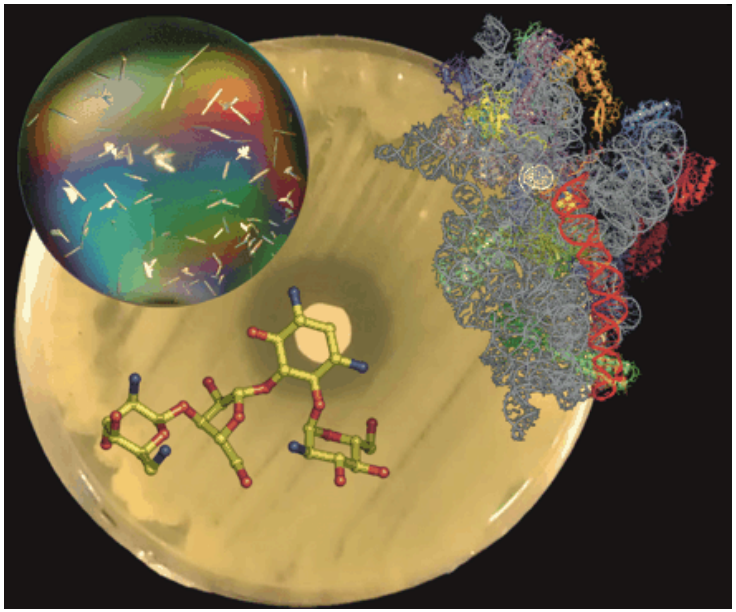
Update on new antibiotics

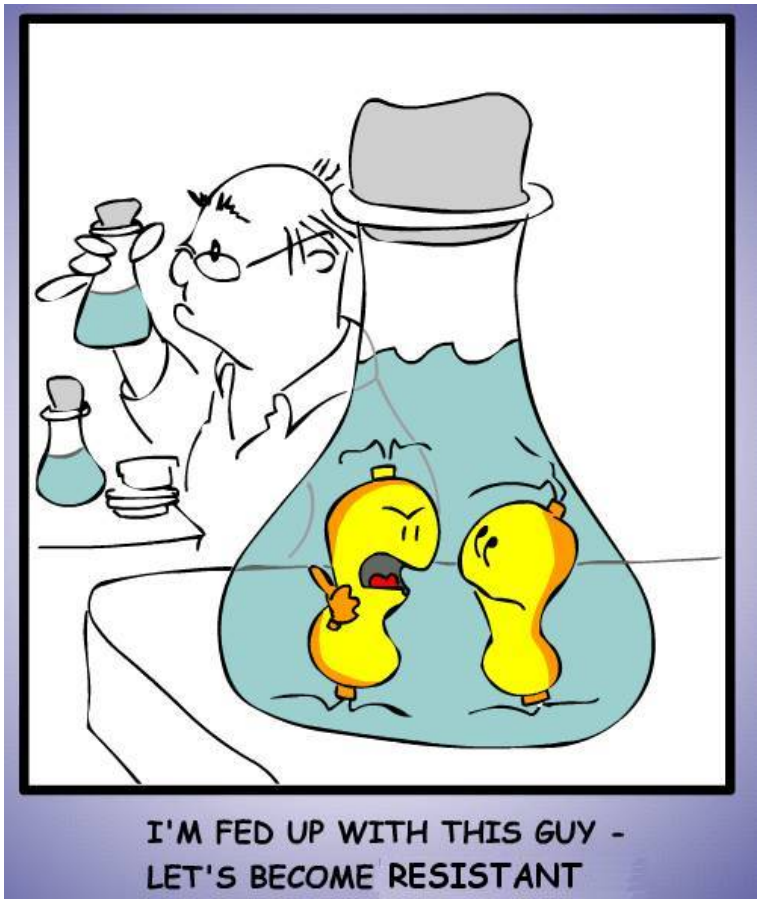


Françoise Van Bambeke
Paul M. Tulkens

Unité de Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute & Centre de Pharmacie clinique

Université catholique de Louvain
http://www.facm.ucl.ac.be/

Do we need new antibiotics in Belgium ?



Do we need new antibiotics in Belgium ?

Journal of Antimicrobial Chemotherapy (2009) **64**, *Suppl. 1*, i29–i36
doi:10.1093/jac/dkp255

JAC

Has the era of untreatable infections arrived?

David M. Livermore*

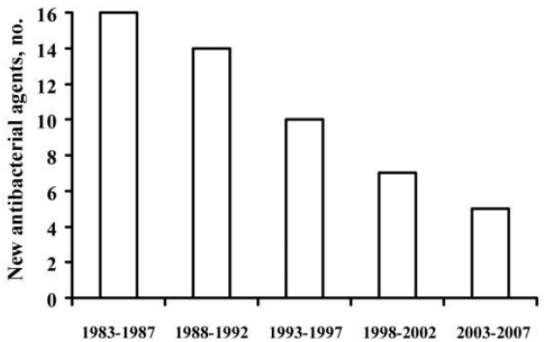
Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Clinical Infectious Diseases 2009; 48:1–12

IDSA REPORT

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

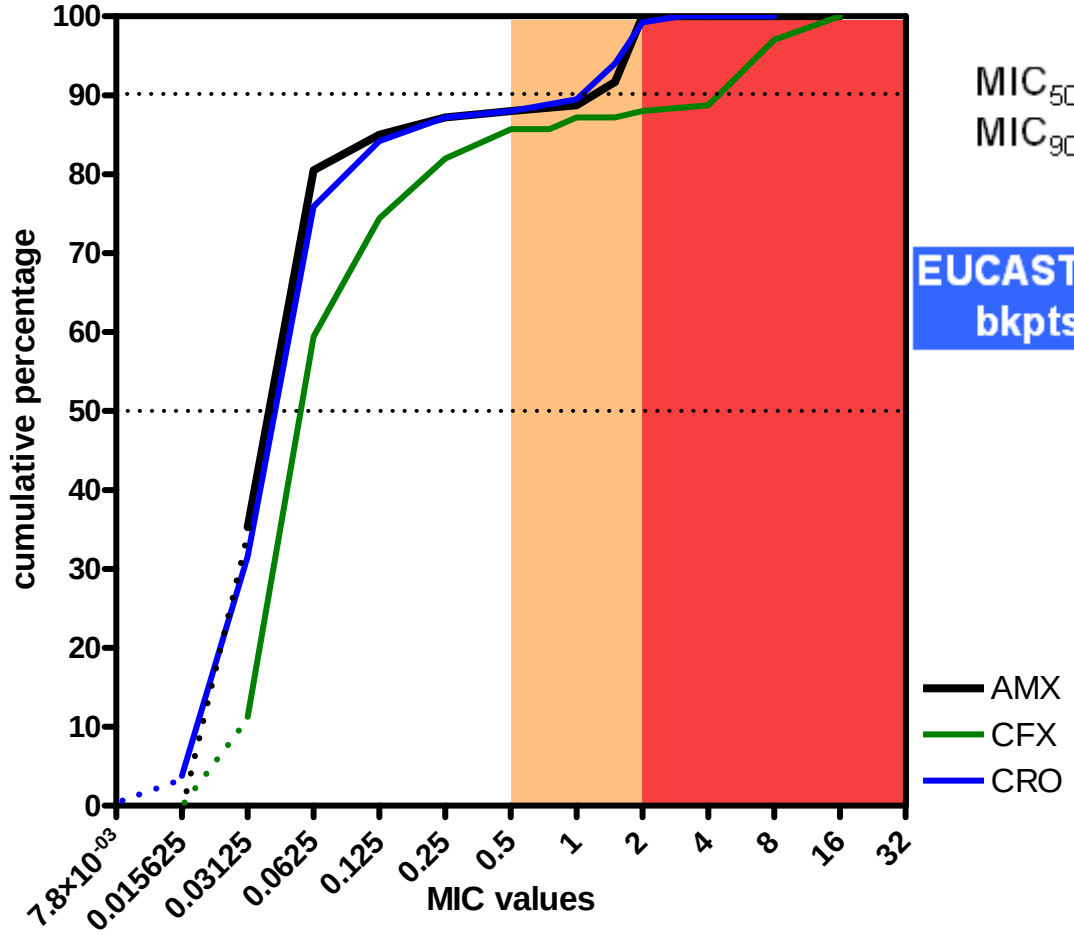
Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]



New antibacterial agents approved in the United States, 1983–2007

S. pneumoniae

133 CAP isolates; beta-lactams

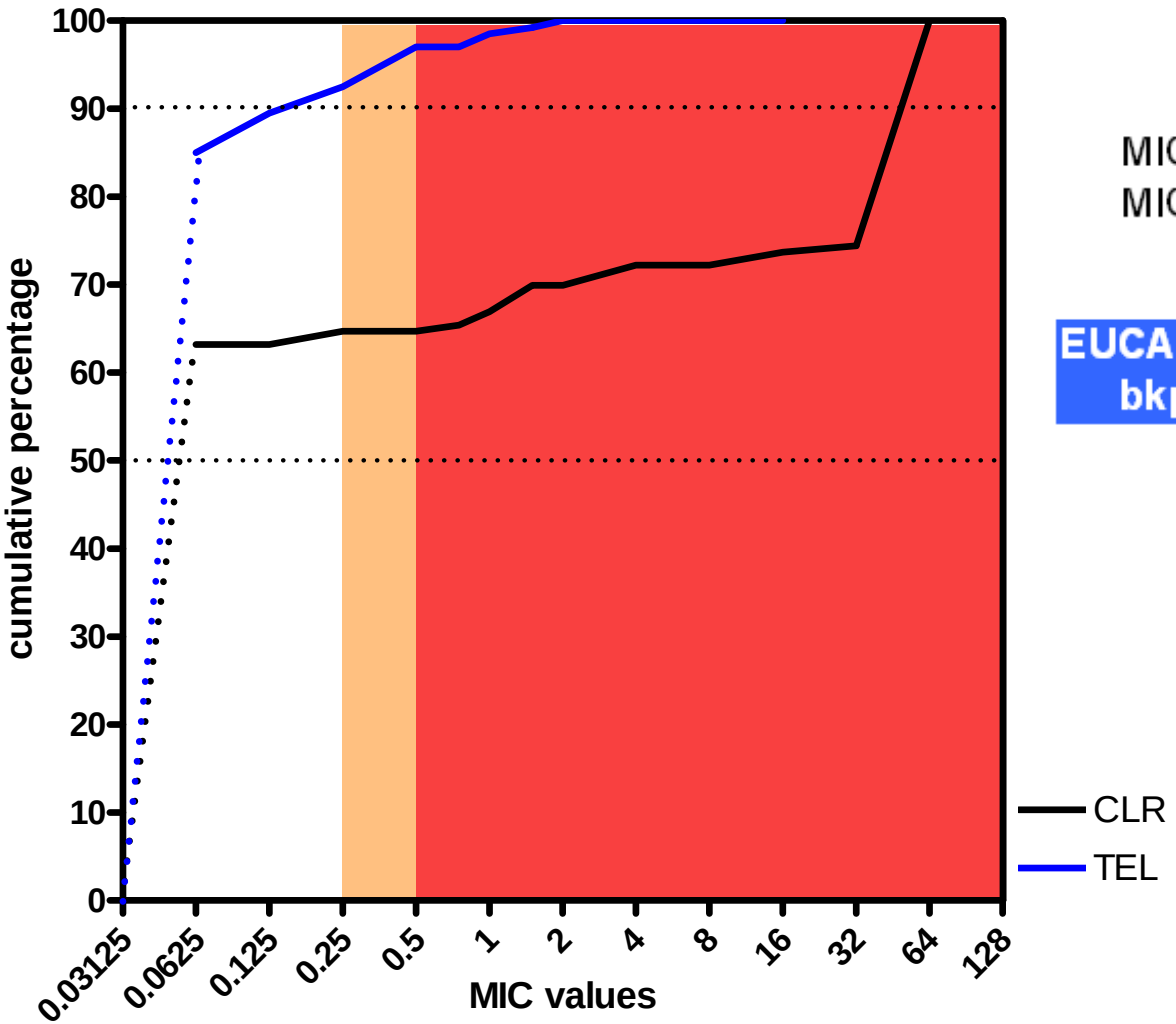


	AMX	CRO	CFX
MIC_{50} (mg/L)	0,06	0,06	0,06
MIC_{90} (mg/L)	1,5	1,5	8
EUCAST bkpts S ≤	0,5	0,5	0,5
EUCAST bkpts R >	2	2	1
S:	88,0 %	88,0 %	85,7 %
I:	12,0 %	11,2 %	1,5 %
R:	0,0 %	0,8 %	12,8 %

Lismond et al. SBIMC 2008

S. pneumoniae

133 CAP isolates; macrolides

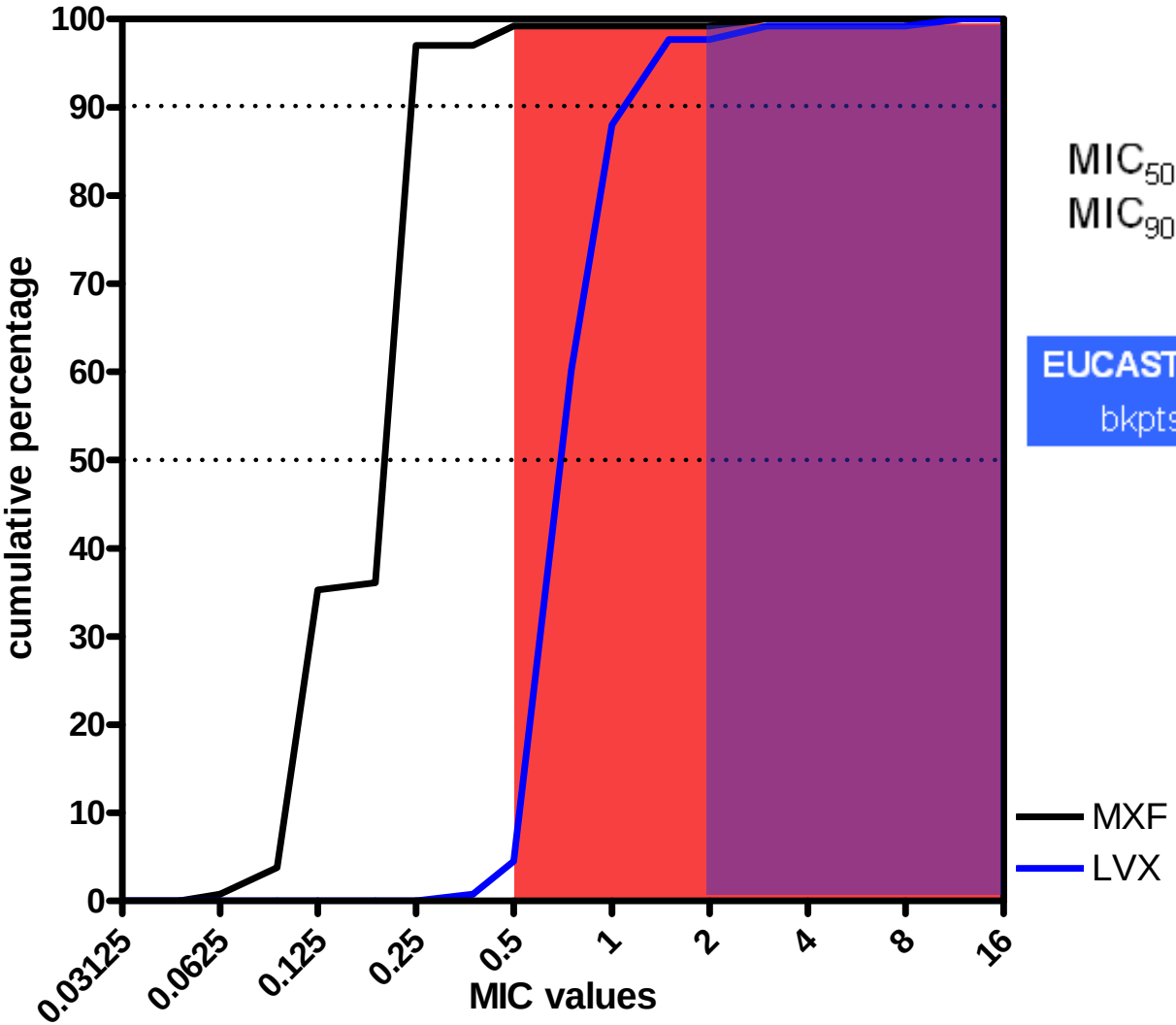


		CLR	TEL
MIC_{50} (mg/L)		≤0,06	≤0,06
MIC_{90} (mg/L)		>32	0,25
EUCAST bkpts	S ≤	0,25	0,25
	R >	0,5	0,5
S:		64,7 %	92,5 %
I:		0,0 %	4,5 %
R:		35,3 %	3,0 %

