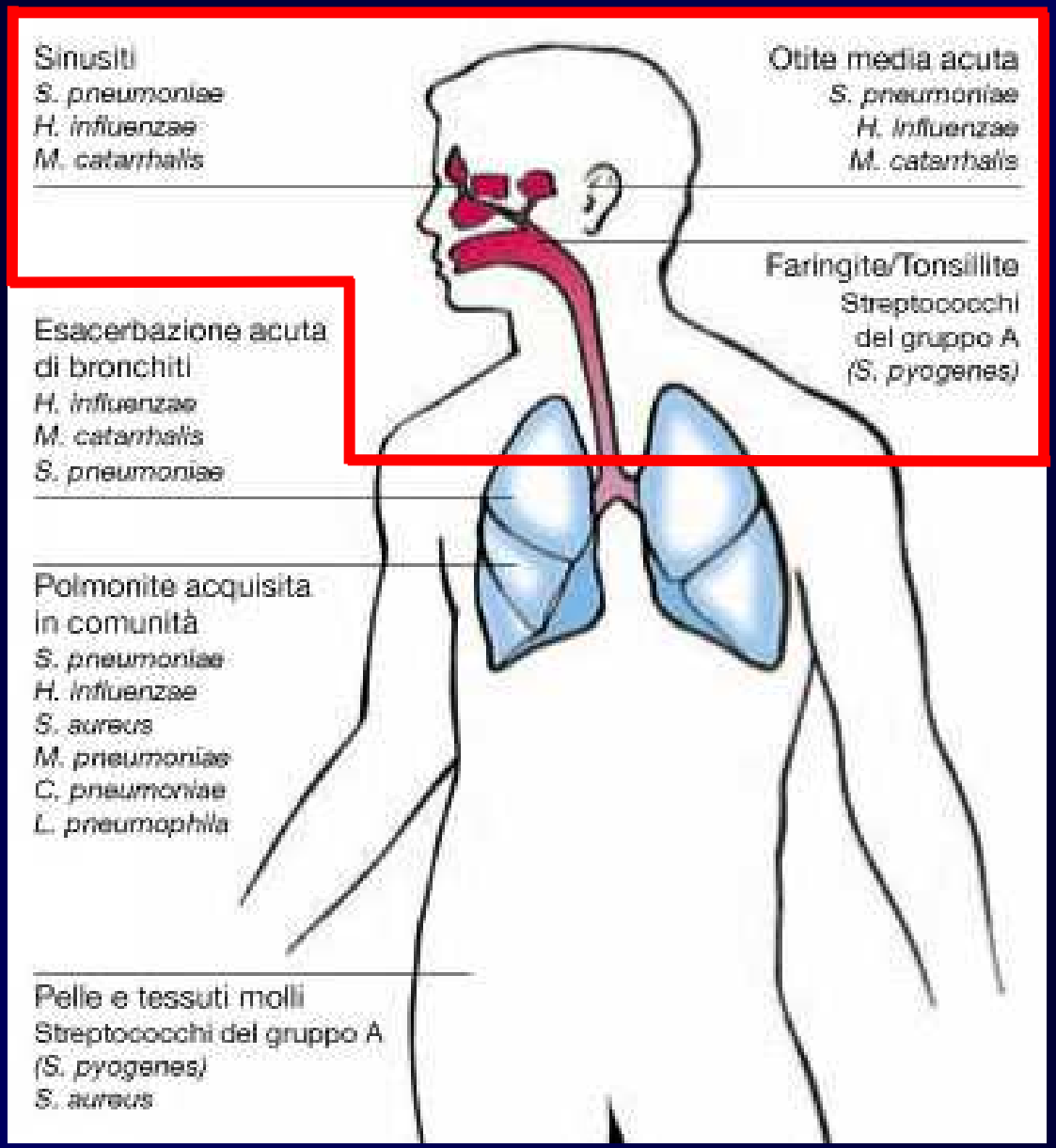
Eziologia batterica nelle infezioni respiratorie



Failure to achieve early bacterial eradication increases clinical failure rate in acute otitis media in young children

Dagan R, Schneider S, Givon-Lavi N, et al.

Pediatric Infectious Disease Journal. 27(3):200-206, March 2008.

Conclusions:

- **In young children with culture-positive AOM, failure to eradicate the pathogen from middle ear fluid within the first few days of treatment leads to a significant risk for clinical failure.**

Persistence of Pathogens Despite Clinical Improvement in Antibiotic-Treated Acute Otitis Media Is Associated With Clinical and Bacteriologic Relapse. Original Studies

Asher, E; Dagan, R; Greenberg, D et al.

Pediatric Infectious Disease Journal. 27(4):296-301, April 2008.

Conclusions:

- Failure to eradicate MEF pathogens during antibiotic treatment is associated with clinical recurrences, even in patients showing clinical improvement/cure at end of treatment
- These recurrences are mostly caused by pathogens initially present in MEF and persisting during treatment

Oral antibiotics with FDA-approved labeling for upper respiratory tract infections in children available in Italy

- **PENICILLIN**
  - amoxicillin (H.D.)
  - amoxicillin-clavulanate (H.D.)

- **CEPHALOSPORINS**
  - **SECOND-GENERATION**
    - cefaclor
    - cefprozil
    - cefuroxime-axetil
  - **- THIRD-GENERATION**
    - cefixime
    - cefpodoxime
    - ceftibuten
    - cefditoren

- **MACROLIDE**
  - azithromycin
  - clarithromycin

McCracken GH, Ann Emerg Med, 2002, mod.

A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media

Noel GJ, Blumer JL, Pichichero ME, et al.

Pediatric Infectious Disease Journal. 27(6):483-9, June 2008.

Conclusions:

- **Levofloxacin was not inferior to amoxicillin/clavulanate for the treatment of recurrent and/or persistent AOM in infants and children**

Antimicrobial drugs

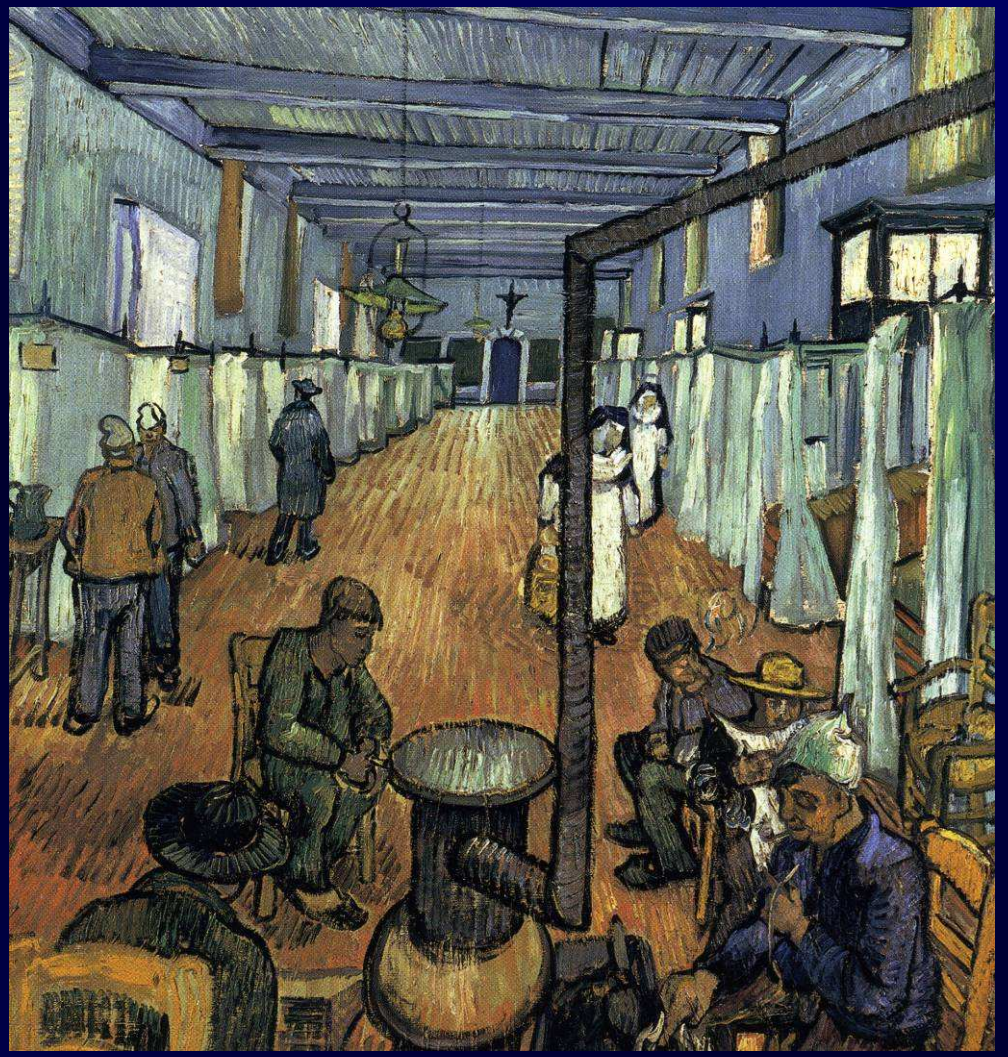
PK/PD parameters predictive of therapeutic outcome

Parameter correlating with efficacy	C_{max}/MIC	AUC/MIC	T > MIC
Examples		New macrolides	Penicillins Cephalosporins Natural macrolides
Organism kill		Concentration-dependent	Time-dependent
Therapeutic goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Nicolau DP, J Infect Chemother, 2003, mod.