Lismond et al. SBIMC 2008

S. pneumoniae

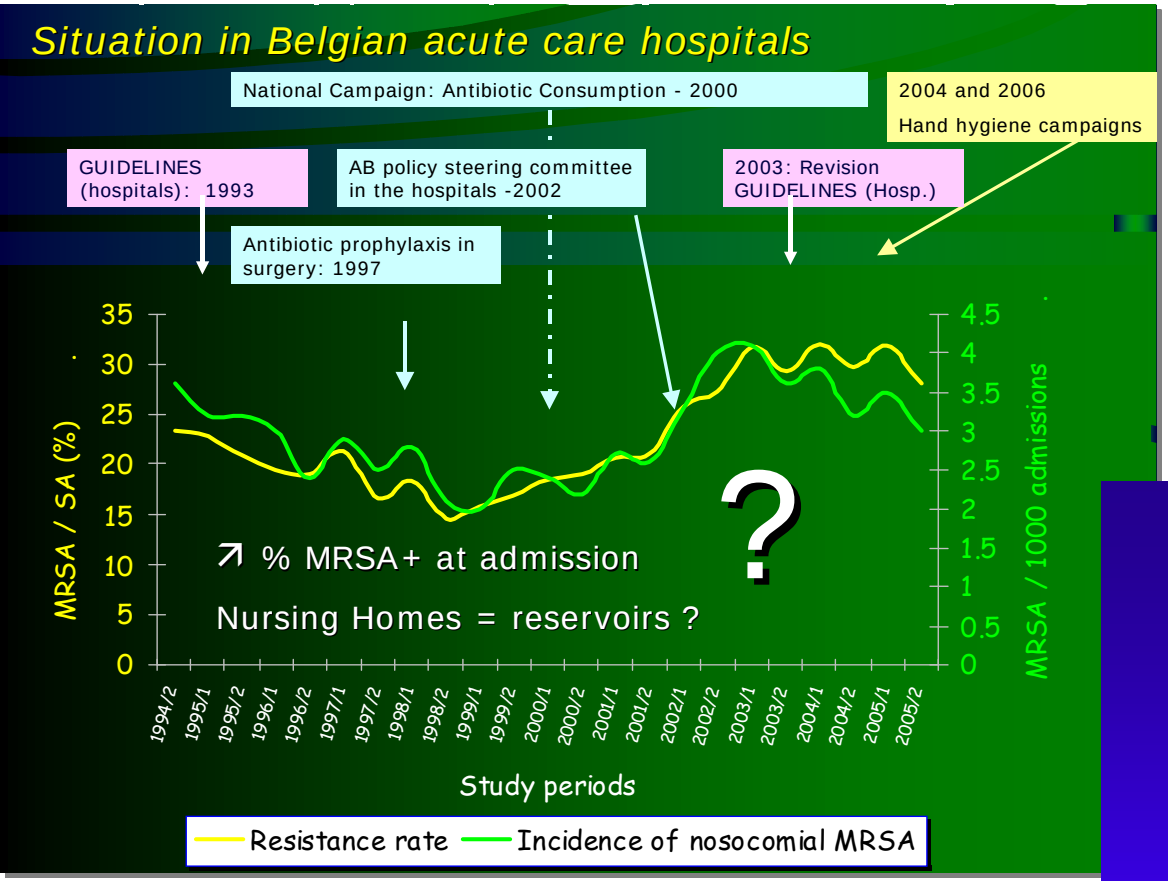
133 CAP isolates; fluoroquinolones



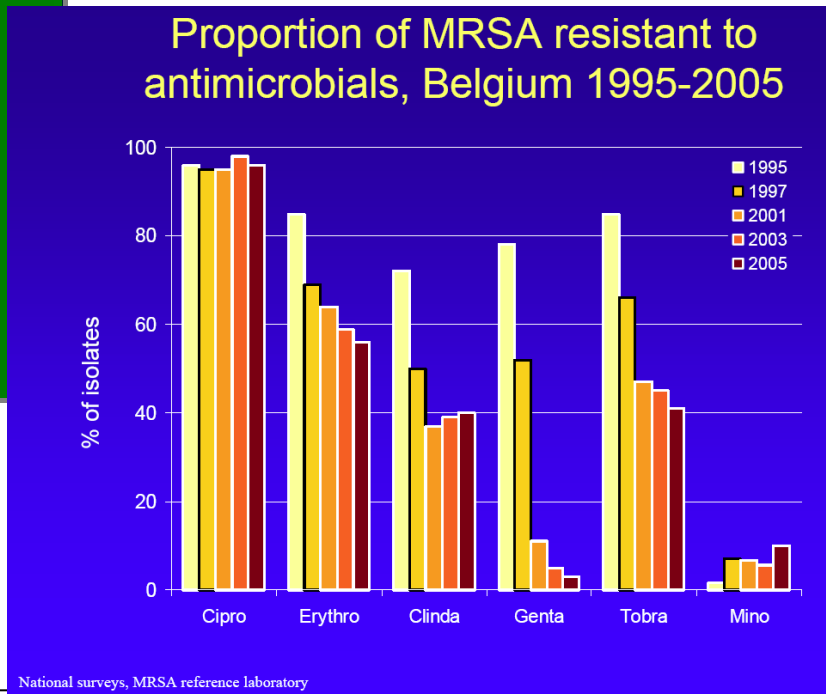
		MXF	LVX
MIC_{50} (mg/L)		0,25	0,75
MIC_{90} (mg/L)		0,25	1,5
EUCAST bkpts	S ≤	0,5	2
	R >	0,5	2
S:		99,2 %	97,7 %
R:		0,8 %	2,3 %

Lismond et al. SBIMC 2008

S. aureus


Situation in Belgian acute care hospitals
National Campaign: Antibiotic Consumption - 2000
2004 and 2006
Hand hygiene campaigns
GUIDELINES (hospitals): 1993
AB policy steering committee in the hospitals -2002
2003: Revision GUIDELINES (Hosp.)
Antibiotic prophylaxis in surgery: 1997
MRSA / SA (%)
MRSA / 1000 admissions
↗ % MRSA+ at admission
Nursing Homes = reservoirs ?
?
Study periods
Resistance rate
Incidence of nosocomial MRSA


GUIDE TO HOSPITAL
MRSA WARD
MRSA CLINIC
MRSA SPECIALIST UNIT
DEPT. OF MRSA
MRSA OLOGY
Frizelda


Proportion of MRSA resistant to antimicrobials, Belgium 1995-2005
% of isolates
1995
1997
2001
2003
2005
Cipro
Erythro
Clinda
Genta
Tobra
Mino
National surveys, MRSA reference laboratory

P. aeruginosa

138 HAP/VAP isolates; 5 ICUs

AB	Global		H1 (n=12)		H2 (n=29)		H3 (n=21)		H4 (n=22)		H5 (n=54)	
	$MIC_{50/90}$	I/R [a]	$MIC_{50/90}$	I/R [a]	$MIC_{50/90}$	I/R [a]	$MIC_{50/90}$	I/R [a]	$MIC_{50/90}$	I/R [a]	$MIC_{50/90}$	I/R [a]
GEN	2/64	25.4	2/64	25.0	2/64	31.0	4/64	28.6	2/32	27.3	2/8	20.4
AMK	4/16	9.4/8.0	4/8	0.0/8.3	4/32	13.3/13.8	8/16	9.5/0.0	4/32	18.2/13.6	8/8	5.6/5.6
ATM	8/32	68.1/29.7	6/32	66.7/33.3	16/32	65.5/34.5	16/32	57.1/33.3	16/128	63.6/36.4	8/32	75.9/22.2
MEM	1/16	12.3/23.9	1/8	25.0/8.3	2/16	6.9/37.9	1/4	14.3/4.8	1/16	4.5/27.3	1/16	14.5/25.5
FEP	8/64	46.4	4/32	33.3	16/64	72.4	8/64	47.6	6/64	36.4	8/64	38.9
CIP	0.25/16	7.2/22.5	0.25/8	8.3/25	0.5/16	6.9/37.9	0.25/16	9.5/23.8	0.19/8	0.0/13.6	0.125/16	9.3/16.7

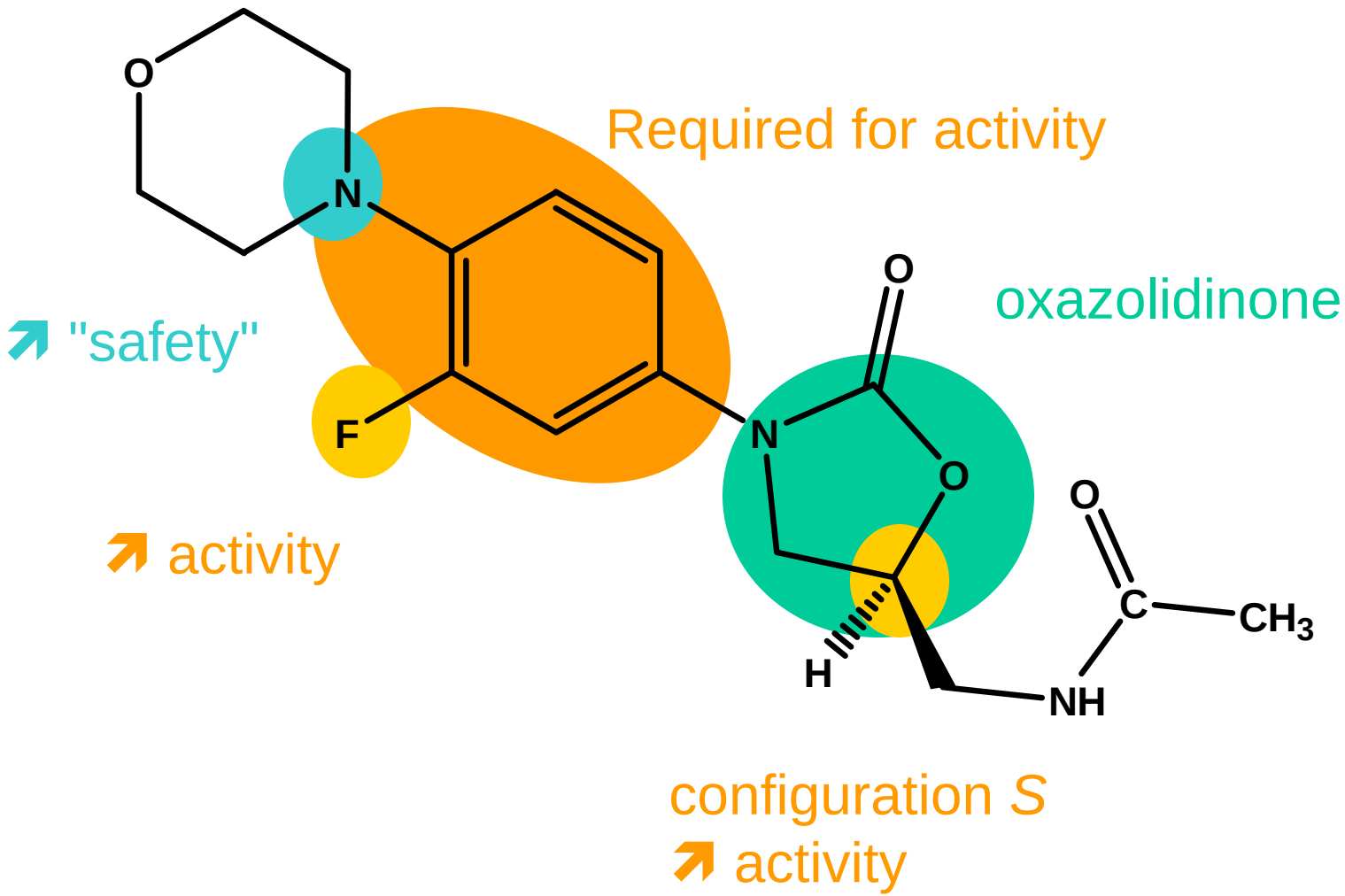
[a] I means > S and ≤ R (for GEN and FEP, only R is given as there is no intermediate according to EUCAST)

Riou et al. ECCMID 2009

LINEZOLID

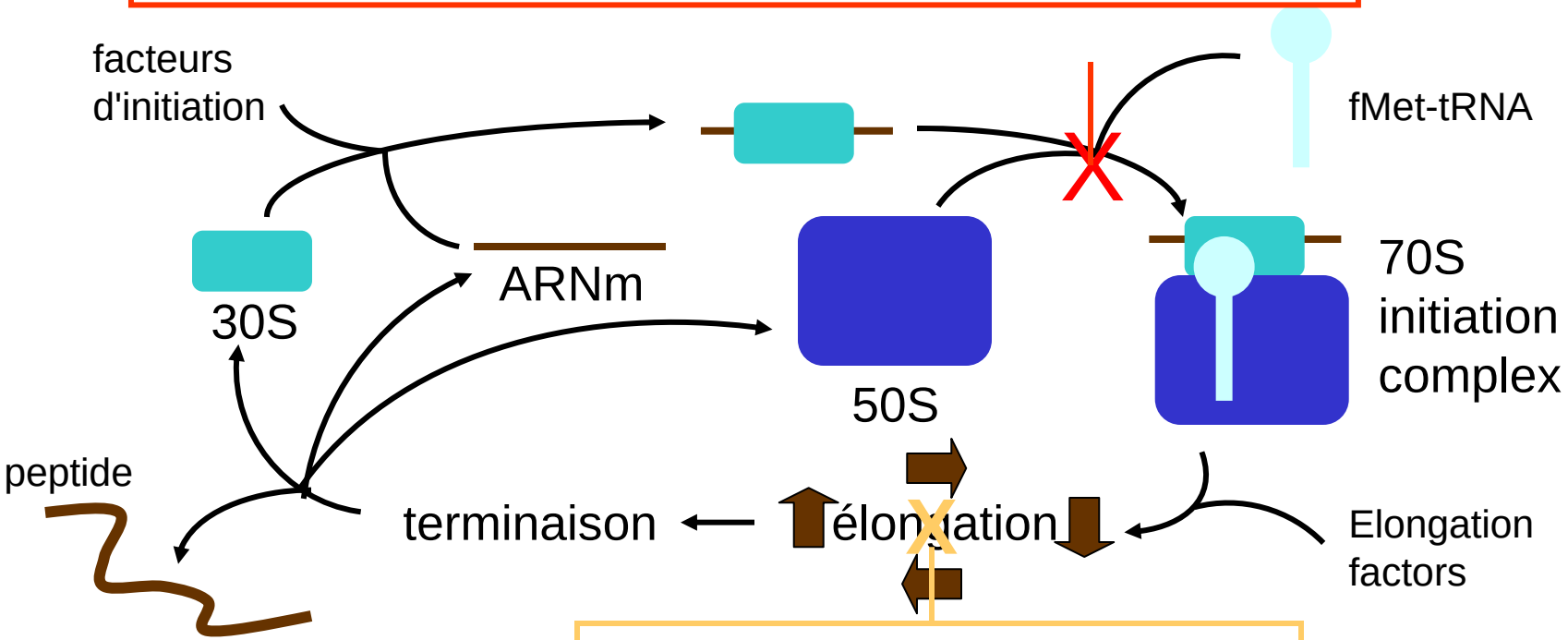

Zyvox Product Center
See Important Safety Considerations Below
Prescribing Information
References
ZYVOX
(linezolid)
ABOUT ZYVOX
INDICATIONS
EFFICACY
TISSUE PENETRATION
SAFETY
DOSING
GUIDELINES
COMPLEX PATIENTS
Some patients have ZYVOX written all over them
ZYVOX is proven treatment for MRSA in complex patients[1,3]
Important Safety Considerations
Nosocomial Pneumonia
With proven efficacy, excellent tissue penetration, and clear and consistent dosing, count on ZYVOX to treat methicillin-resistant Staphylococcus aureus (MRSA) in patients with nosocomial pneumonia whose conditions are complicated by renal insufficiency[1,3]
Important Safety Considerations
Learn more »
MRSA
Complicated Skin and Skin Structure Infections (cSSSI)
ZYVOX has a 100% bioavailable oral formulation you can count on to treat cSSSI due to MRSA in patients whose conditions are complicated by diabetes and renal insufficiency[4,5]
Important Safety Considerations
Learn more »
RSVP—the Reimbursement Solutions, Verification, and Payment HELPline 1-888-327-7787
Reimbursement support and patient assistance program to help patients gain access to the Pfizer medicines they need
Read more about the American Thoracic Society/Infectious Diseases Society of America guidelines for MRSA »

Linezolid: chemical structure



Mode of action of linezolid

oxazolidinones bind to 50S
and prevent the formation of the initiation complex



macrolides
lincosamides
tetracyclines

chloramphenicol
aminoglycosides

Different target

➡ NO
- antagonism
- cross-resistance

Tsuji *et al*. (2005) In Antimicrobial therapy and vaccines, ed. Yu, 223-42

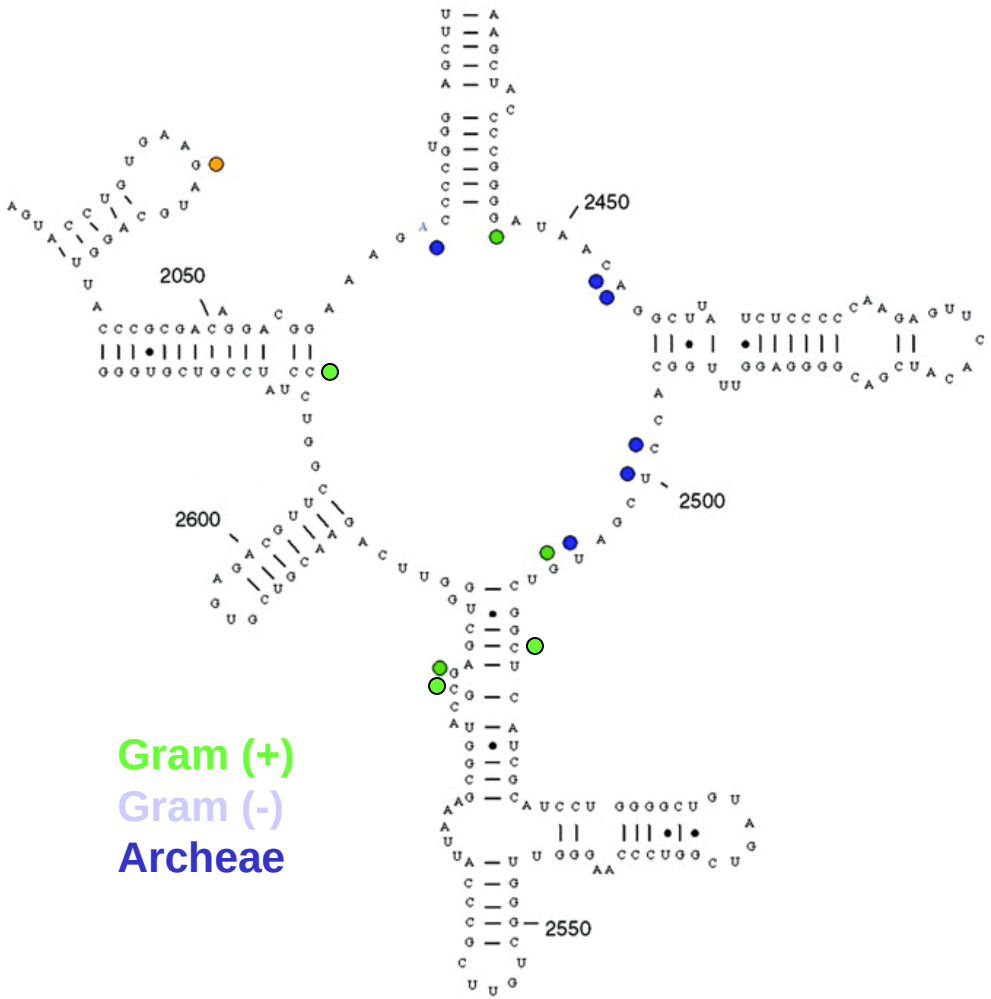
Mechanisms of resistance to linezolid

mutations in 23S RNA ⟵ Gram (+)

Gram (-)
intrinsic resistance

↓

efflux



bactérie	MIC	
	control	+ pump inhib.
E. coli	128	16
E. aerogenes	256	32

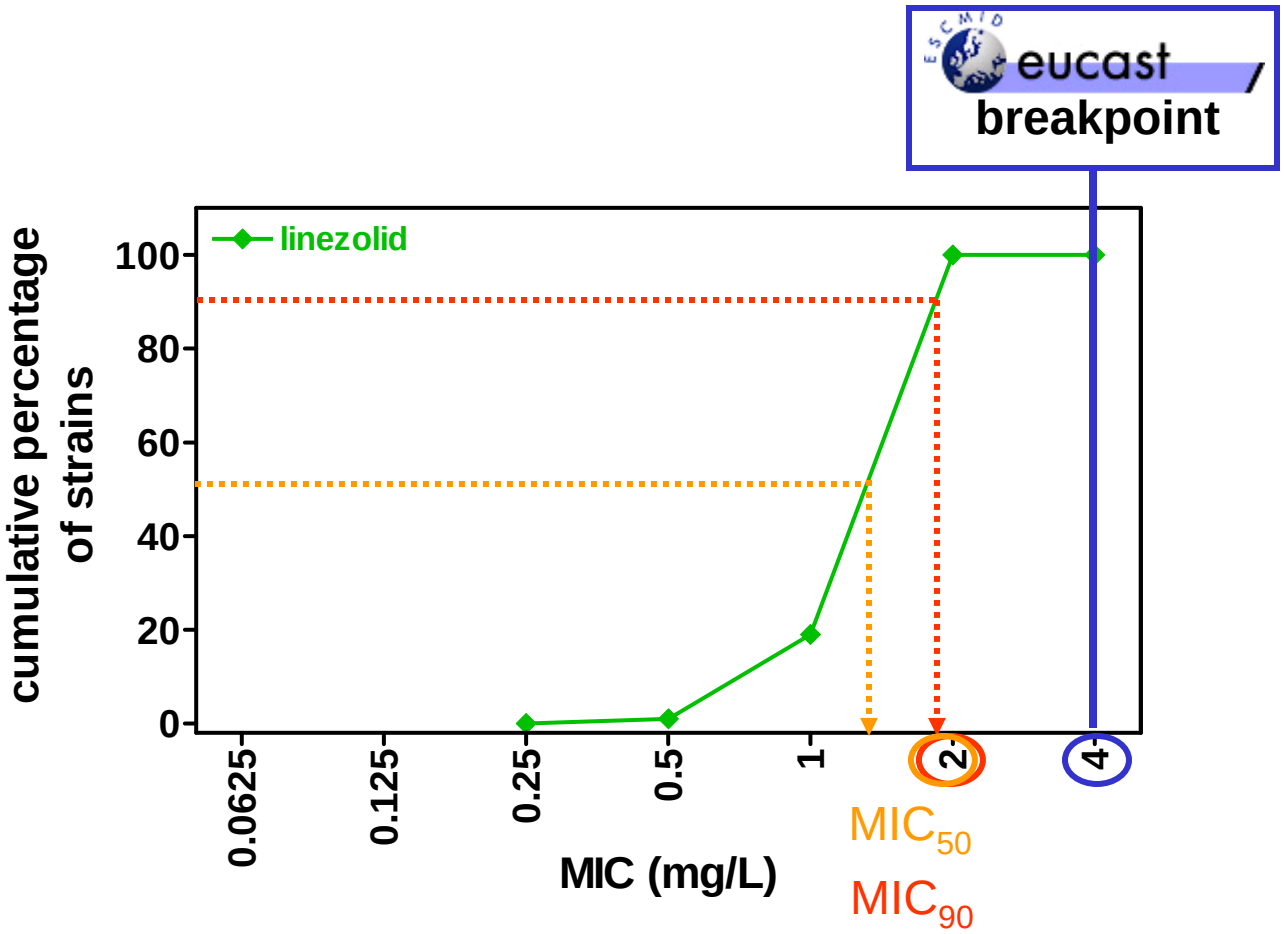
Xiong et al. (2000) J. Bacteriol. 182: 6325-31
Colca et al. (2003) J. Biol. Chem. 278: 21972-79

Schumacher et al. JAC (2006) 57:344-48

In vitro activity

in vitro activity of linezolid on MRSA

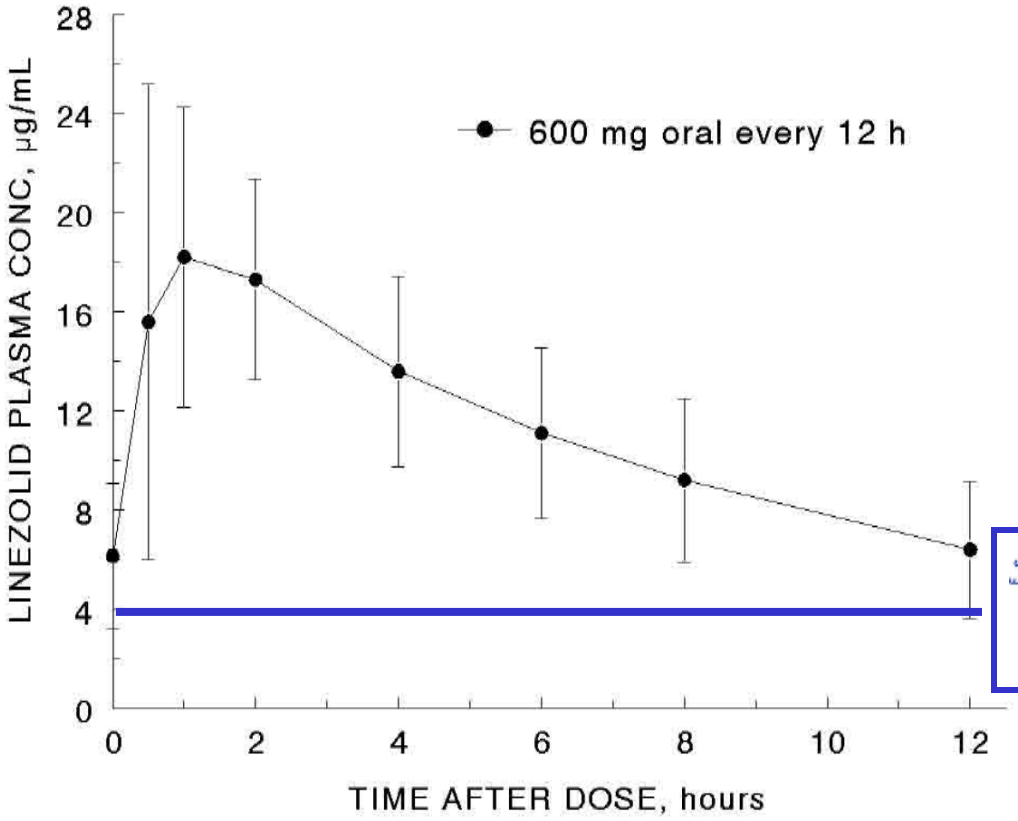
MIC distribution for 511 MRSA isolated in 2003 in 112 Belgian hospitals



Denis et al., AAC (2006) 50:2680-5

Pharmacokinetics / Pharmacodynamics

linezolid PK/PD - application to humans



S. aureus

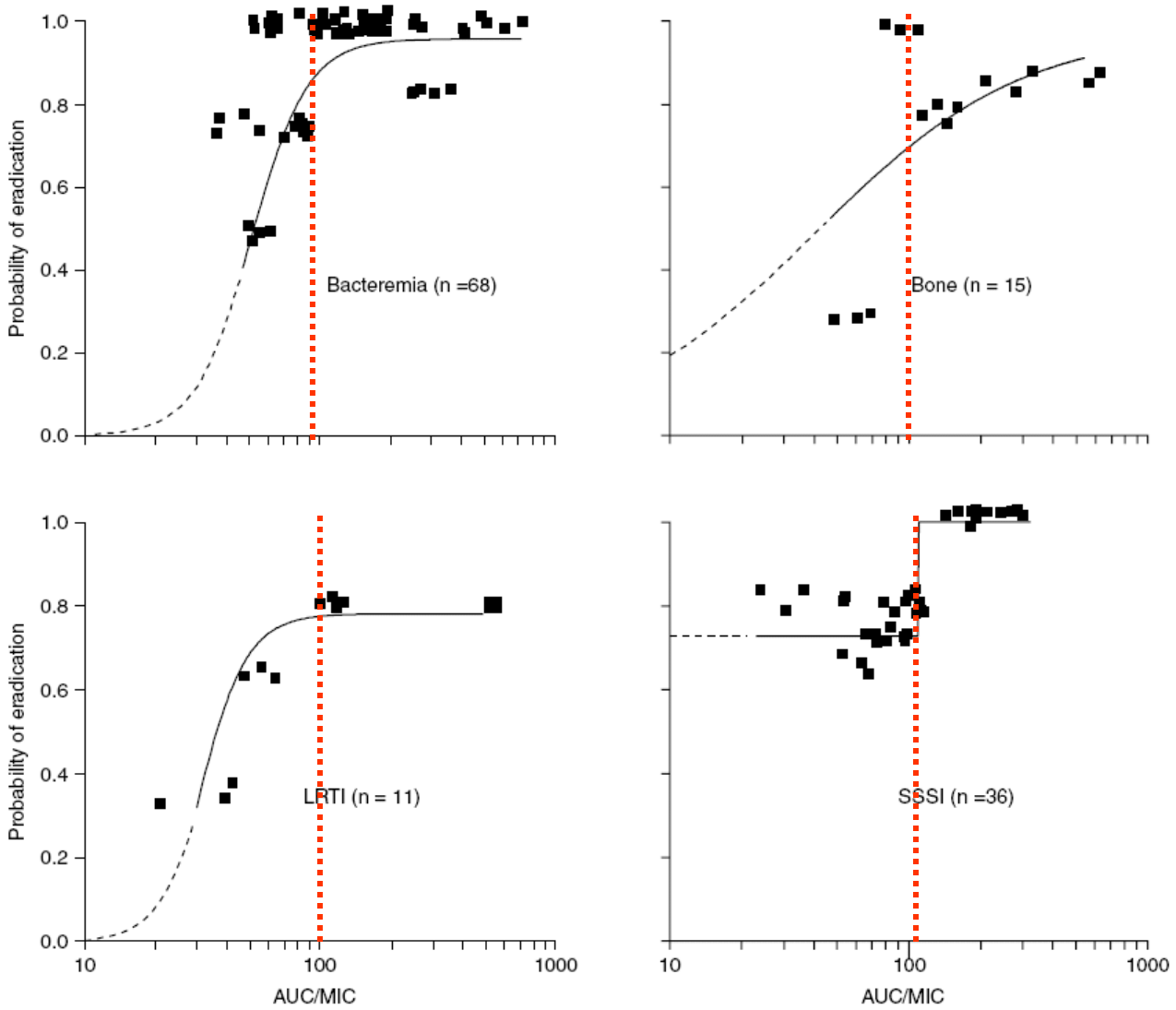
eucast **breakpoint**

Figure 1. Plasma Concentrations of Linezolid in Adults at Steady-State Following Oral Dosing Every 12 Hours (Mean ± Standard Deviation, n=16)

Zyvox® package insert

How to optimize linezolid dosage ?

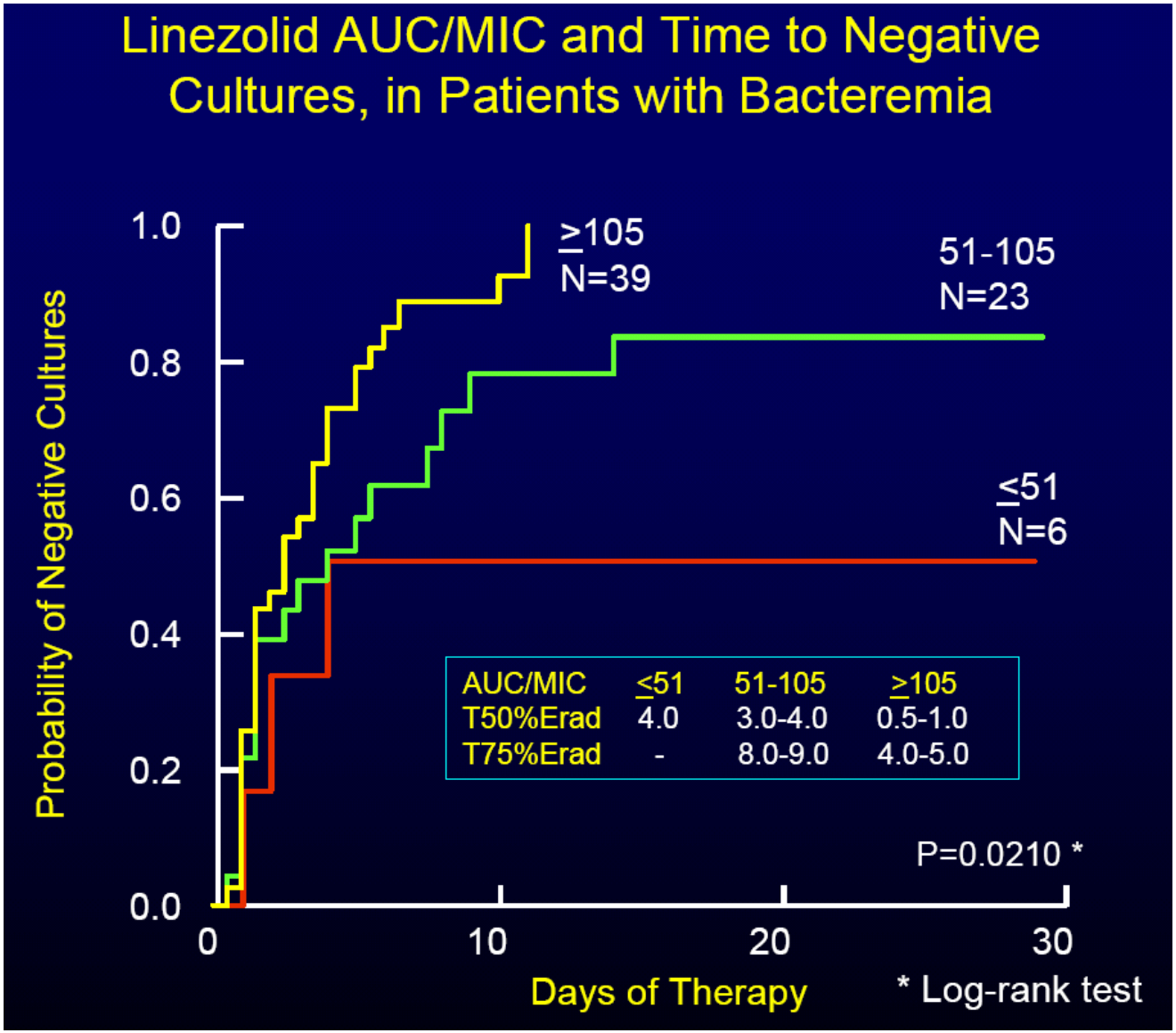
288 patients; linezolid 600 mg IV q12h



AUC /MIC > 100 for different types of infections

Rayner et al. Clin. Pharmacokinet. (2003) 42:1411-23

How to optimize linezolid dosage ?