MACROLIDI

The Sick-Ward of the hospital in Arles



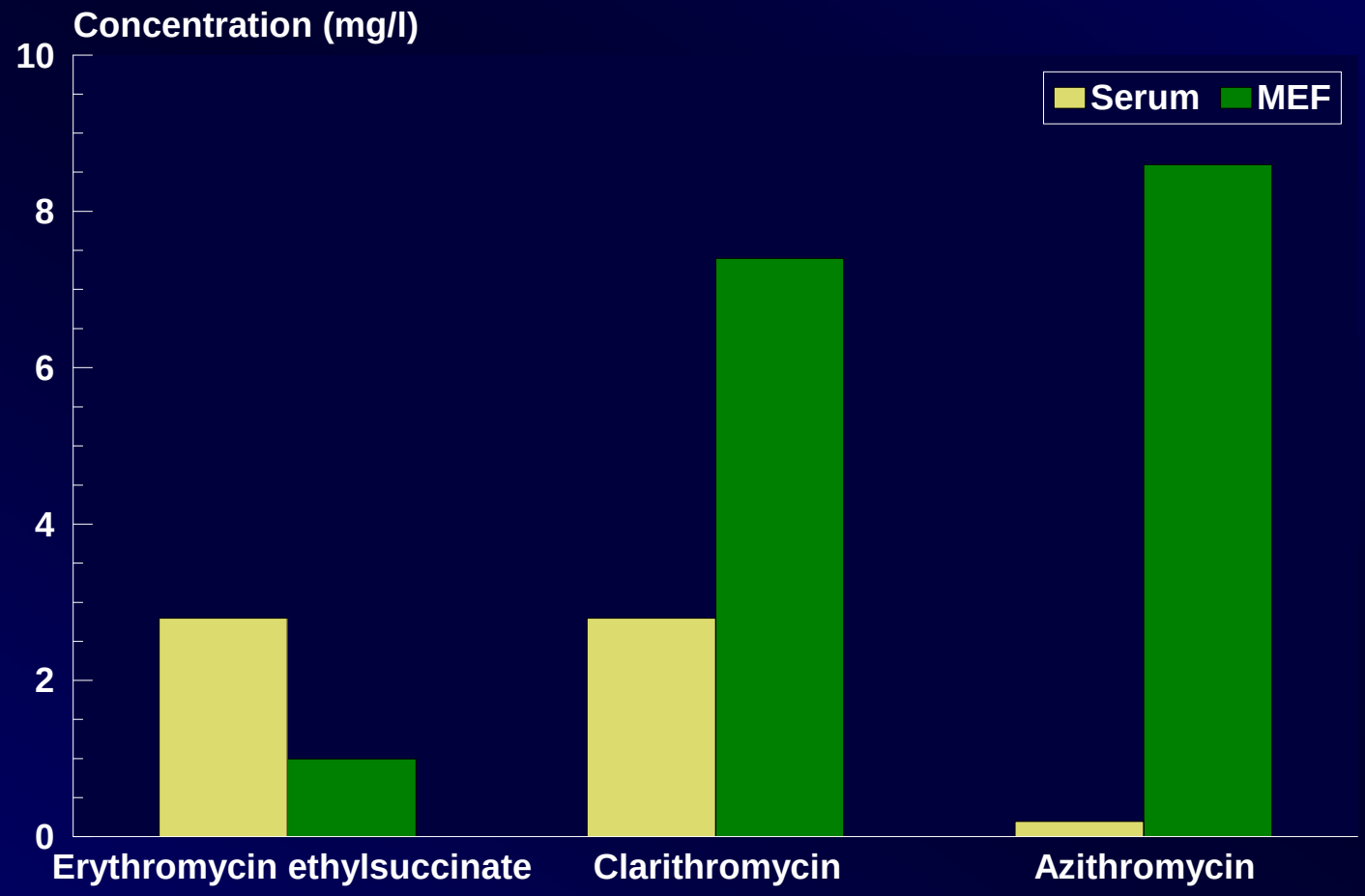
Vincent Van Gogh - 1889

Principali parametri farmacocinetici dei macrolidi

Parametro	Eritromicina	Roxitromicina	Claritromicina	Azitromicina
Biodisponibilità (%)	≤ 20	60	55	37
C_{max} (mg/l)	0,6 - 3,2	7 - 11,8	0,9 - 3,5	0,2 - 0,4
Legame farmaco-proteico (%)	65 - 90%	> 90%	65 - 70%	12 - 50%
t1/2 (h)	1,5 - 3	9 - 13	4 - 5	>40
Conc. Polmone (ELF) (mg/Kg)	4.2	5.6	29,5	3,9
Conc. tonsilla (mg/Kg)	0,9 - 1,4	1,8 - 2,7	5,3 - 6,7	7,4 - 14,2
Tessuti/siero	0,5 - 3,0	0,2 - 3,0	1,0 - 7,0	1,0 - >30,0
Posologia (mg/h)	250/6-500/12	150-300/12-24	500/12	500/24

Macrolides

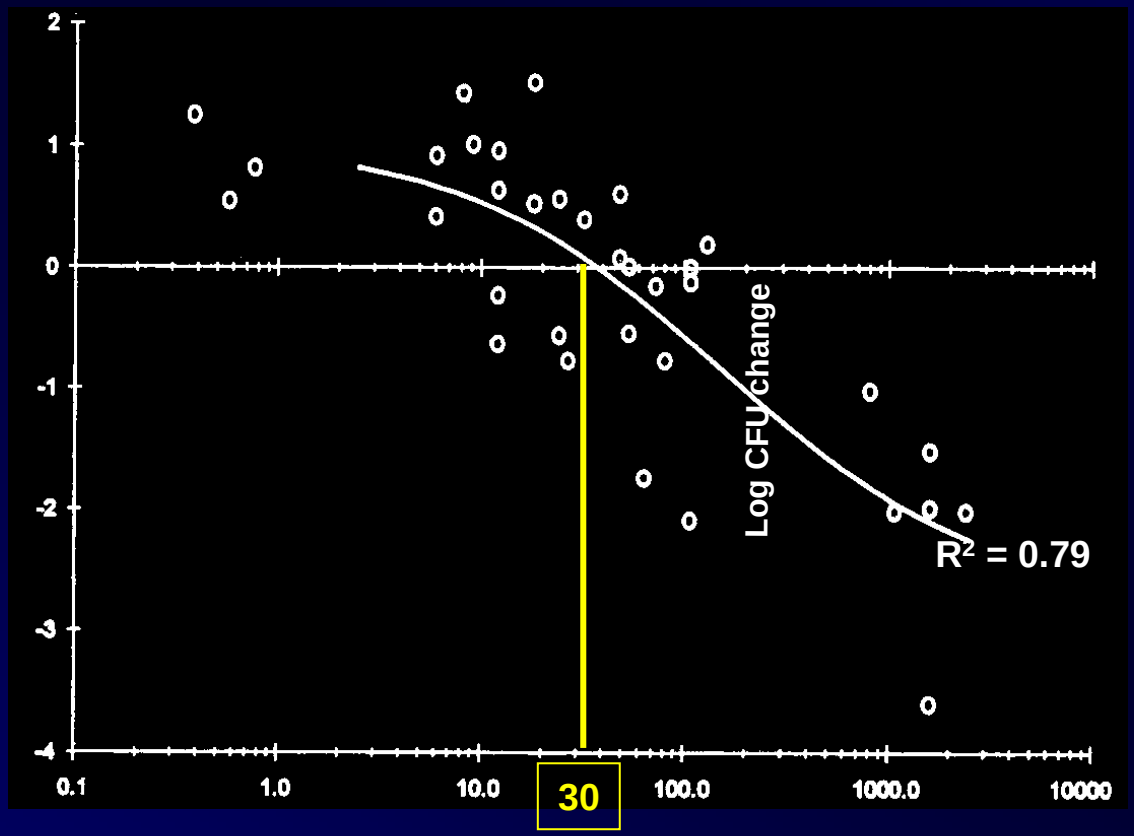
Serum and middle ear fluid (MEF) levels with standard regimens



Harrison CJ, Pediatr Infect Dis J, 1997

Clarithromycin
Murine model of pneumococcal pneumonia

PK/PD correlation



AUC/MIC

Tessier PR et al., Antimicrob Ag Chemoter, 2002

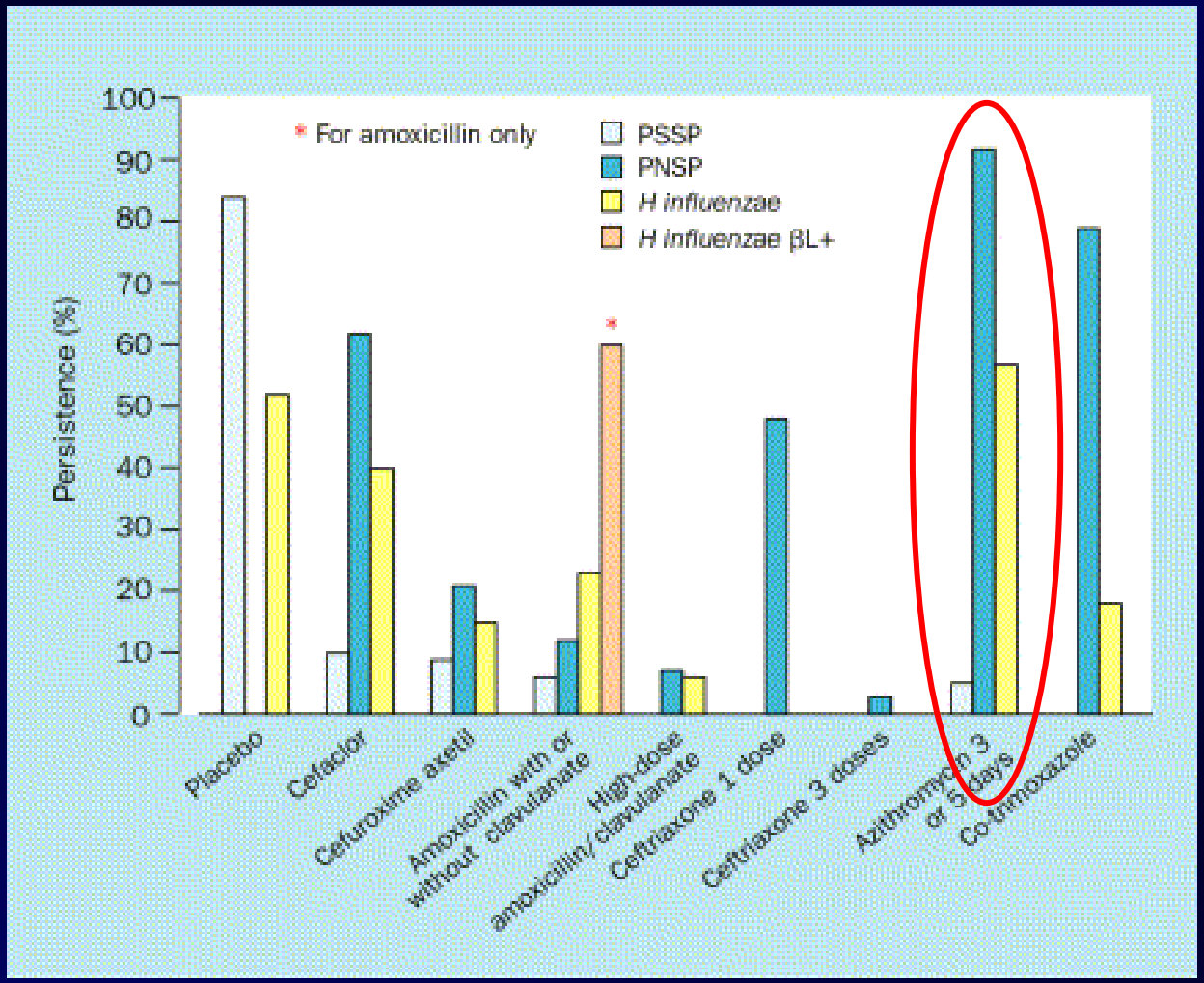
PK/PD parameters of macrolides in URTIs

	Azithromycin 500mg p.o. ODx3 days		Clarithromycin 250mg p.o. BIDx4-5 days	
Parameter	**Serum**	**TONSIL**	**Serum**	**TONSIL**
C_{max} (mg/l)	0.13-0.41	12.1	1.8-2.1	5.3 -6.7
AUC (mg/l·h)	2.4-2.6	69.1	9.2	71.2-74.7
$AUC/MIC_{0.5}$	5.0	138	18.4	142-149
$AUC/MIC_{2.0}$	1.2	34.6	4.6	35.6-37