Forrest et al. AAC & Clin. Pharmacother. (2003)

How to optimize linezolid dosage ?

administration
twice daily

↓

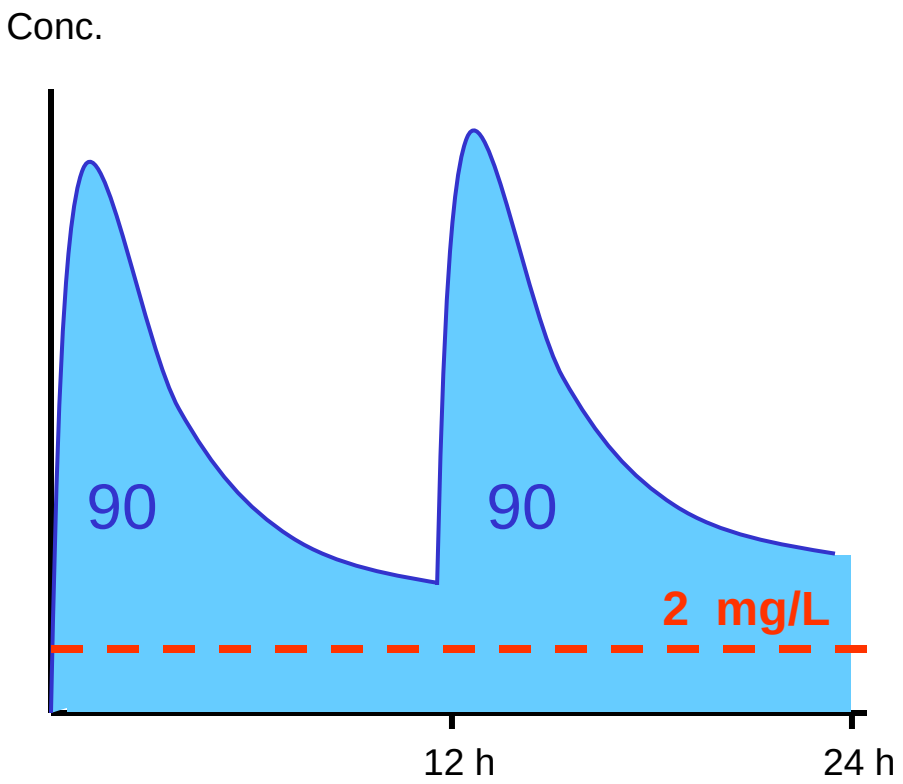
600 mg
AUC = 90 mg.h/L

↓

AUC / MIC = 100 h^{-1}

↓

MIC = AUC / 100
(90 x 2) / 100 ~ 2 mg/L



Conventional dose (600 mg X 2) allows to cover MIC≤ 2 mg/L

PK/PD du linezolid - application to humans

dose / admin. route	compartment	AUC	AUC/MIC (2 mg/L)	AUC/MIC (4 mg/L)
			MIC $_{90}$ Belgium	***EUCAST Breakpoint***
600 mg iv BID	serum	180	90	45
600 mg po BID (at steady state)	serum	200-270	100-135	50-68
	adip. tissue	200	100	50
	muscle	235	118	59
	ELF	200…600	100…200	50…100

no modification if RI or HI

Conte et al., AAC (2002) 46:1475-80
Brier et al., AAC (2003) 47:2775-80
Dehghanyar et al., AAC (2005) 50:2367-71
Boselli et al., Crit. Care Med. (2005) 33:1529-33

FDA

Information for Healthcare Professionals

Linezolid
(marketed as Zyvox)

Linezolid: where are therapeutic failures ?

FDA ALERT [3/16/2007]: FDA is issuing this alert to advise you of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin (comparator antibiotics) in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. In this study, patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study.

The following table summarizes deaths by baseline pathogen (all culture sources).

Type of organism	Linezolid N=363	Comparator N=363
	Number died N=78	Number died N=58
Gram positive only	37/222 (16.7%)	37/215 (17.2%)
Gram negative only	4/15 (26.7%)	1/11 (9.1%)
Gram positive and Gram negative	16/46 (34.8%)	7/39 (17.9%)
No organism	20/76 (26.3%)	12/92 (13%)
Other	1/4 (25%)	1/6 (16.7%)

Current indications in Belgium

Linezolid

- **infections de la peau et des tissus mous, ne peut s'utiliser QUE**
  - si démonstration que l'infection est due à un Gram(+) sensible
  - en absence d'autres alternatives et en combinaison avec un anti Gram(-) si infection mixte suspectée
- **pneumonie nosocomiale / communautaire ne peut s'utiliser QUE**
  - si infection suspectée à un Gram(+) sensible
  - en combinaison avec un anti Gram(-) si infection mixte suspectée

Vancomycine

- **infections graves staphylococciques résistantes à la méthicilline**.
- **infection staphylococcique sévère chez des patients allergiques** à la pénicilline ou chez des patients qui n'ont pas répondu à un traitement aux pénicillines ou aux céphalosporines.
- **endocardite** à streptocoque ou entérocoque (+ AG); prophylaxie de l'endocardite bactérienne chez les patients allergiques à la pénicilline
- **entérocolite** staphylococcique et colite pseudomembraneuse à *C. difficile*.

Therapeutic failures with vancomycin: link with MICS

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2008, p. 3315–3320 Vol. 52, No. 9
0066-4804/08/$08.00+0 doi:10.1128/AAC.00113-08

Relationship between Vancomycin MIC and Failure among Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia Treated with Vancomycin▽

T. P. Lodise,[1,2]* J. Graves,[1] A. Evans,[3] E. Graffunder,[4] M. Helmecke,[4] B. M. Lomaestro,[5] and K. Stellrecht[3]

Albany College of Pharmacy, Pharmacy Practice Department, Albany, New York[1]; Ordway Research Institute, Albany, New York[2]; Albany Medical Center Hospital, Department of Pathology and Laboratory Medicine, Albany, New York[3]; Albany Medical Center Hospital, Department of Epidemiology, Albany, New York[4]; and Albany Medical Center Hospital, Department of Pharmacy, Albany, New York[5]

TABLE 1. Comparison of outcomes between high (≥1.5 mg/liter) and low (<1.5 mg/liter) vancomycin MICs

Outcome	High MIC (n = 66)	Low MIC (n = 26)	P value
Overall failure[a]	24 (36.4)	4 (15.4)	0.049
30-day mortality[a]	12 (18.2)	3 (11.5)	0.5
Microbiologic failure[a]	6 (9.1)	0 (0)	0.18
Recurrence within 60 days[a]	11 (16.7)	1 (3.8)	0.17
Hospital length of stay after blood culture collection, median (IQR)	21 (9.0–43.0)	10.5 (9.0–16.5)	0.02
Switched to alternative antibiotic[a]	13 (19.7)	2 (7.7)	0.21

[a] All data presented are no. (percent) of patients.

MICs : Vancomycin and other anti-MRSA

Correlation Between Vancomycin MIC Values and the MIC Values of Other Gram-positive Agents Among Patients with MRSA Bloodstream Infections

Drugs	Index vancomycin MIC value	Geometric Mean MIC	Mode MIC	Range MIC	MIC 50	MIC 90
Daptomycin	≥1.5	0.56	1.5	0.19-1.5	0.50	0.75
	<1.5	0.39	0.5	0.13-0.75	0.38	0.75
Linezolid	≥1.5	0.89	0.75	0.38-2.0	0.75	1.50
	<1.5	0.88	0.75	0.75-1.5	0.75	1.00
Tigecycline	≥1.5	0.17	0.19	0.09-0.25	0.19	0.25
	<1.5	0.15	0.16	0.09-0.25	0.13	0.20
Teicoplanin	≥1.5	1.82	2.0	1.0-4.0	2.00	2.00
	<1.5	1.34	1.0	0.5-2.0	1.50	2.00

Lodise et al. AAC (2009) 53:5141-4

Vancomycin: where are therapeutic failures ?

Journal of Infection (2008) 57, 110–115

Clinical failures of appropriately-treated methicillin-resistant *Staphylococcus aureus* infections

Julia C. Dombrowski [a,*], Lisa G. Winston [a,b]

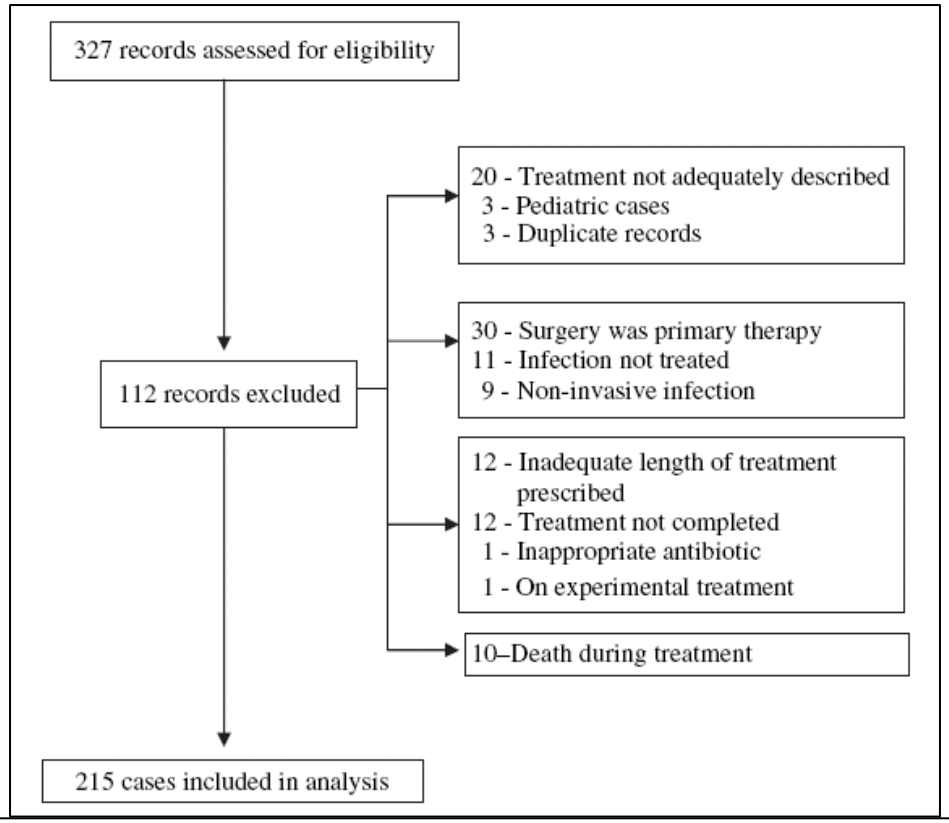


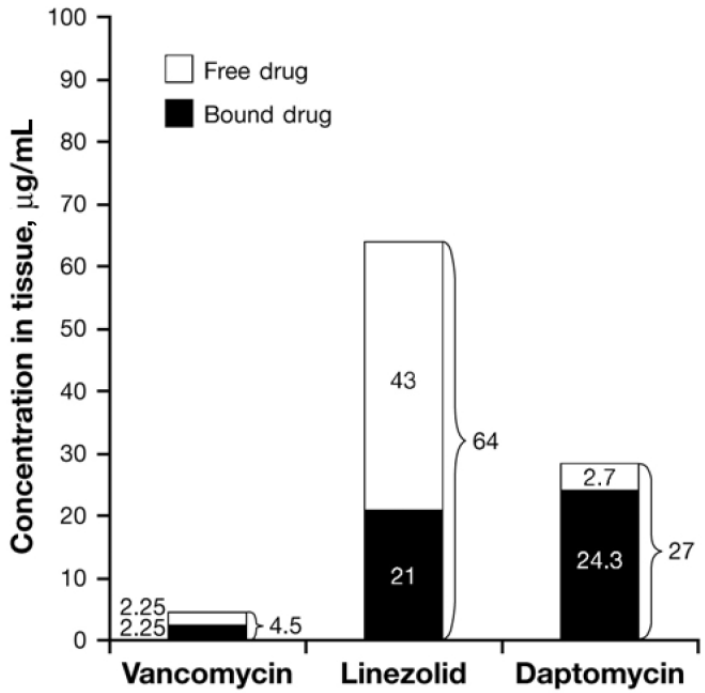
Table 2 Treatment and outcome by site of infection

Site	Total	Failure (%)	Treatment duration (days)	Monotherapy (%)
Osteomyelitis	81	37 (46)	42.9 (SD 5.1)	55 (68)
Bloodstream (without endocarditis)	42	5 (12)	25.8 (14.5)	32 (76)
Pneumonia	45	8 (18)	24.3 (14.8)	36 (80)
Endocarditis	32	5 (16)	37.4 (8.4)	19 (59)
Joint	23	1 (4)	39 (5.7)	19 (83)
Epidural abscess	18	5 (28)	40.1 (3.6)	12 (67)
Surgical site	15	4 (27)	34.6 (9.2)	13 (87)
Meningitis	1	0 (0)	42 (0)	1 (100)
Overall (by patient)[a]	215	53 (23)	see note	157 (73)

NOTE. Data not included since treatment duration was based primarily on site of infection.
[a] 25% of patients had infections at more than one site.

Vancomycin: where are therapeutic failures ?

What about drug distribution ?



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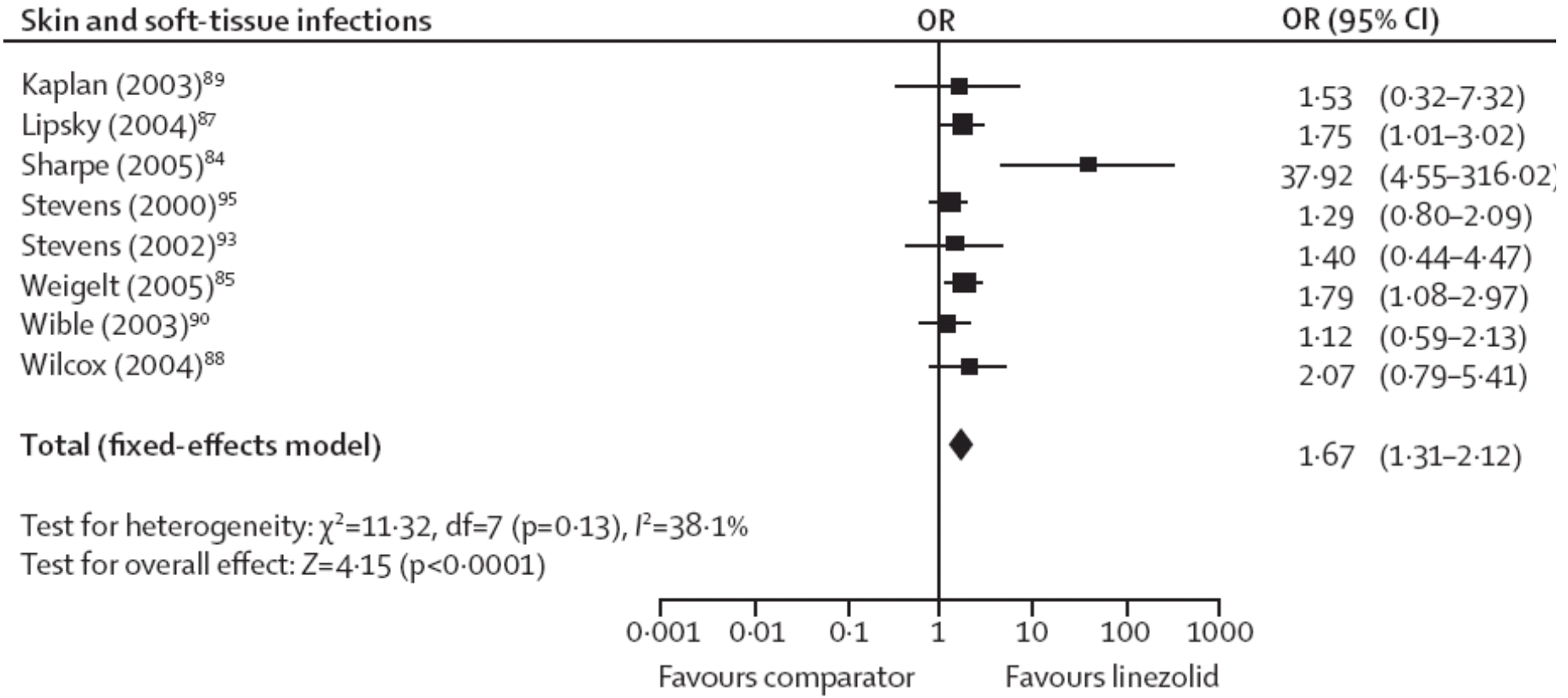
Stevens, Clin. Infect. Dis. (2006) 42 : S51-57

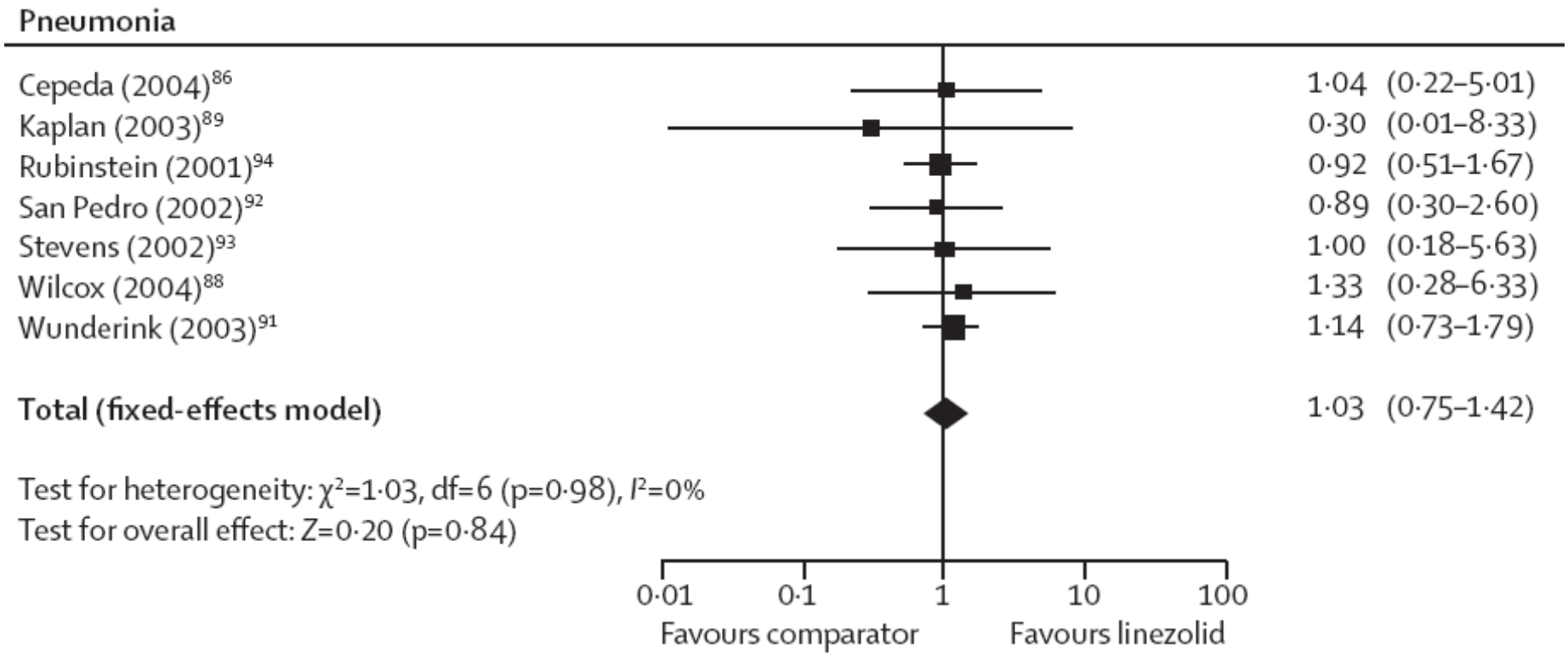
Clinical efficacy

Vancomycin vs linezolid: skin and soft tissues infections



Falagas et al. Lancet Infect Dis. (2008) 8:53-66

Vancomycin vs linezolid: pneumonia



Falagas et al. Lancet Infect Dis. (2008) 8:53-66

Vancomycin vs linezolid: pneumonia

Intensive Care Med (2004) 30:388–394
DOI 10.1007/s00134-003-2088-1

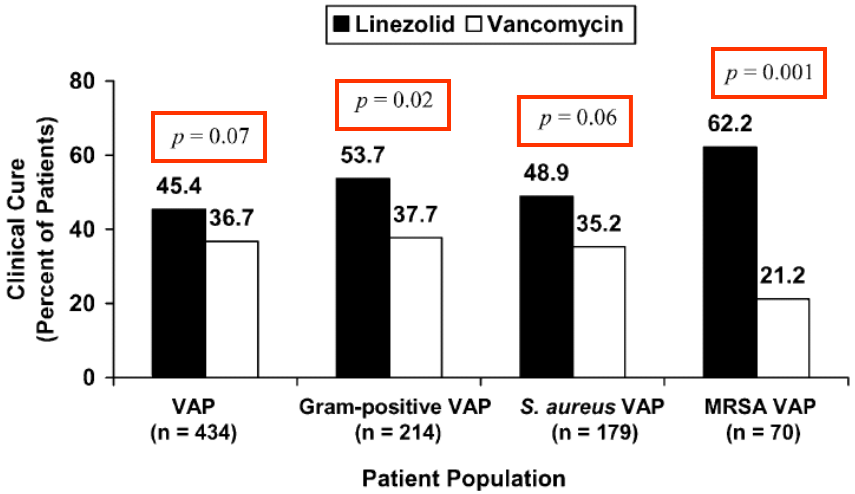
ORIGINAL

Marin H. Kollef
Jordi Rello
Sue K. Cammarata
Rodney V. Croos-Dabrera
Richard G. Wunderink

Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin

282-262 patients

Clinical efficacy



Bacterial eradication

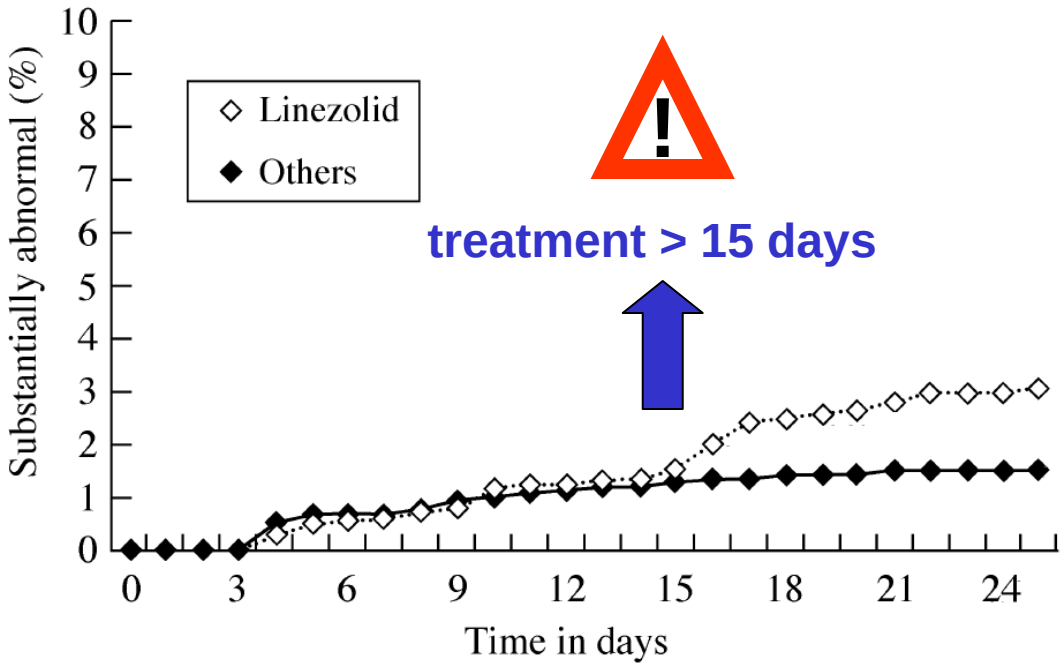
Table 3 Bacterial eradication rates (*ITT* intention to treat, *MRSA* methicillin-resistant *S. aureus*, *VAP* ventilator-associated pneumonia)

	Linezolid		Vancomycin		*p*
	n	%	*n*	%	
ITT Gram-positive VAP	63/128	49.2	44/112	37.6	0.067
ITT *S. aureus*	41/90	45.6	31/93	33.3	0.091
ITT MRSA VAP	23/38	60.5	8/35	22.9	0.001

Safety profile

Severe adverse reactions with linezolid

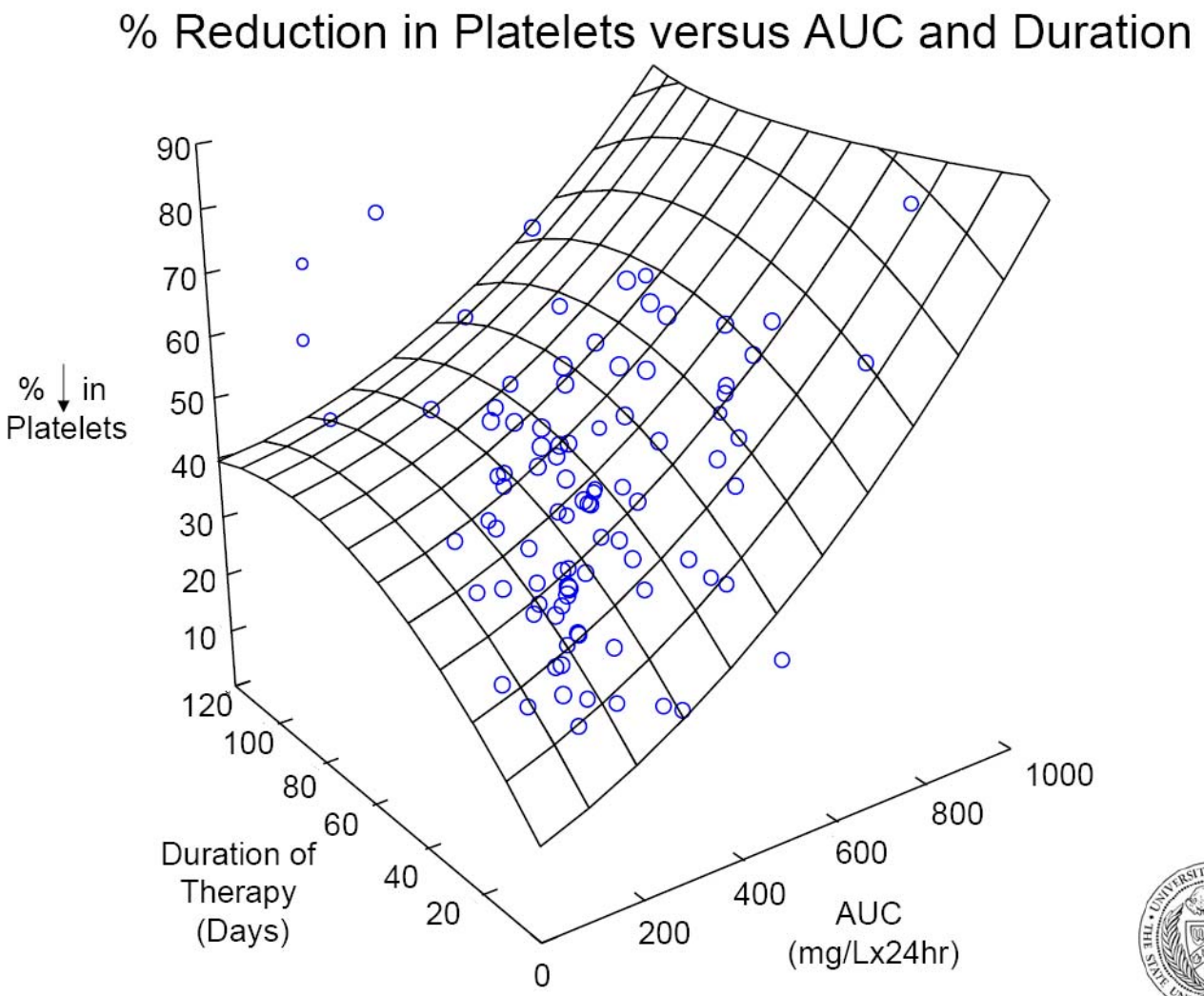
Thrombocytopenia:
2046 "linezolid" patients versus 2001 "comparator" patients in phase III



Phase III comparator-controlled trials: cumulative percentage of patients with at least one substantially low platelet count (<75% of lower limit of normal and/or baseline).

Gerson et al., AAC (2002) 46:2723-6

What about toxicodynamics ?



Forrest et al. ICAAC (2000) abstract 283

Severe adverse reactions with linezolid

neuropathy case reports

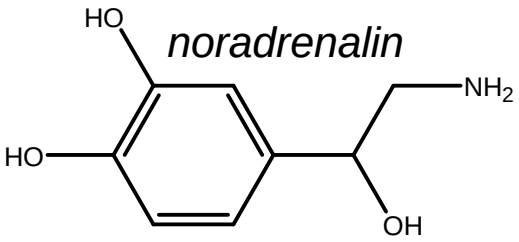
Infection (n)	Months of therapy	Side-effect	Linezolid discontinued	Resolution (follow-up, months)
MRSA (1)	6	SLPPN	Yes	No (2)
*(3)	Mean 3·2	PN NOS	2 of 3	*(*)
MRSA (1)	6	SLPPN/ON	Yes	ON yes, PN no (5)
MRSA (2)	10	ON	Yes	1 yes (9), 1 partial (6)
Nocardia (1)	4	PN NOS	Yes	Yes (*)
NTM/nocardia (5)	Mean 6·4	SLPPN	2 of 5	1 of 5 (*)
MDR TB (1)	*	*	No	*(17)
Nocardia farcinica (1)	4	ON	Yes	Yes (8)
Actinomyces odontolyticus	6	SLPPN	Yes	No
NTM (1)	*	PPN NOS	Yes	No (?)
NTM (1)	7	PN NOS	*	*
Nocardia (1)	6	PPN NOS	*	*
MRSA (1)	12	PN, ataxia	No	No (*)
MRSA (1)	3	PN NOS	*	*

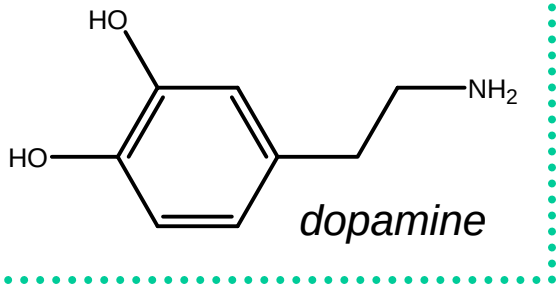
*Data not provided. MRSA=meticillin-resistant *Staphylococcu reus*, NTM=non-tuberculous mycobacteria, SLPPN=stocking-like painful peripheral neuropathy, PN NOS=peripheral neuropathy not otherwise specified, ON=optic neuropathy, P NOS=painful peripheral neuropathy location not specified.

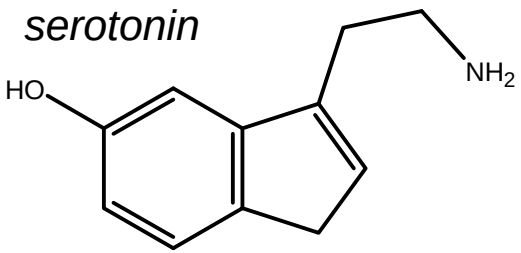
treatment > 28 days

Bressler et al., Lancet Infect. Dis (2004) 4:528-31

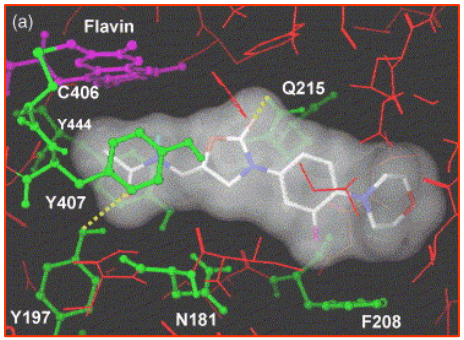
Interactions with linezolid





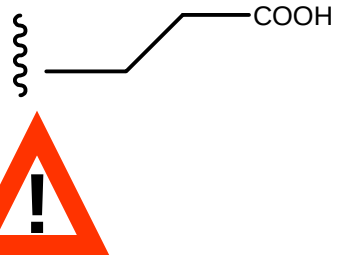


SEROTONINERGIC SYNDROME
hypertension
tachycardia
(cerebral hemorrhage)
(headache)