Chu S-y et al., 1993; Patel KB et al., 1995, 1996; Fraschini F et al. 1991;
Blandizzi C et al. 2002; Foulds G et al., 1990;

Acute otitis media in children

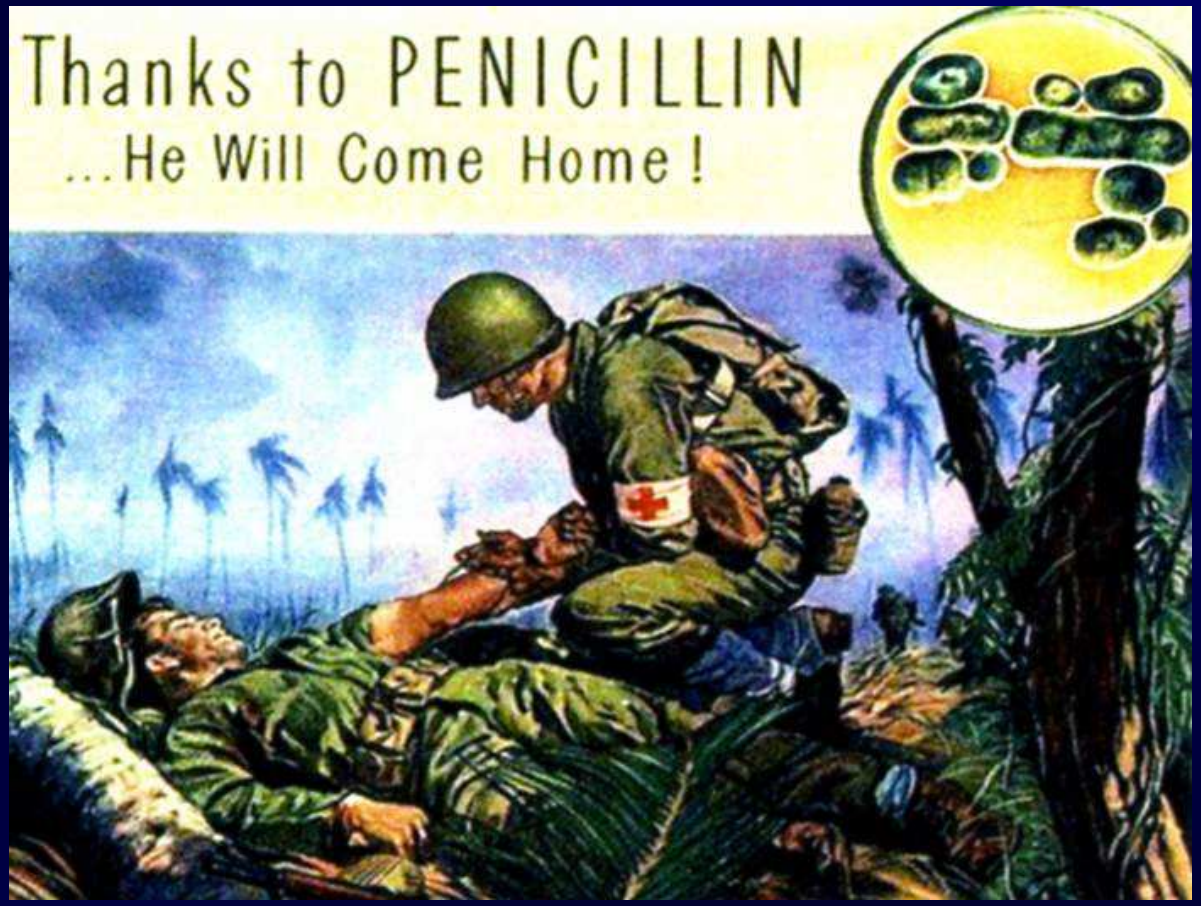
Bacteriological eradication rates



Dagan R & Leibovitz E, The Lancet Infect Dis, 2002

A poster from World War Two

BETALATTAMINE



Acute otitis media in children*

Pharmacodynamic target attainment of oral beta-lactams** for AOM-causing pathogens

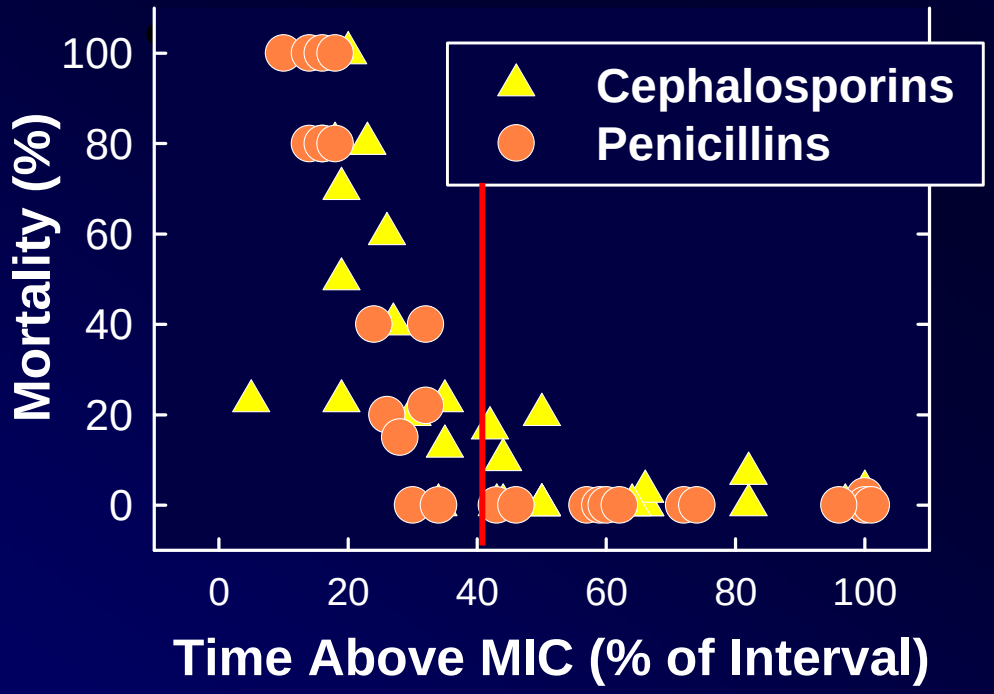
Co-amoxi/clav (45 mg/kg BID)	85.7%
Amoxicillin (30 mg/kg TID)	70.8%
Cefpodoxime proxetil (5 mg/kg BID)	87.5%

* mean age = 12.5 months
** amoxicillin, co-amoxiclav, cefprozil, cefuroxime-axetil, cefpodoxime-proxetil, ceftibuten – 5000 patients MonteCarlo simulation

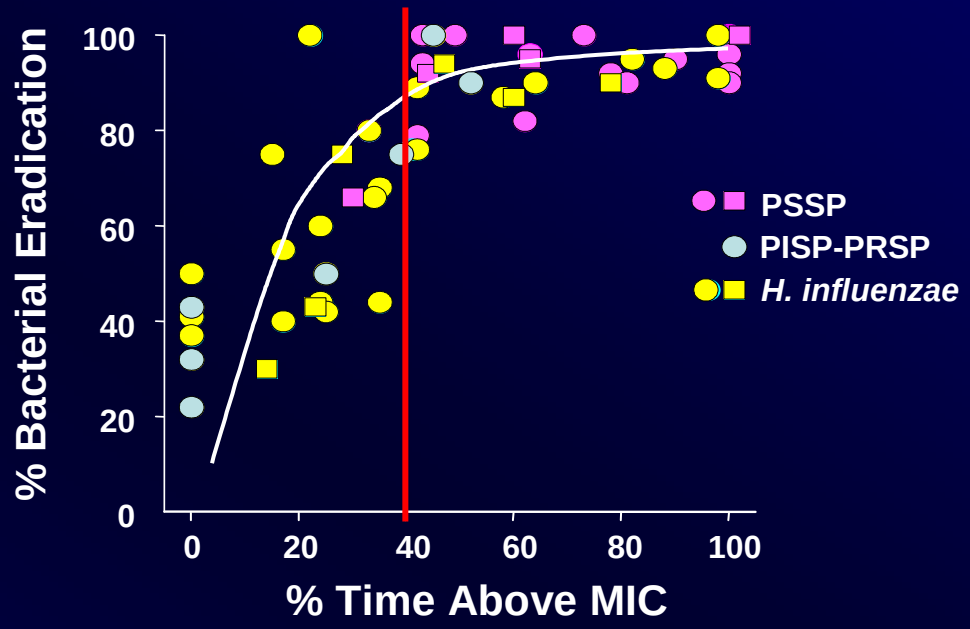
Fallon RM et al., Pediatr Drugs, 2008

Relationship between T>MIC for β-Lactams with survival in animal models and bacterial eradication in otitis media and sinusitis

Animals – Literature review



Double Taps in Otitis Media / Sinusitis



PSSP = penicillin-susceptible *S. pneumoniae;* PISP = penicillin-intermediate *S. pneumoniae;* PRSP = penicillin-resistant *S. pneumoniae.*