Mono Amino Oxydase
A & B

linezolid



Association with drugs
- ↗ synthesis
- ↗ liberation
- ↘ metabolism
- ↘ recapture

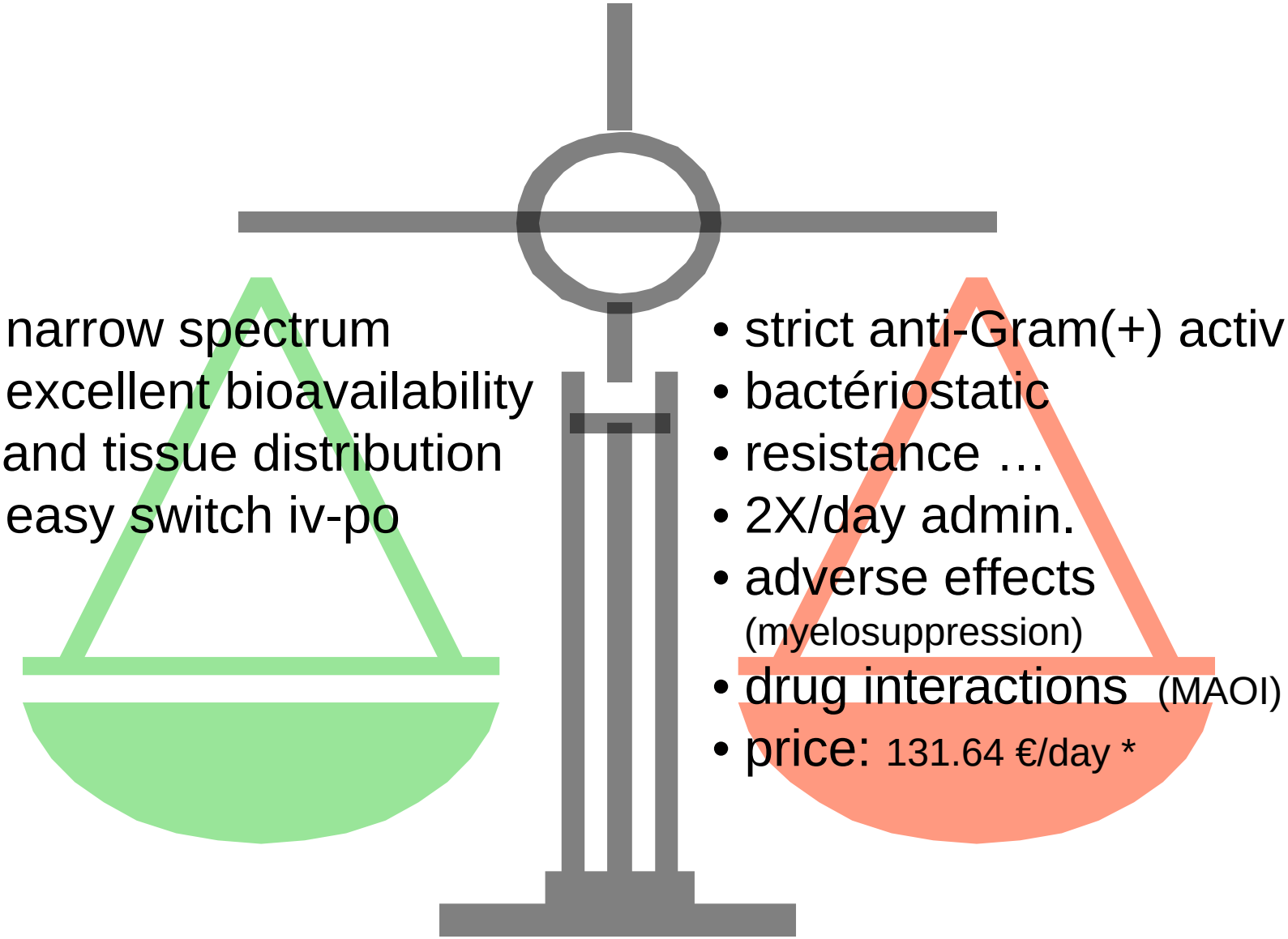
of neurotransmettors

- are agonists of receptors

Association with tyramine-rich food

Taylor et al., CID (2006) 43:180-7

Linezolid: pros and cons



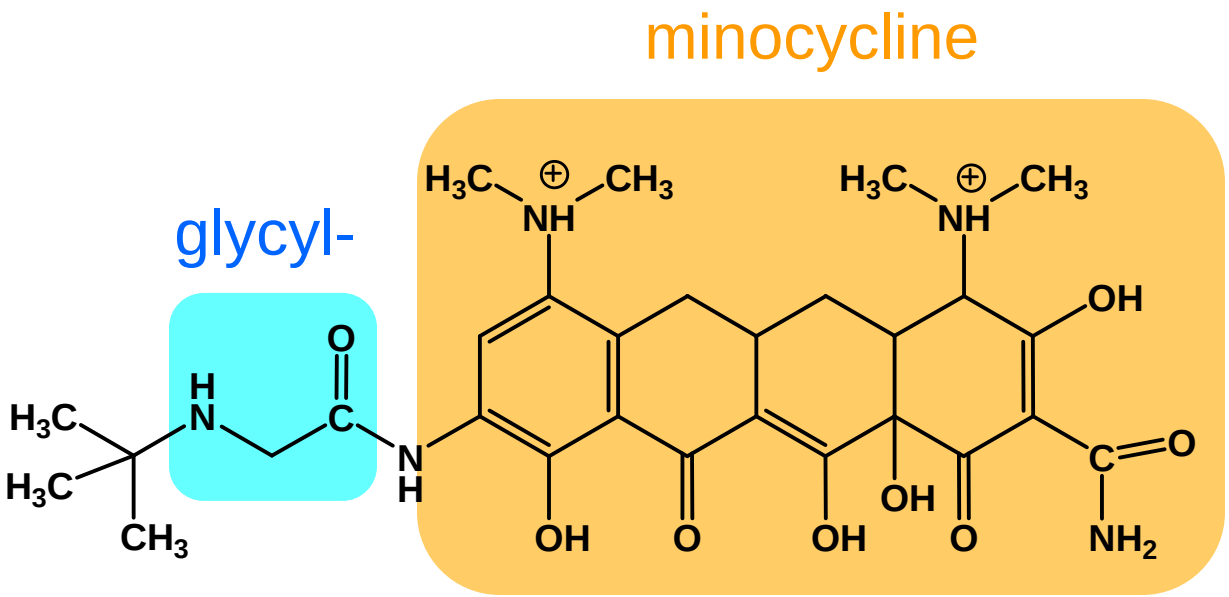
- narrow spectrum
- excellent bioavailability and tissue distribution
- easy switch iv-po

- strict anti-Gram(+) activity
- bactériostatic
- resistance …
- 2X/day admin.
- adverse effects (myelosuppression)
- drug interactions (MAOI)
- price: 131.64 €/day *

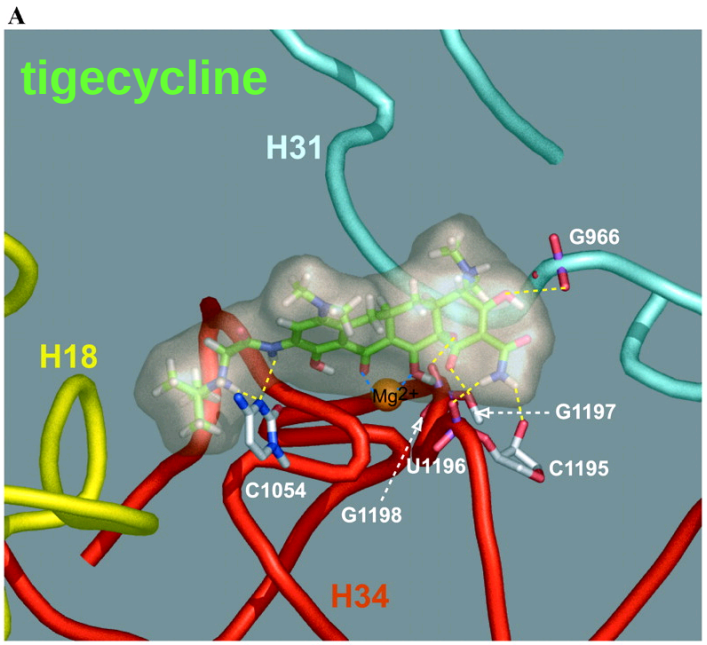
vanco : 60-80 €/jour

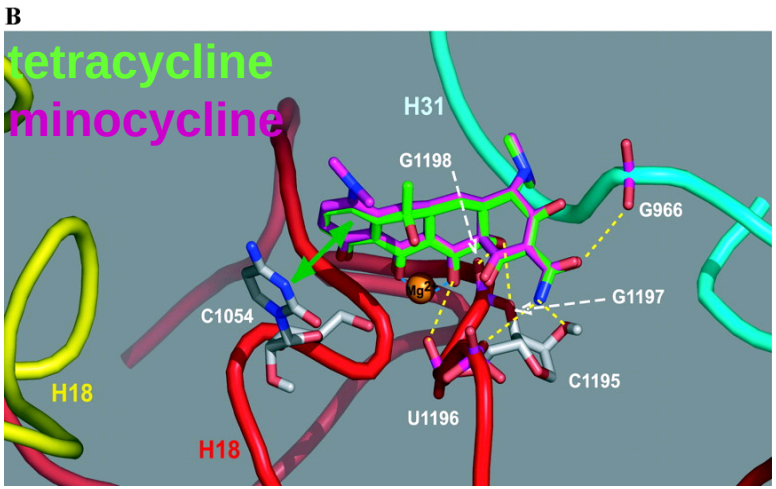
TIGECYCLINE

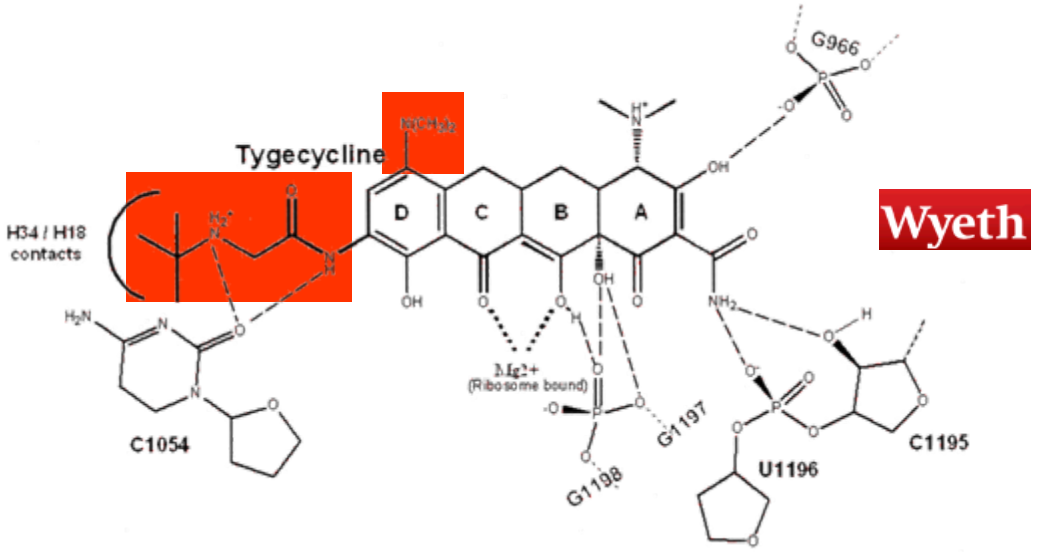
Tigecycline: a glycylcycline



Tigecycline mode of action







- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps; but remains susceptible to broad spectrum efflux pumps of Gram(-) (MexXY in *P. aeruginosa*)

Olson et al., AAC (2006) 50:2156-66

In vitro activity

Tetra- and glycyl-cyclines: activity and resistance

species	phenotype	tetracycline	minocycline	tigecycline
E. coli	susceptible	1	1	0.25
	Efflux (Tet)	> 32	16	0.5
	Ribosomal protection	> 32	> 32	0.25
S. aureus	susceptible	0.12	0.06	0.25
	Efflux (Tet)	> 32	0.25	0.5
	Ribosomal protection	> 32	4	0.25

Petersen et al., AAC (1999) 43:738-44

Tetra- and glycyl-cyclines: activity and resistance

what about *Pseudomonas* ?

phenotype	MIC (mg/L)
WT	8
Δ mexXY	0.5

Dean et al., AAC (2003) 47:972-8

Tigecycline in vitro activity

phenotype	MIC 50	MIC 90	range
A. baumanii	0.5	1	< 0.008-16
MDR *A. baumanii*	0.5	1	< 0.008-8
P. aeruginosa	8	> 32	< 0.008->32
E. cloacae	0.5	2	< 0.008->32
E. coli	0.12	0.25	< 0.008-8
MRSA	0.12	0.25	< 0.008-1
S. pneumoniae	0.03	0.06	< 0.008-1

Garrison et al., Diagn Microbiol Infect Dis. (2009) 65:288-99

Pharmacokinetics / Pharmacodynamics

Tigecycline: pharmacokinetics

Initial bolus: 100 mg; followed by 50 mg q12h

parameter	healthy volunteers (n=5)	cSSSTI (n=43)
Cmax (mg/L)	0.621	0.40
Cmin (mg/L)	0.145	0.14
AUC $_{24h}$ (mg.h/L)	6.14	4.48

low !

but needs to be considered in the light of MICs

Van Wart et al., JAC (2006) 50:3701-7
McGowan, JAC (2008) 62: suppl.1 i11-i16

Tigecycline: pharmacokinetics

	tissue	AUC_{24h} (mg.h/L)	serum/tissue AUC ratio
Single dose: 100 mg	bile	2815	537
	bladder	120	23
	colon	17.3	2.6
	lung	9.19	2
	bone	2.05	0.4
	synovial fluid	1.68	0.31
	CSF	0.46	0.11
100 mg + 6x50 mg q12h	ELF	4.54	1.31
	alveolar MΦ	268	77.5

routes of elimination

Rodvold, JAC (2006) 58:1221-9

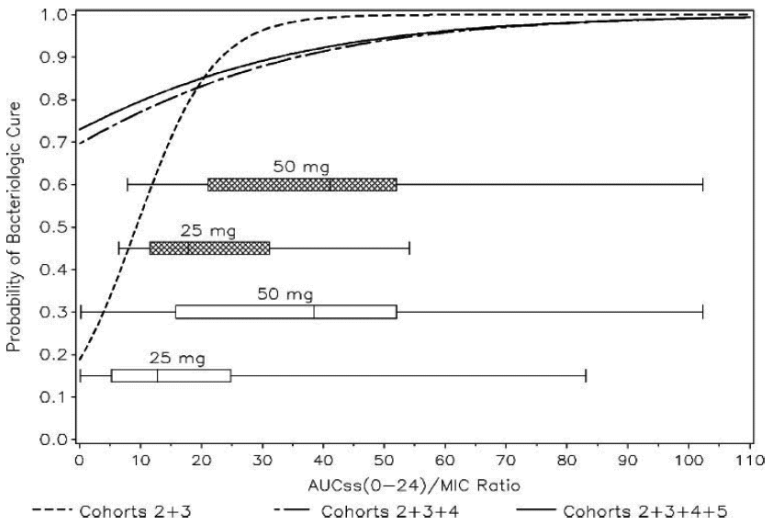
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

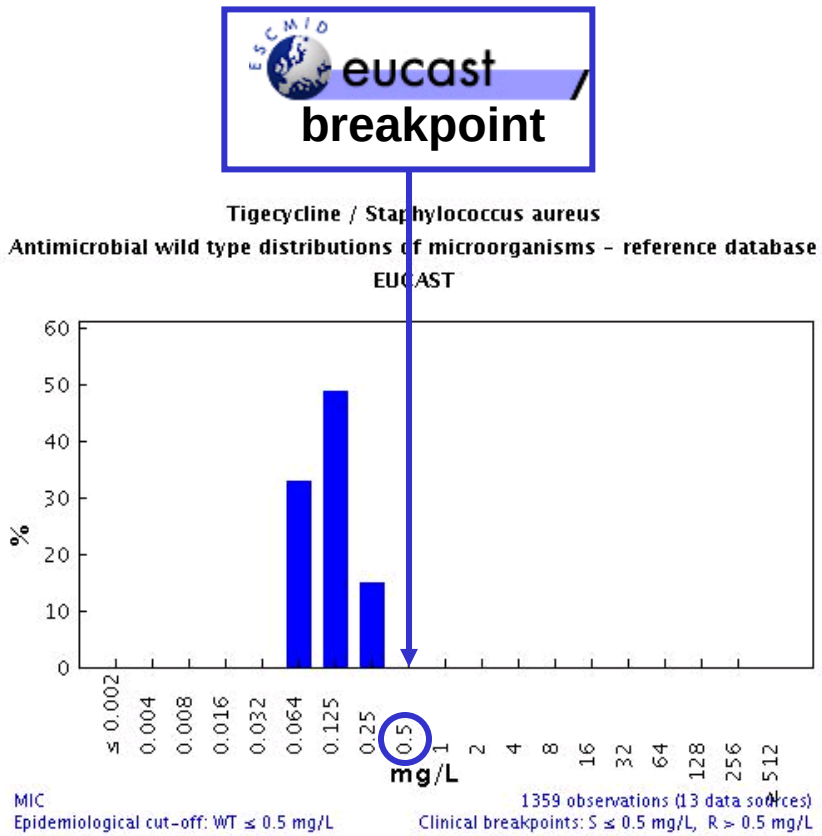
Tigecycline: setting up the breakpoint

Pharmacodynamic breakpoint for Gram(+) infections

AUC/MIC ≥ 17.9

MIC ≤ 17.9/4.48 = 0.25 mg/L





to avoid splitting the WT distribution …

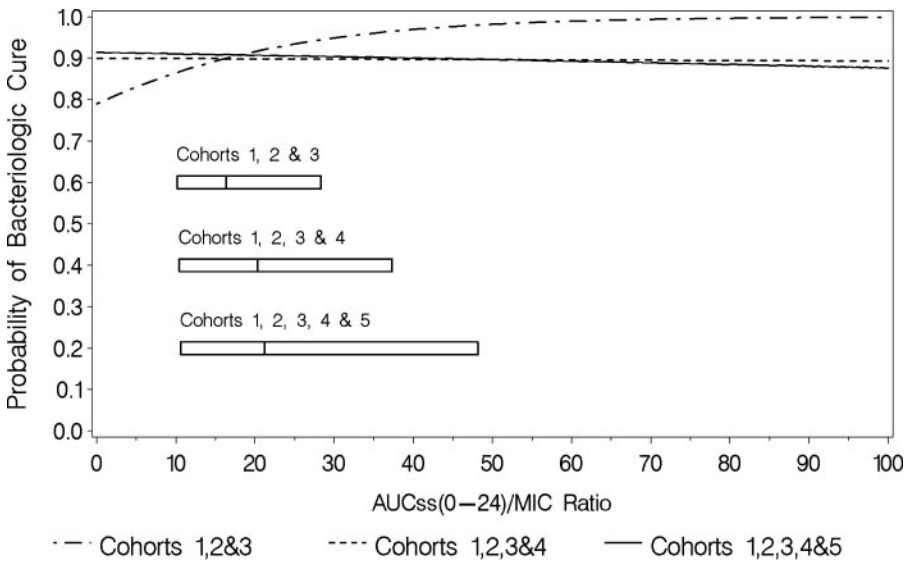
Meagher et al., AAC (2007) 52:204-10

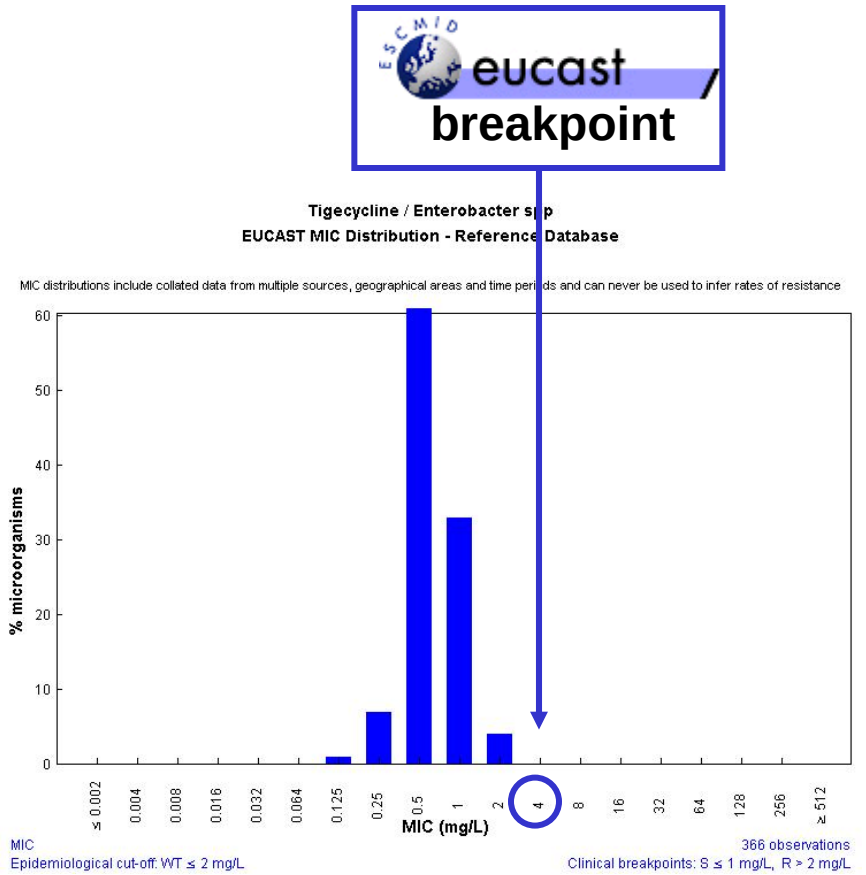
Tigecycline: setting up the breakpoint

Pharmacodynamic breakpoint for Gram(-) infections

AUC/MIC ≥ 6.96

MIC ≤ 6.96/4.48 = 1.5 mg/L



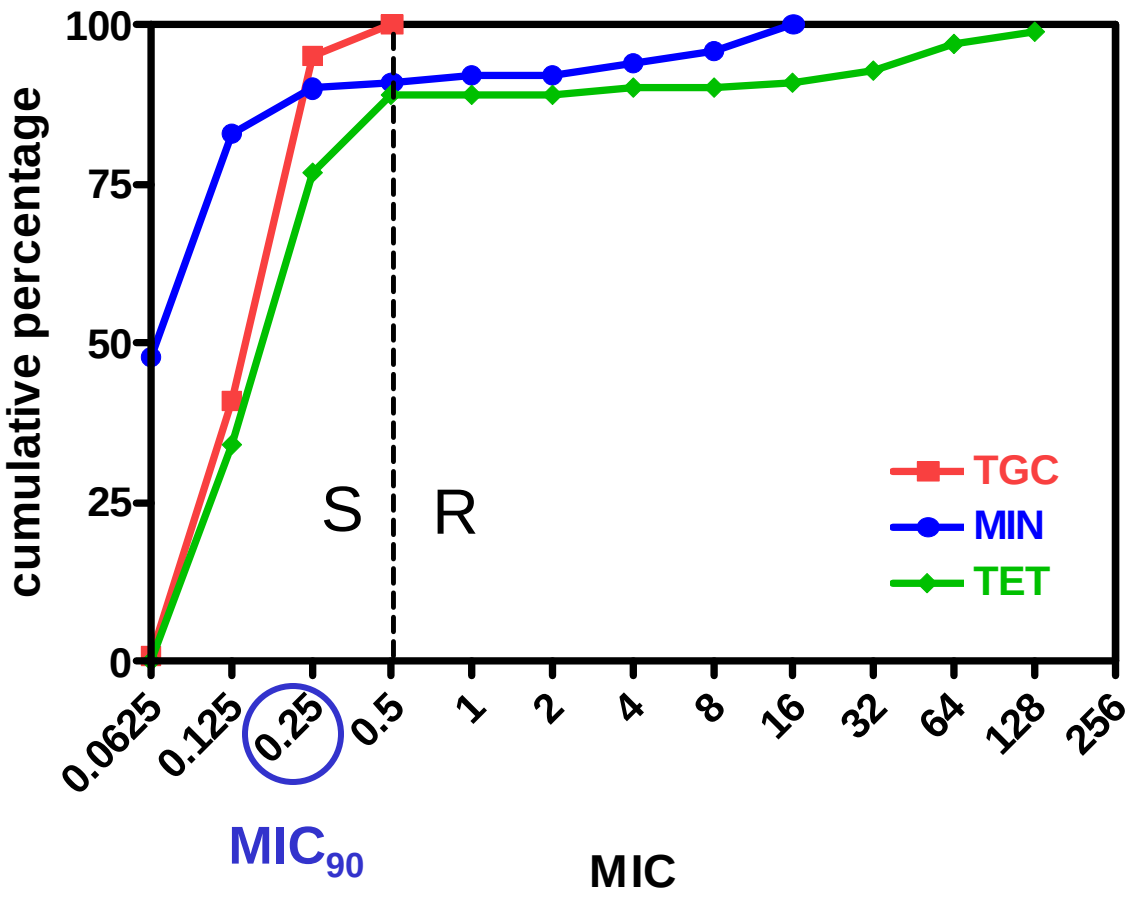


to avoid splitting the WT distribution …

Passarell et al., AAC (2008) 51:1939-45

Tigecycline breakpoint: how does it fit with Belgian MICs ?

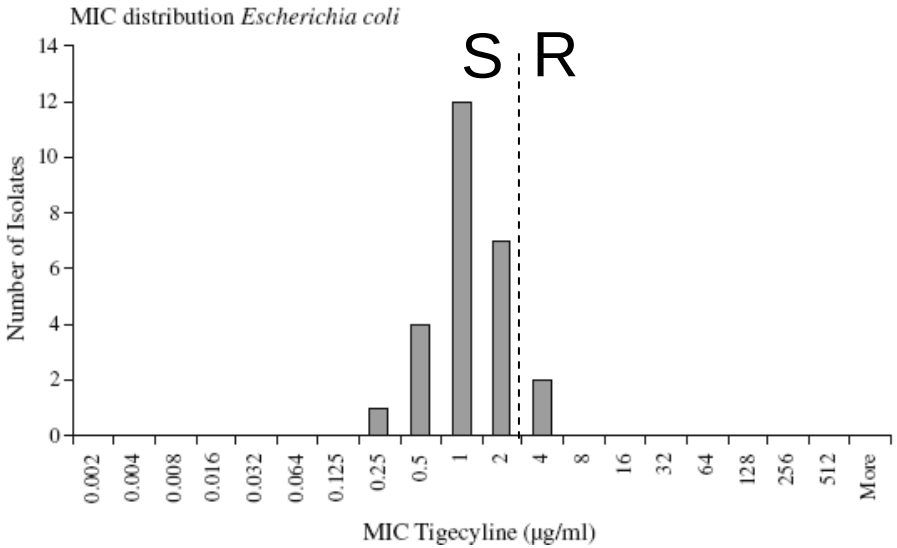
511 MRSA isolates from 112 Belgian hospitals

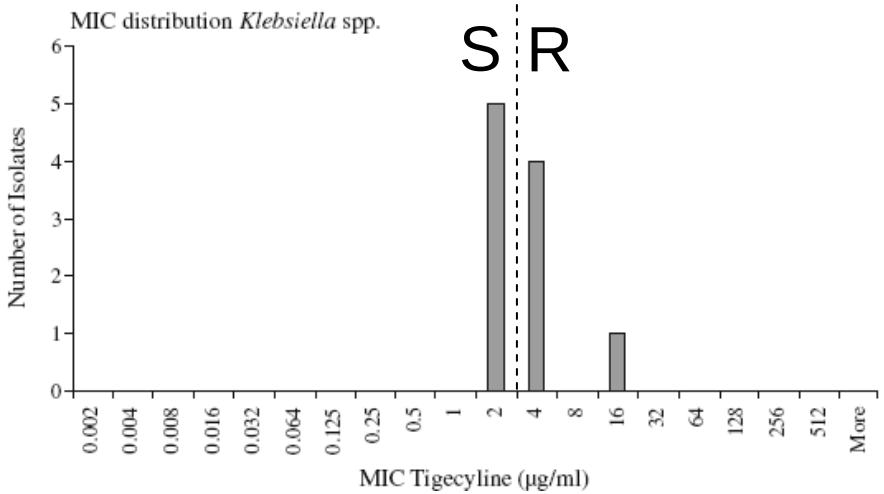


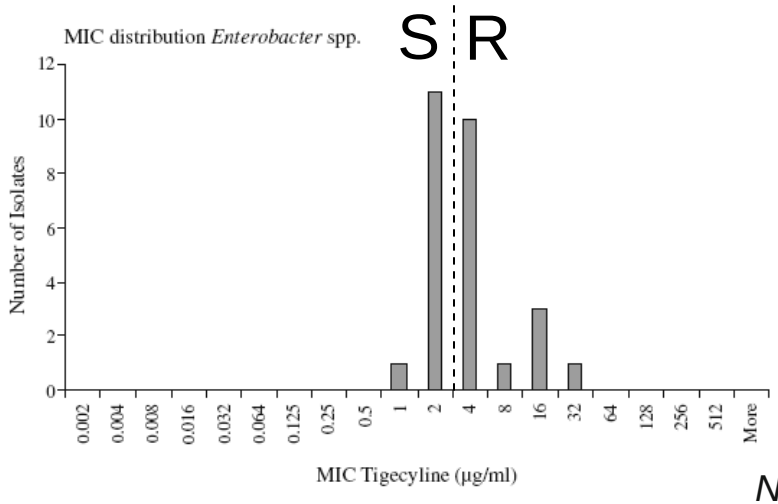
Denis et al., AAC (2006) 50:2680-85

Tigecycline breakpoint: how does it fit with Belgian MICs ?

Belgian isolates of Gram(-) (The GZA St. Augustinus/St. Vincentius/St. Jozef, Wilrijk)







Naesens et al. Eur J Clin Microbiol Infect Dis (2009) 28:381–384

PK/PD of Tigecycline in different compartments

Dose and admin. route	compartment	AUC	AUC/MIC (0.25 mg/L)	AUC/MIC (0.5 mg/L)
			MIC $_{90}$ in Belgium	***EUCAST Breakpoint***
100 mg iv	serum	5.2	20.8	10.4
	lung	9.2	36.8	18.4
	bone	2.1	8.4	4.2
	synovial fluid	1.7	6.8	3.4

Rodvold et al., JAC (2006) 58:1221-29

Clinical efficacy

Tigecycline clinical experience

Phase 3 - Skin and skin structure infections

Microbiological eradication rates of selected baseline isolates at the test-of-cure visit (microbiologically evaluable population).

Isolate	Tigecycline		Vancomycin-aztreonam	
	No. of patients/total	Percentage of patients (95% CI)	No. of patients/total	Percentage of patients (95% CI)
Staphylococcus aureus				
Methicillin resistant	25/32	78.1 (60.0–90.7)	25/33	75.8 (57.7–88.9)
Methicillin susceptible	119/134	88.8 (82.2–93.6)	109/120	90.8 (84.2–95.3)
Streptococcus pyogenes	30/32	93.8 (79.2–99.2)	25/27	92.6 (75.7–99.1)
Streptococcus agalactiae	7/8	87.5 (47.3–99.7)	11/13	84.6 (54.6–98.1)
Streptococcus anginosus[a]	14/16	87.5 (61.7–98.4)	6/7	85.7 (42.1–99.6)
Enterococcus faecalis (non–vancomycin resistant)	14/16	87.5 (61.7–98.4)	22/24	91.7 (73.0–99.0)
Escherichia coli	24/29	82.8 (64.2–94.2)	27/30	90.0 (73.5–97.9)
Bacteroides fragilis	8/8	100.0 (63.1–100.0)	4/5	80.0 (28.4–99.5)

NOTE. ND, not determined.

[a] Includes *S. anginosus, S. anginosus ana, Streptococcus intermedius,* and *Streptococcus constellatus.*

Ellis-Grosse et al., Clin. Infect. Dis. (2005) 41:S341-53

Tigecycline clinical experience

Phase 3 – MRSA serious infections

TGC 100 mg/ 50 mg q12h vs VAN 1g q12h; 7-28 days

clinical response

(rate of cure) at TOC assessment in patients with MRSA infection

APACHE II Score	Site of infection	Tigecycline *n/N*	Tigecycline % (95% CI)	Vancomycin *n/N*	Vancomycin % (95% CI)
ME population					
≤15	cSSSI	50/58	86.2 (74.6–93.9)	19/22	86.4 (65.1–97.1)
	other	17/21	81.0 (58.1–94.6)	6/6	100.0 (54.1–100.0)
>15	cSSSI	1/1	100.0 (2.5–100.0)	1/1	100.0 (2.5–100.0)
	other	2/6	33.3 (4.3–77.7)	0/2	0.0 (0.0–84.2)
overall		70/86	81.4 (71.6–89.0)	26/31	83.9 (66.3–94.5)
m-mITT population					
≤15	cSSSI	54/69	78.3 (66.7–87.3)	19/22	86.4 (65.1–97.1)
	other	17/22	77.3 (54.6–92.2)	7/7	100.0 (59.0–100.0)
>15	cSSSI	1/1	100.0 (2.5–100.0)	1/1	100.0 (2.5–100.0)
	other	3/8	37.5 (8.5–75.5)	0/3	0.0 (0.0–70.8)
overall		75/100	75.0 (65.3–83.1)	27/33	81.8 (64.5–93.0)

APACHE, Acute Physiologic and Chronic Health Evaluation; cSSSI, complicated skin and/or skin structure infection; ME, microbiologically evaluable; m-mITT, microbiological modified intent-to-treat.

microbiological response

population	tigecycline	vancomycin
ME	80.2 % (69/86)	83.9 % (26/31)
MRSA m-mITT	74 % (74/100)	81.8 % (27/33)

Florescu et al., JAC (2008) 62 Suppl 1:i17-28.