Craig WA. *Infect Dis Clin North Am.* 2003;17:479-501

Cefprozil 6 mg/kg BIDx4 days

Survival studies in mice infected with S. pneumoniae strains

MIC	T > MIC %	Mortality	
		no. animals	%
0.1- 0.5	82 - 100	3/147	2.0
1.0 - 2.0	50 - 66	1/155	0.6
3.0 - 4.0	35 - 42	27/109	24.8
> 4.0	5 - 19	50/121	41.3

Nicolau DP et al., Antimicrob Ag Chemother, 2000

Cefaclor MR 750 mg BIDx10 days in 36 pts with AECB

PK/PD correlations

MIC*	n. cases	Cmax/MIC	T>MIC %	% bacteriological result
< 2.0	26	10 - 90	> 40%	100
2.0 - 4.0	5	1 - 10	> 40%	100
> 4.0	5**	0 - 1	≤ 40%	0

*8 *S. pneumoniae* Pen-S; 5 *S. pneumoniae* Pen-R; 15 *H. influenzae*; 8 *M. catarrhalis*
**4 *S. pneumoniae* Pen-R; 1 *H. influenzae*

Cazzola M. et al., J Chemother, 2000

Parametri farmacocinetici di betalattamine orali in pediatria

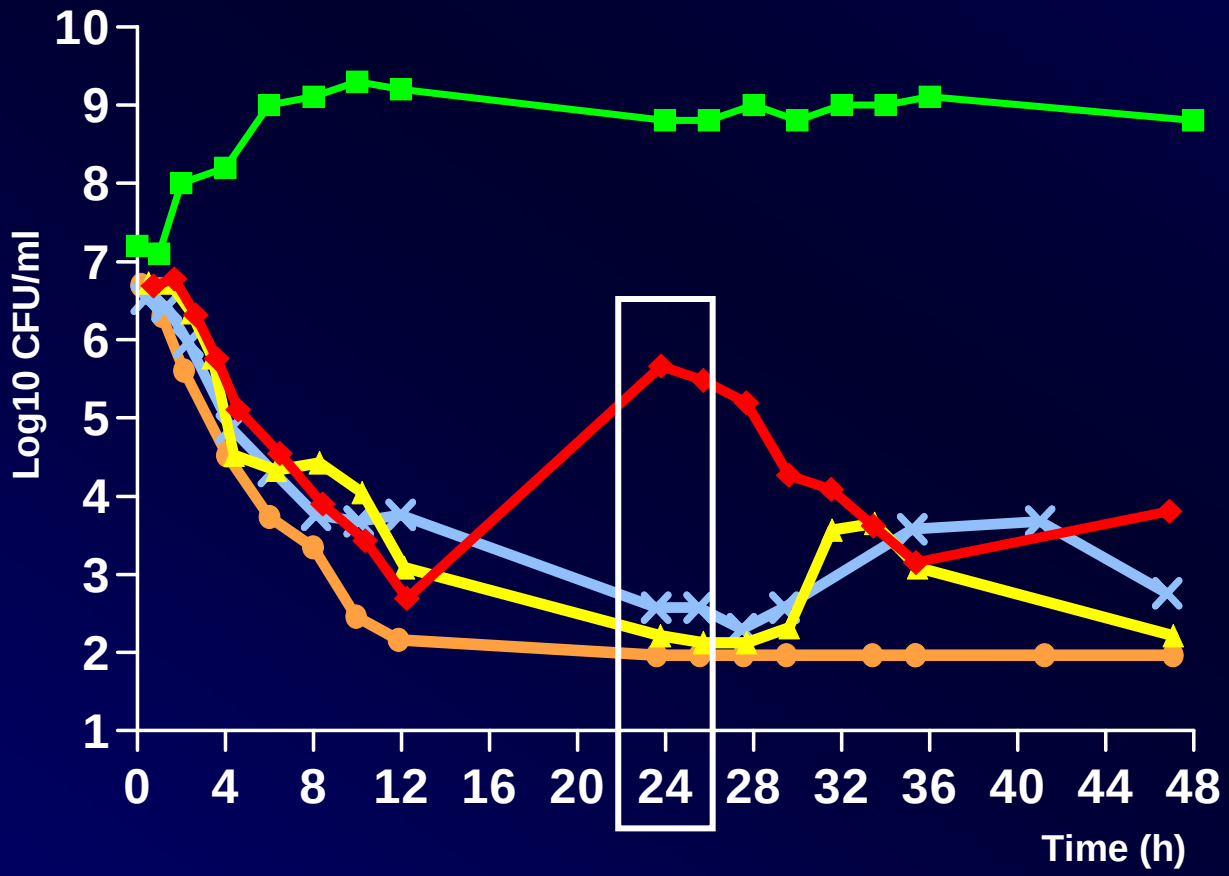
Betalactam	Dose (mg/kg)	C_{max} (mg/l)	T_{max} (h)	$t_{½}\beta$ (h)	fu (%)	Bioavail. (%)	Dosing inter. (h)	Linear kinetics
Amox/Clav*	22.5/3.2	12.0/5.5	1.3	1.2/1.0	75/60	90/75	12	yes
Cefaclor*	20	13.1	1.0	1.0	71	95	8/12	yes
Cefprozil*	15.0	11.2	1.2	1.6	60-70	89	12	yes
Cefuroxime axetil**	15.0	5.1	2.7	1.4	--	35-50	12	yes
Cefixime*	8.0	3.1	4.5	4.1	15	40-50	24	no
Ceftibuten*	9.0	8.6	2.0	2.1	70	85	24	yes/no***
Cefpodoxime proxetil**	6.0	3.1	3.0	2.3	46	50	12	yes

* intrinsic bioavailability ** prodrug *** for doses > 9 mg/kg

Periti P et al., 1988; Mandell GL et al., 1996; Klepser ME et al., 1995; Greenwood D, 1989

S. pneumoniae 237 pen-S

Bacterial activities of oral betalactams*

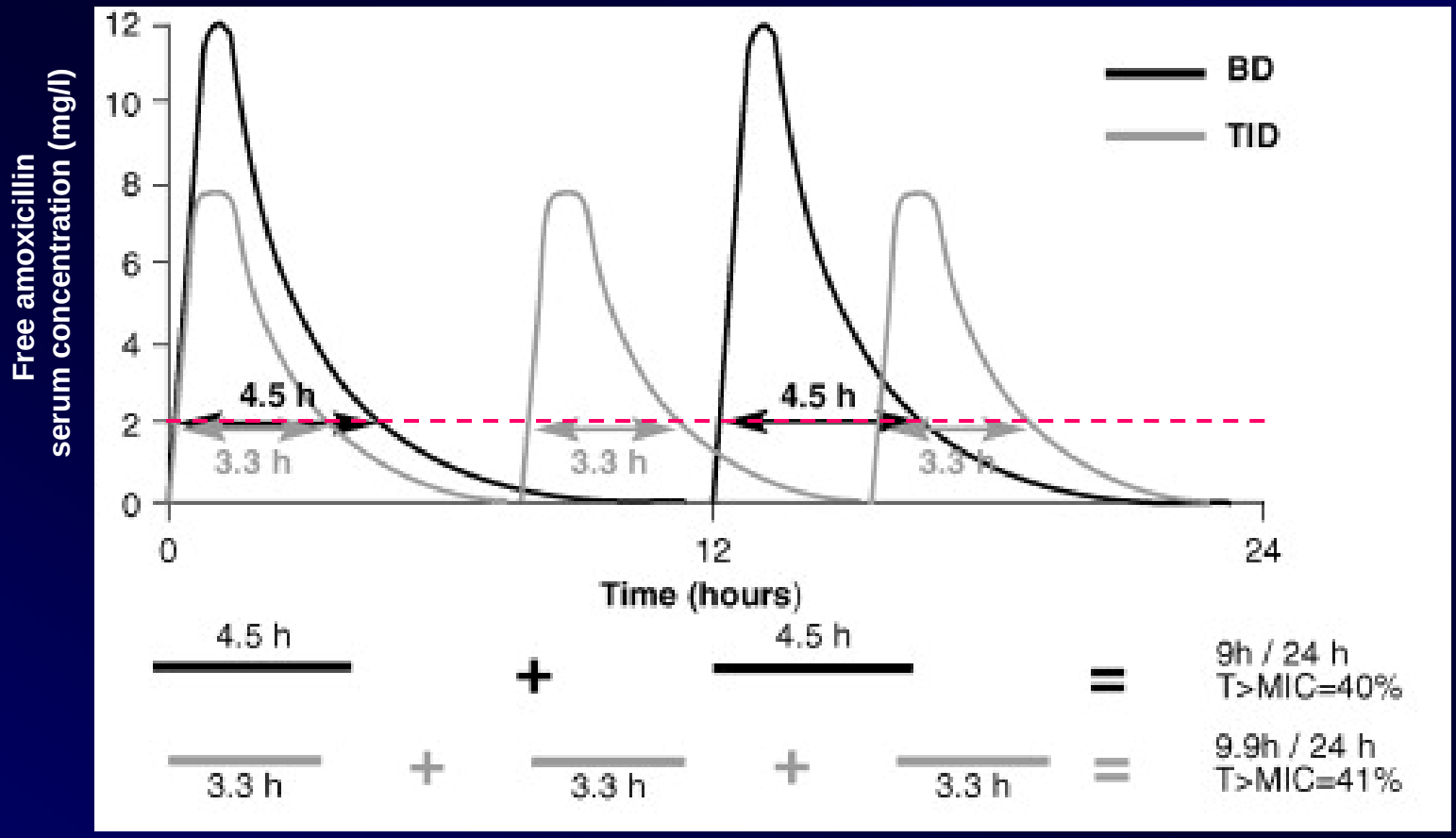


Control
Penicillin VK 26 mg/kg QD
Cefprozil 15 mg/kg BID
Cefaclor 13.4 mg/kg TID
Cefixime 8 mg/kg OD

* In vitro model simulating human pharmacokinetics
Cappelletty DM & Rybak MJ, 1996

Co-amoxiclav

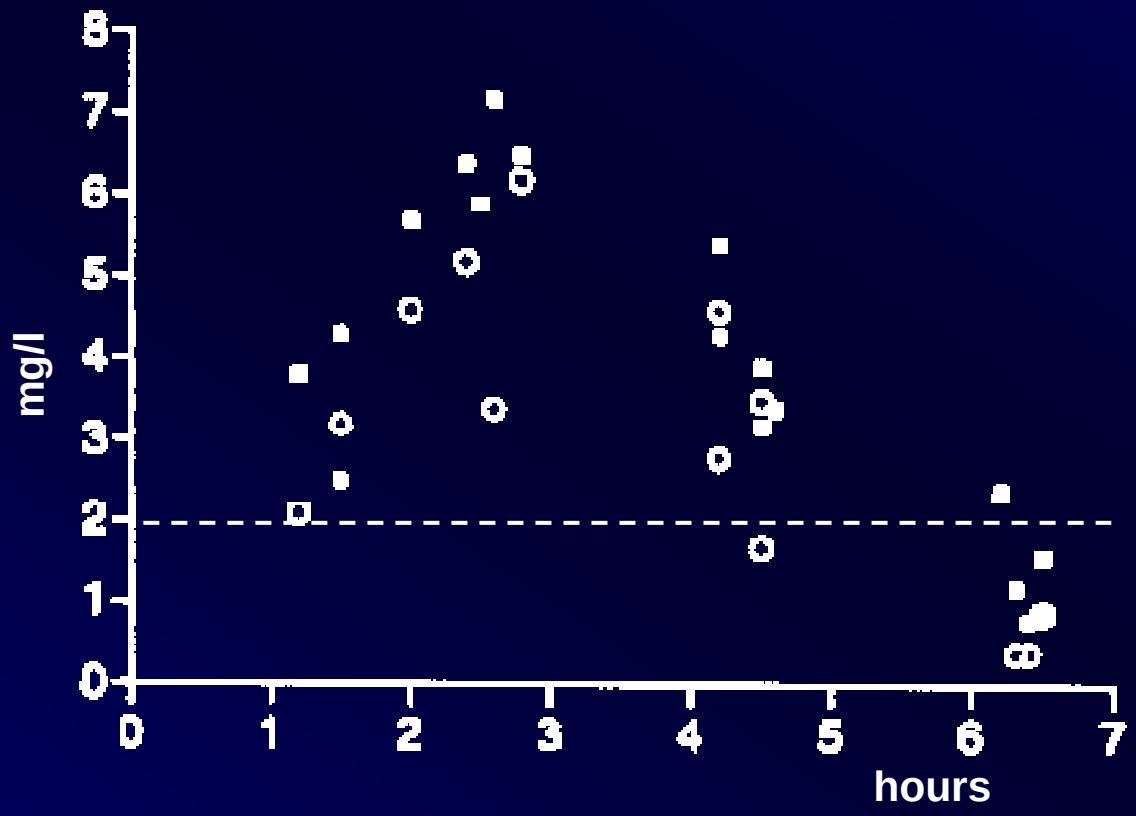
Theoretical free drug serum concentration time curve for 500 mg TID and 875 mg BD



Bax R, Int J Antimicrob Agents, 2007

Amoxicillin 20mg/kg*

Concentrations in middle ear fluid



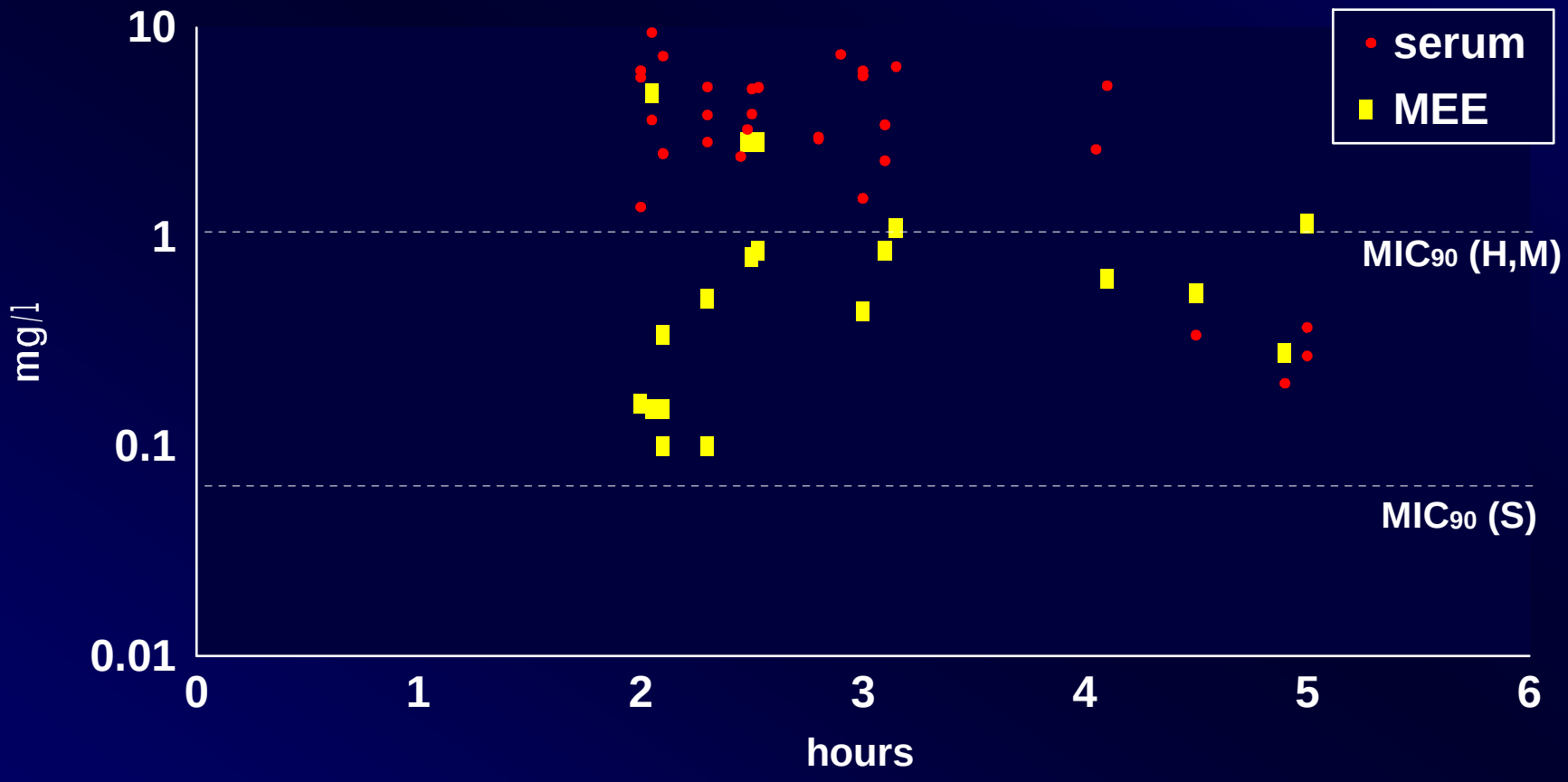
	AUC (mg/l·h)
■ free-cell fluid	23.0
○ total	16.8

*administered as amoxicillin/clavulanic acid (4:1 ratio)

Scaglione F et al., Antimicrob Agents Chemother, 2003

– – – – breakpoint S≤ 2mg/l for S. pneumoniae (CLSI)

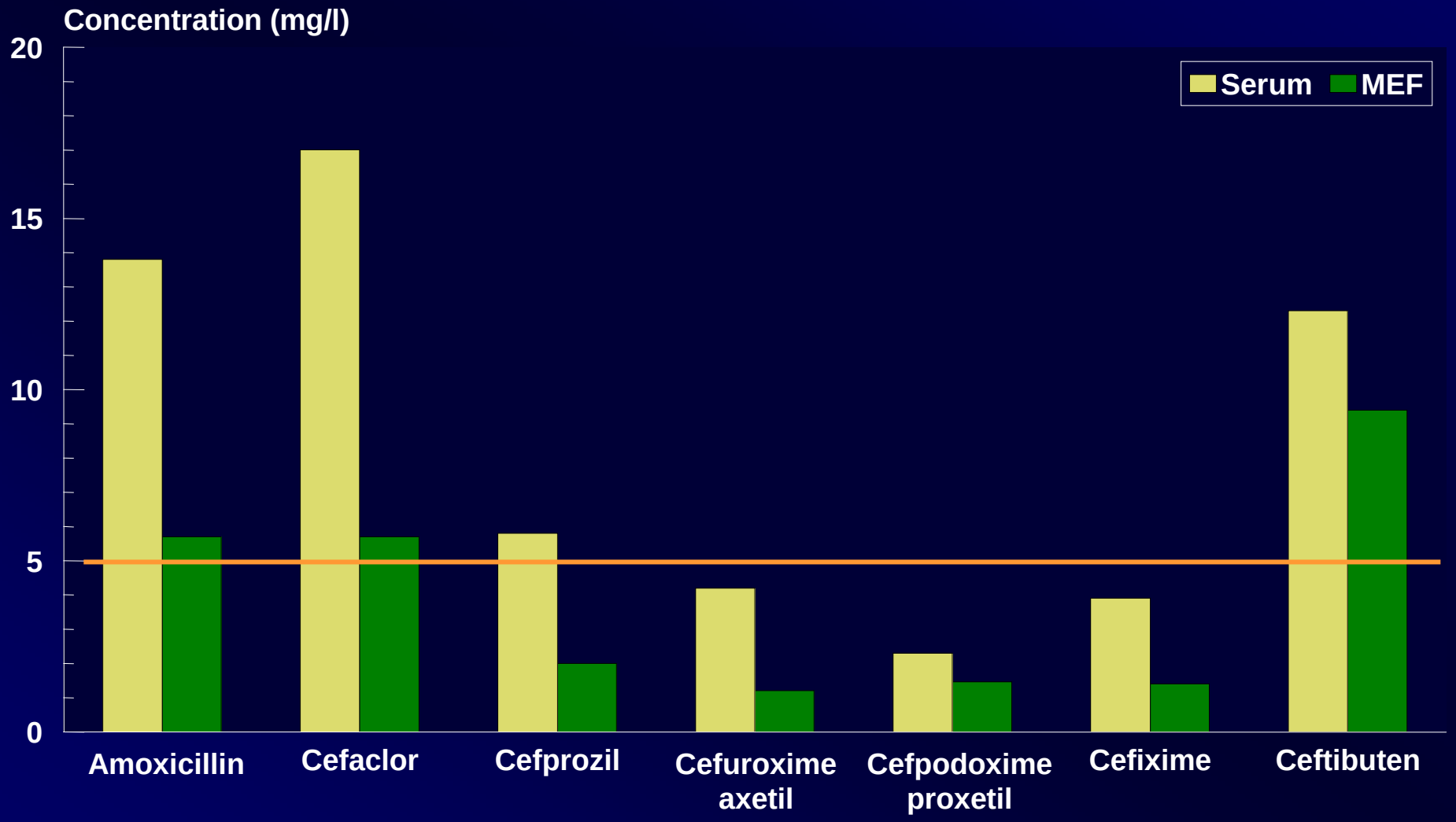
Cefuroxime axetil 250 mg (31 children)



H=H. influenzae, M=M. catarrhalis, S=S. pneumoniae
Haddad et al., 1991

Betalactams

Serum and middle ear fluid (MEF) levels with standard regimens



Harrison CJ, Pediatr Infect Dis J, 1997, modified

Concentrazioni medie (mg/l) di betalattamine orali nella mucosa dei seni mascellari in corso di rinosinusite acuta

Molecola	Dose (mg/l)	Ore	Conc. Mucosa (mg/kg)	T/S
Amoxi/Clav	250/125	2	0,3 – 0,2	0,1/0,11
Cefaclor	500	1 – 3	6	0,6/0,8
Cefuroxima axetil	250	2,0 – 4,5*	0,2 – 1,2	0,38
Cefetamet pivoxil	500	4*	2,21	0,54
Cefpodoxima proxetil	100	3	0,57	0,33

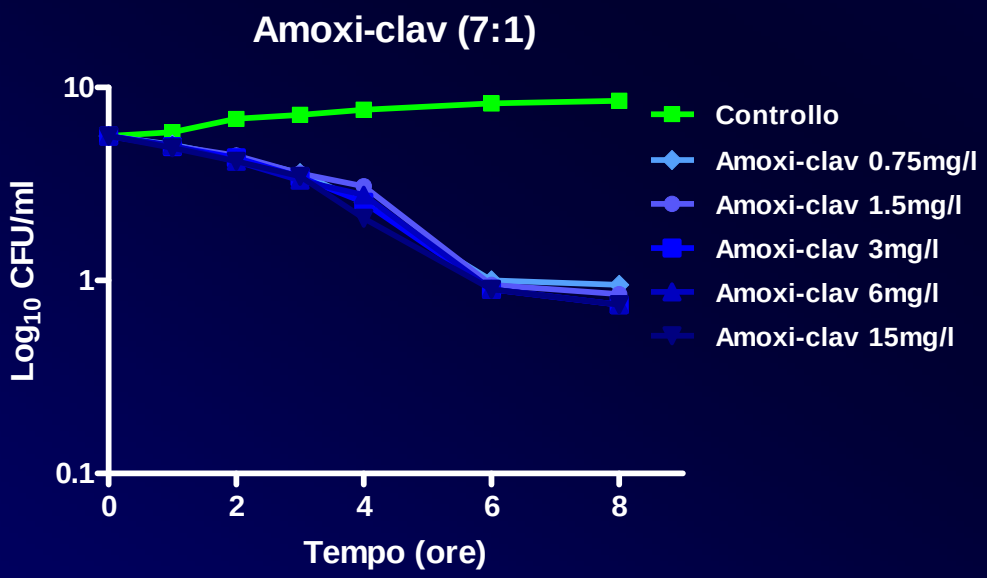
* Dopo l'ultima dose

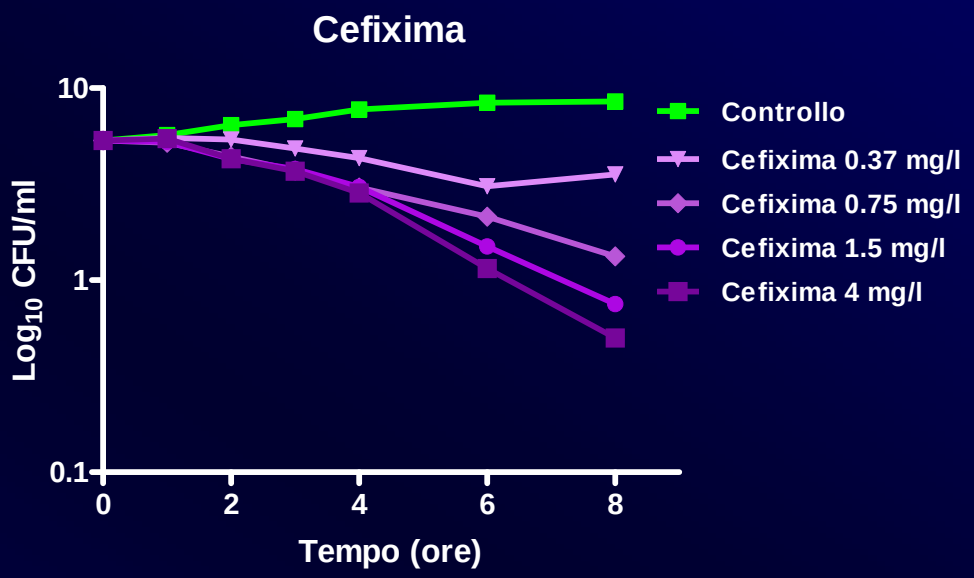
Iwasawa T, 1982; Karma P et al., 1991; Kawamura S et al., 1983; Kropec A et al., 1988; Sides GD et al., 1988; Stoeckel R et al., 1996; Todd PA et al., 1990; modificata

Antimicrobial drugs and infections

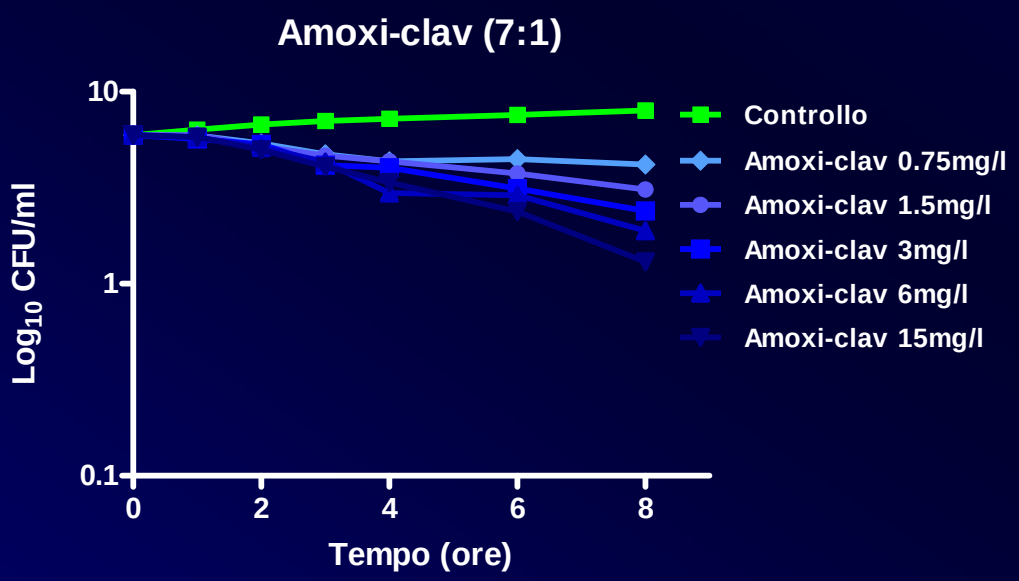
- **Low attention to possible kinetic differences due to infection site, severity and patient' characteristics**

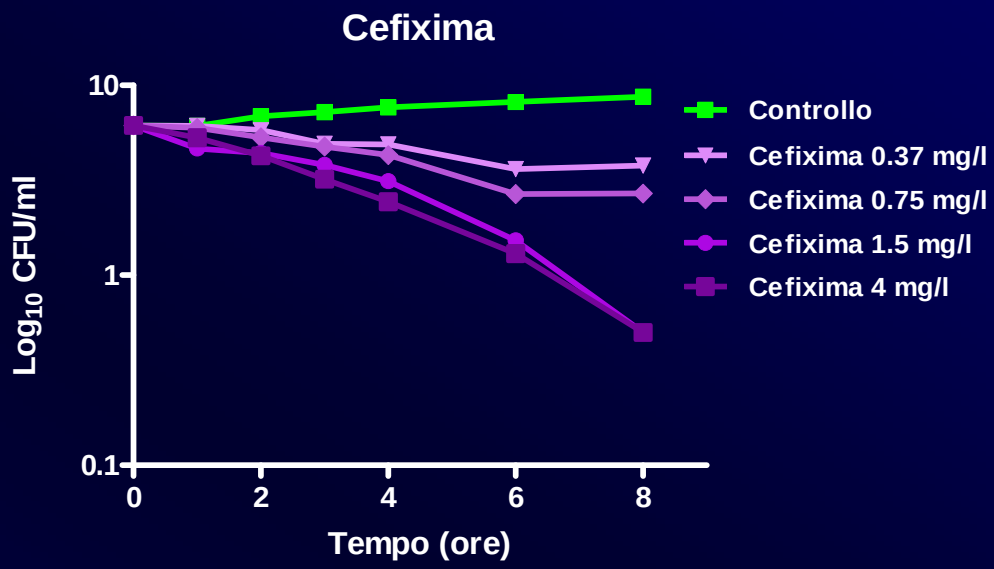
Curve di batteriocidia *S. pneumoniae* (medie)





Curve di batteriocidia *H. influenzae* (medie)





Amoxicillin

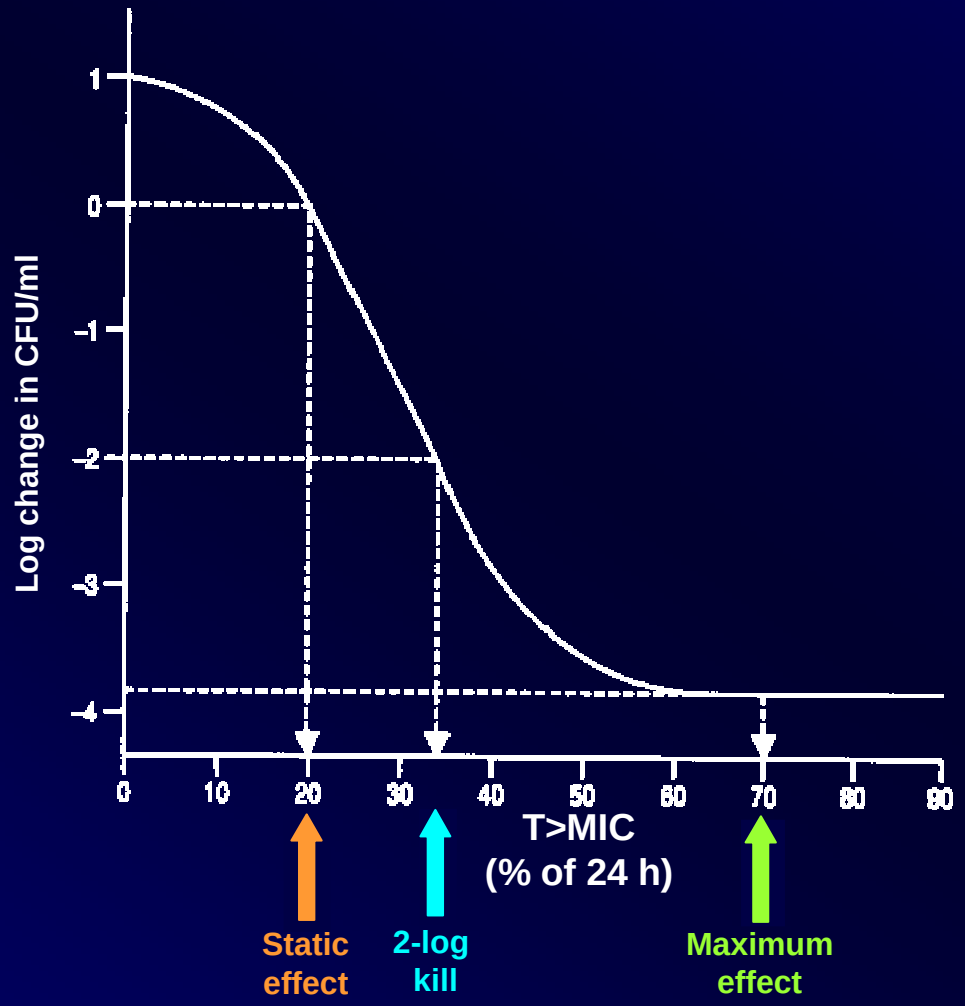
S. pneumoniae T > MIC (% of dose interval)

		T > MIC	
MIC (mg/l)	Dose	Mean	Range
0.5	15mg/kg three times daily	89	57-100
	25mg/kg twice daily	76	40-100
1	15mg/kg three times daily	79	49-106
	25mg/kg twice daily	65	37-100
2	15mg/kg three times daily	62	13-98
	25mg/kg twice daily	51	12-100

MacGowan AP, Clin Microbiol Infect, 2004, Fonseca W AAC 2003

Betalactams

Relationship between T > MIC and eradication



MacGowan AP, Clin Microbiol Infect, 2004

Cumulative fraction of response (CFR) for evaluated oral β-lactam regimens against *S. pneumoniae* and *H. influenzae*

Antibacterial regimen	CFR (%) *S. pneumoniae* (n = 124)	CFR (%) *H. influenzae* (n = 56)
Amoxicillin 13.3 mg/kg q8h	76.2	56.1
Amoxicillin 30 mg/kg q8h	84.7	63.1
Amoxicillin 45 mg/kg q12h	76.9	56.0
Amoxicillin/clavulanic acid 45 mg/kg q12h	76.6	90.7
Cefpodoxime 5 mg/kg q12h	65.4	99.6
Cefprozil 15 mg/kg q12h	70.7	15.4
Ceftibuten 9 mg/kg q24h	NA	96.4
Cefuroxime 15 mg/kg q12h	55.1	11.4

Fallon RM et al., Pediatr Drugs, 2008

Betalattamine orali

(T>MIC_{90})*

dei comuni patogeni respiratori

	Posologia	*H. influenzae*		*M. Catarrhalis*
		β -	β +	
Amoxi-clav	45/6.4mg/kg BID	60	30-50	40
Cefixima	8mg/kg OD	85	85	50
Ceftibuten	9mg/kg OD	50	50	70
Cefpodoxima-proxetil	6mg/kg BID	50	50	60
Cefaclor	20mg/kg BID	50	30-40	40
Cefuroxima axetil	15mg/kg BID	50	40	40

* Valori delle MIC_{90} desunti dal lavoro di Stefani et al., 2008

Betalattamine orali

(T>MIC_{90})*

dei comuni patogeni respiratori

	Posologia	*S. pneumoniae*		
		Pen S	Pen I	Pen R
Amoxi-clav	45/6.4mg/kg BID	100	40-60	15
Cefixima	8mg/kg OD	60	0	0
Ceftibuten	9mg/kg OD	70	0	0
Cefpodoxima-proxetil	6mg/kg BID	100	25	0
Cefaclor	20mg/kg BID (TID)	80	20	0
Cefuroxima-axetil	15mg/kg BID	80	20	0

* Valori delle MIC_{90} desunti dal lavoro di Stefani et al., 2008

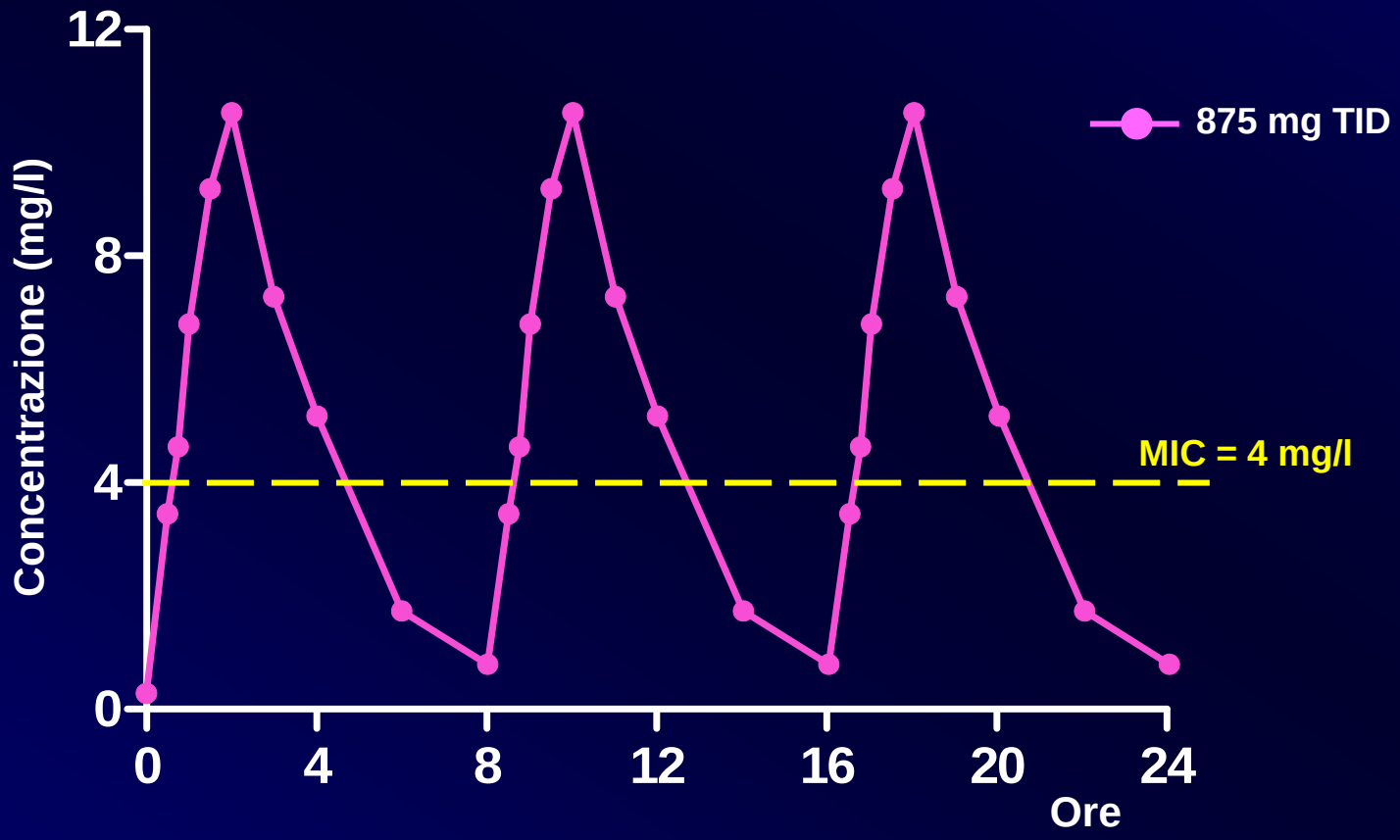
Oral cephalosporins

"Difficult to treat" infections

- **Non linear pharmacokinetics (cefixime, cefetamet pivoxil) (c*eftibuten with doses>400 mg or 9 mg/kg*)**
  - **reduced intervals between doses**
- **Linear pharmacokinetics (cefaclor, cefprozil, cefuroxime axetil)**
  - **increased pro-dose amount**

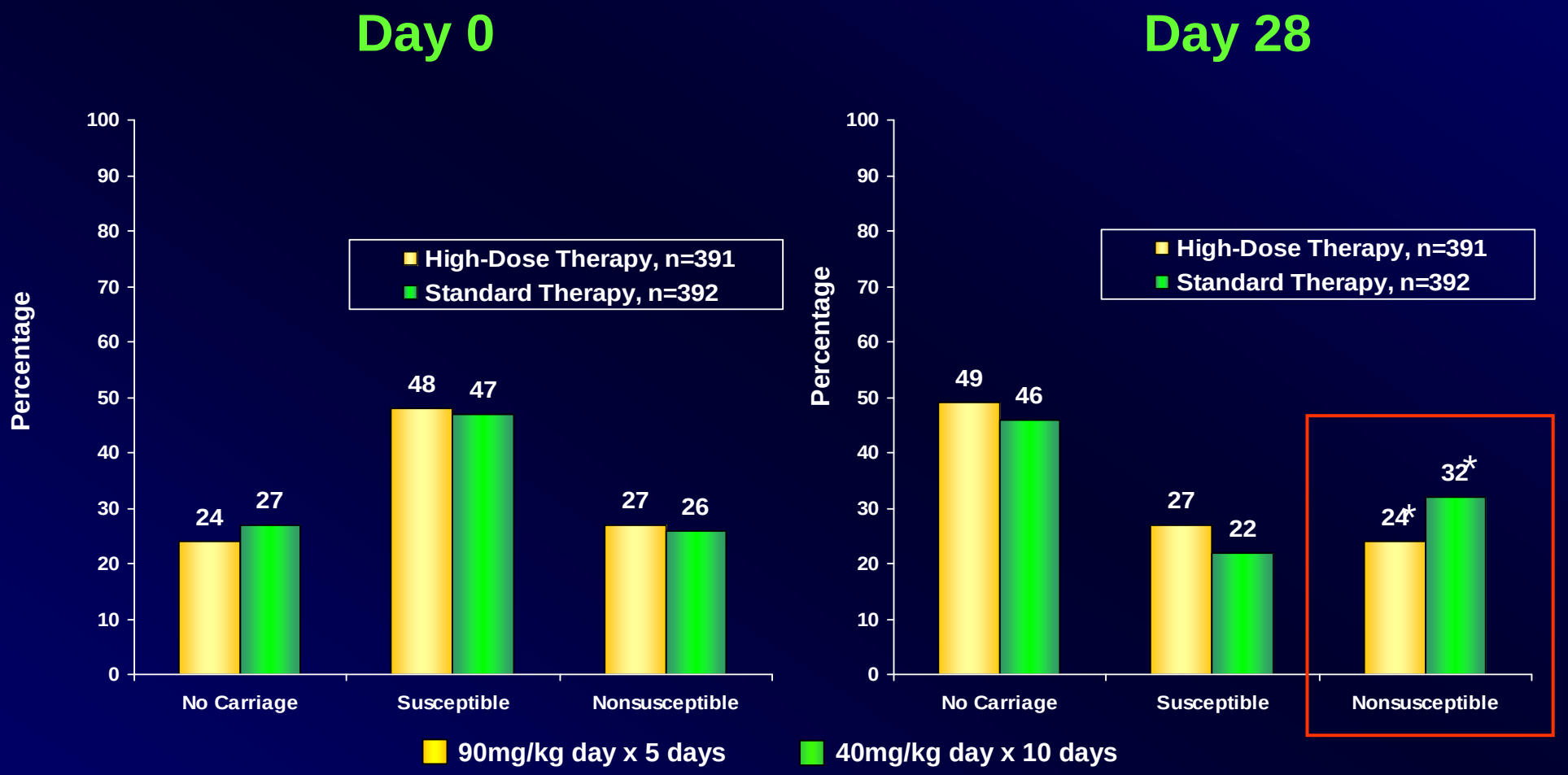
Co-amoxivclav

Concentrazioni ematiche dopo somministrazione orale



Novelli A et al., 1987

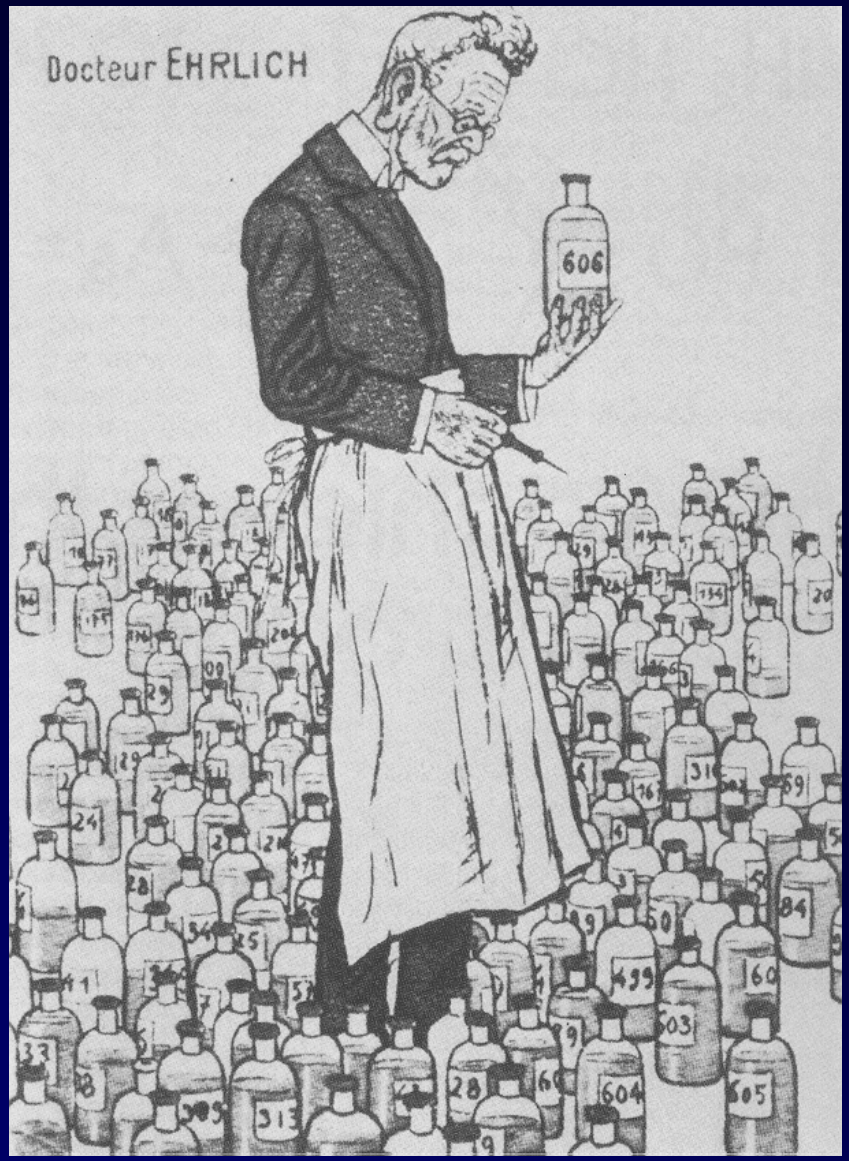
Pneumococcal nasopharyngeal colonization after amoxicillin therapy



*p = 0.04 χ^2 test

Schrag SJ et al., JAMA, 2001

Conclusioni (I)

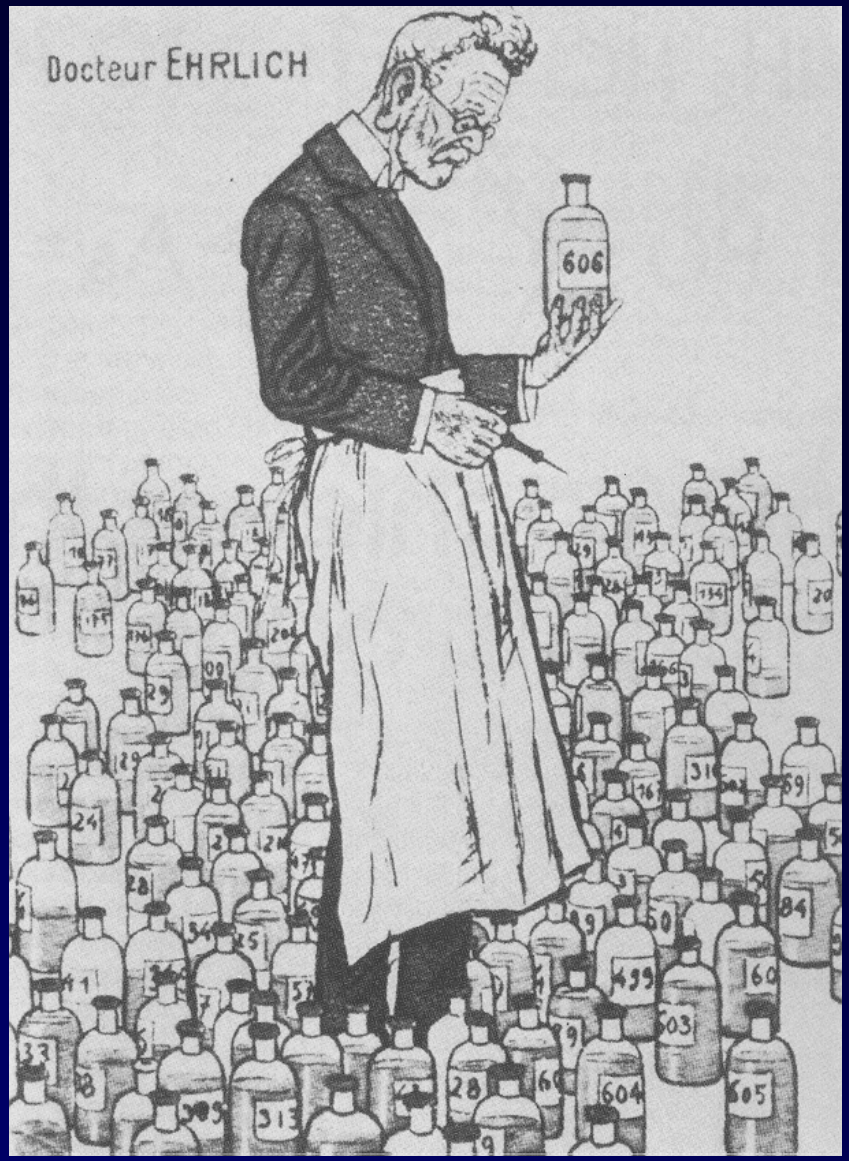


Le betalattamine orali rivestono un ruolo primario per motivi di spettro, di cinetica e di tollerabilità

La amoxicillina, soprattutto in associazione al clavulanato, ed alcune cefalosporine sono in grado di soddisfare i parametri PK-PD per un potenziale successo clinico.

I macrolidi semisintetici hanno favorevoli prerogative cinetiche, sono generalmente ben tollerati, ma possono avere problemi di chemioresistenza

Conclusioni (II)



E’ importante minimizzare il tempo di presenza di livelli sub-ottimali di antibiotico

La scelta della giusta dose e di adeguati intervalli costituisce un contributo essenziale per ottenere la risposta clinica ottimale e prevenire l’emergenza di patogeni resistenti

Spesso, anche nelle infezioni respiratorie di comunità, per le condizioni generali del paziente, per la presenza di malattie concomitanti ed in funzione della gravità e/o sede dell’infezione, dobbiamo adeguare le nostre scelte posologiche in modo da raggiungere i livelli massimi dei parametri PK-PD e garantire così un potenziale successo clinico