Tigecycline clinical experience

Phase 2/3 – CAP:

TGC 100 mg/ 50 mg q12h vs LVX 500 mg q24h or q12h; 7-14 days

Distribution of patients by Fine score and estimated CURB-65 Score (mITT population)

	Tigecycline (n = 424)	Levofloxacin (n = 422)	Total (n = 846)
FINE score, n (%)			
I	80 (18.9)	105 (24.9)	185 (21.9)
II	147 (34.7)	118 (28.0)	265 (31.3)
III	113 (26.7)	115 (27.3)	228 (27.0)
IV	82 (19.3)	81 (19.2)	163 (19.3)
V	2 (0.5)	3 (0.7)	5 (0.6)
CURB-65 score, n (%)			
0	140 (33.0)	149 (35.3)	289 (34.2)
1	162 (38.2)	149 (35.3)	311 (36.8)
2	88 (20.8)	89 (21.1)	177 (20.9)
3	31 (7.3)	30 (7.1)	61 (7.2)
4	3 (0.7)	5 (1.2)	8 (0.9)

Clinical cure rates by baseline respiratory pathogen (ME population)

Isolate	Tigecycline			Levofloxacin		
	n/N	%	95% CI	n/N	%	95% CI
C. pneumoniae[a]	18/19	94.7	74.0–99.9	26/27	96.3	81.0–99.9
H. influenzae	14/17	82.4	56.6–96.2	13/16	81.3	54.4–96.0
Haemophilus parainfluenzae	5/5	100.0	47.8–100.0	10/10	100.0	69.2–100.0
L. pneumophila[b]	10/10	100.0	69.2–100.0	6/6	100.0	54.1–100.0
M. catarrhalis	3/3	100.0	29.2–100.0	3/5	60.0	14.7–94.7
M. pneumoniae[a]	37/39	94.9	82.7–99.4	44/48	91.7	80.0–97.7
S. pneumoniae (all)	84/91	92.3	84.8–96.9	88/99	88.9	81.0–94.3
S. pneumoniae (PISP)	4/4	100.0	39.8–100.0	6/6	100	54.1–100.0
S. pneumonia (PRSP)	3/3	100.0	29.2–100.0	6/6	100.0	54.1–100.0

Most are non-severe patients … but:

Bacteriemic patients

tigecycline	levofloxacin
90.9 % (20/22)	72.2 % (13/18)

Tanaseanu et al., Diagn Microbiol Infect Dis. (2008) 61:329-38

Tigecycline clinical experience

Phase 3 – HAP/VAP (withdrawn):

TGC 100 mg/ 50 mg q12h vs IMI 500-1000 mg q8h (adj. AB if MRSA or P.a.); 7-14 days

clinical response

patients	population	tigecycline	imipenem/cilastatin
VAP/HAP	CE	67.9 %	78.2 %
	mITT	62.7 %	67.6 %
Non-VAP	CE	75.4 %	81.3 %
	mITT	69.3 %	71.2 %

microbiological response

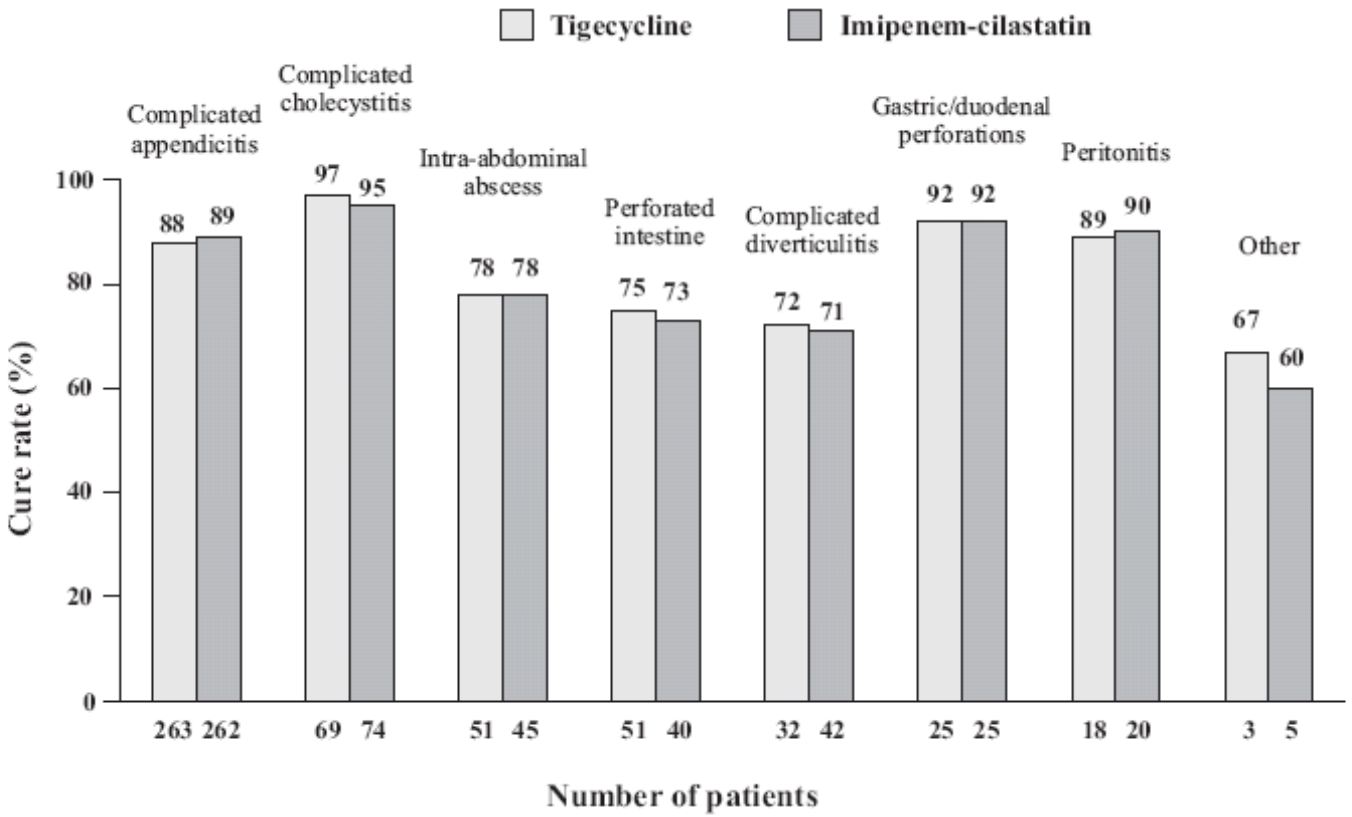
patients	species	tigecycline	imipenem/cilastatin
Non VAP	MRSA	47.1 % (8/17)	78.9 % (15/19)

EMEA/382036/2008

Tigecycline clinical experience

Phase 3 – cIAI:

TGC 100 mg/ 50 mg q12h vs IMI 500 mg q8h; 5-14 days



Babinchak et al., CID 2005;41:S354–S367; Peterson, IJAA (2008) 32 S215-222

Tigecycline clinical experience

Journal of Antimicrobial Chemotherapy (2008) **62**, *Suppl. 1*, i29–i40
doi:10.1093/jac/dkn249

JAC

A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including *Enterobacter* species, *Acinetobacter baumannii* and *Klebsiella pneumoniae*

Objectives: To evaluate the efficacy and safety of tigecycline in patients with selected serious infections caused by resistant Gram-negative bacteria, or failures who had received prior antimicrobial therapy or were unable to tolerate other appropriate antimicrobials. Secondary objectives included an evaluation of the microbiological efficacy of tigecycline and *in vitro* activity of tigecycline for resistant Gram-negative bacteria.

Methods: This open-label, Phase 3, non-comparative, multicentre study assessed the efficacy and safety of intravenous tigecycline (100 mg initially, then 50 mg 12 hourly for 7–28 days) in hospitalized patients with serious infections including complicated intra-abdominal infection; complicated skin and skin structure infection (cSSSI); community-acquired pneumonia (CAP); hospital-acquired pneumonia, including ventilator-associated pneumonia; or bacteraemia, including catheter-related bacteraemia. All patients had infections due to resistant Gram-negative organisms, including extended-spectrum β-lactamase-producing strains, or had failed on prior therapy or could not receive (allergy or intolerance) one or more agents from three classes of commonly used antibiotics. The primary efficacy endpoint was clinical response in the microbiologically evaluable (ME) population at test of cure (TOC). Safety data included vital signs, laboratory tests and adverse events (AEs).

Results: In the ME population at TOC, the clinical cure rate was 72.2% [95% confidence interval (CI): 54.8–85.8], and the microbiological eradication rate was 66.7% (95% CI: 13.7–78.8). The most commonly isolated resistant Gram-negative pathogens were *Acinetobacter baumannii* (47%), *Escherichia coli* (25%), *Klebsiella pneumoniae* (16.7%) and *Enterobacter* spp. (11.0%); the most commonly diagnosed serious infection was cSSSI (67%). The most common treatment-emergent AEs were nausea (29.5%), diarrhoea (16%) and vomiting (16%), which were mild or moderate in severity.

Conclusions: In this non-comparative study, tigecycline appeared safe and efficacious in patients with difficult-to-treat serious infections caused by resistant Gram-negative organisms.

Safety profile

Tigecycline clinical experience

Table 5. Incidence (%) of common treatment-emergent adverse events in tigecycline phase III studies

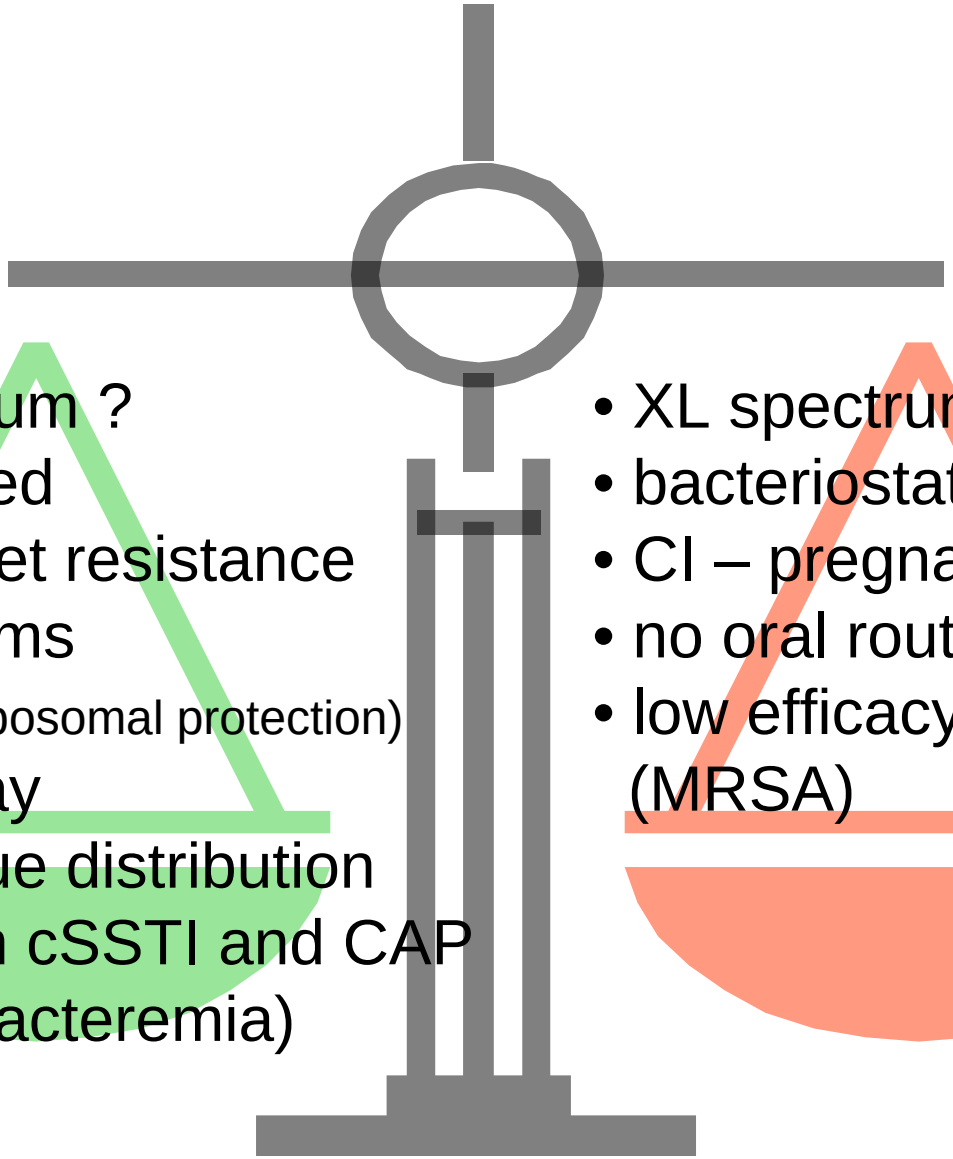
Adverse event	Incidence (%)		*P*-value
	Tigecycline (*N* = 1,415)	Comparator[a] (*N* = 1,382)	
Nausea	29.5	15.8	<0.001
Vomiting	19.7	10.8	<0.001
Diarrhoea	12.7	10.8	0.127
Thrombocythaemia	6.1	6.2	0.937
Phlebitis	1.8	3.8	0.002
Rash	2.4	4.1	0.011
Infection	8.3	5.4	0.003
Bilirubinemia	2.3	0.9	0.004
ALT increase	5.6	4.7	0.305
AST increase	4.3	4.4	0.926

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

[a] Vancomycin plus aztreonam (complicated skin and soft tissue infections), imipenem/cilastatin (complicated intra-abdominal infections), or linezolid (resistant pathogens).

Peterson, IJAA (2008) 32 S215-222

Tigecycline : pros and cons



- XL spectrum ?
- not affected by some tet resistance mechanisms (Tet efflux, ribosomal protection)
- once-a-day
- large tissue distribution
- efficient in cSSTI and CAP (MRSA; bacteremia)

- XL spectrum ?
- bacteriostatic
- CI – pregnancy, children
- no oral route
- low efficacy in HAP/VAP (MRSA)

DORIPENEM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To treat today's gram-negative infections*†
When the situation is critical, call for the potency of DORIBAX®
Indicated for adults in the treatment of cIAI and cUTI, including pyelonephritis
Excellent gram-positive, gram-negative, and anaerobic coverage
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Carbapenem potency that breaks through today's gram-negative pathogens
Proven in vitro activity vs P aeruginosa, Enterobacteriaceae, and A baumannii
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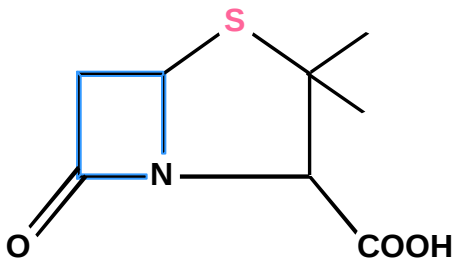
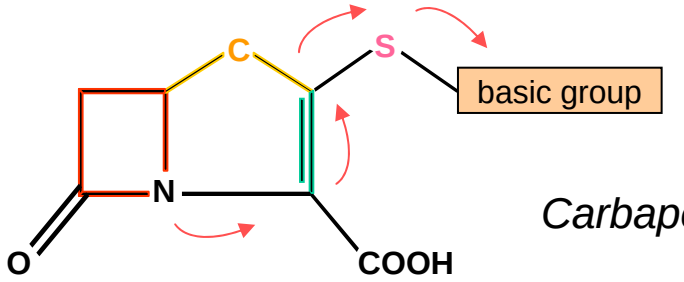
Penams and carbapenems



Penam → Penicillins



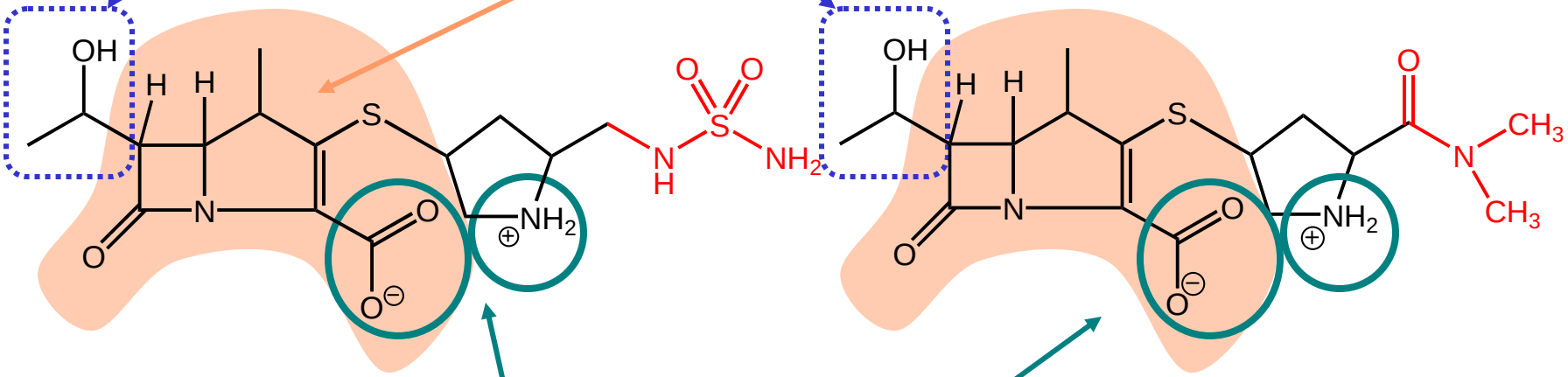
Carbapenem → imipenem

greater intrinsic activity due to larger instability of the β-lactam ring because of C1-C2 double bond and electroattractig effect of the basic group

Structure of the molecules

no lateral chain
methyl subst.
➔ Resistance to β-lactamases

No endocyclic S
➔ Strong binding to PBP
➔ VERY broad spectrum



doripenem

meropenem

Zwitterion
➔Penetration in Gram(-),
including *Pseudomonas*

In vitro activity

In vitro activity against selected Gram-(-) bacteria

Range of MIC_{90} values

Pathogen	MIC_{90}, μg/mL		
	Doripenem	Meropenem	Imipenem
Gram negative			
Escherichia coli	0.03	0.016–0.03	0.12–0.25
Klebsiella pneumoniae	0.06–0.12	0.03–0.12	0.25–0.5
Klebsiella oxytoca	0.06	0.03	0.5
Proteus mirabilis	0.5	0.12	4.0
Proteus vulgaris	0.5	0.12	2.0
Morganella morganii	0.25	0.06	2.0
Citrobacter freundii	0.03–0.06	0.03–0.06	0.5–1.0
Enterobacter cloacae	0.06	0.06	0.5
Serratia marcescens	0.25–0.5	0.12	1.0–2.0
Pseudomonas aeruginosa	1.0–2.0	2.0–4.0	2.0–8.0
Stenotrophomonas maltophilia	>32.0	>32.0	>32.0
Burkholderia cepacia	8.0	8.0	32.0
Haemophilus influenzae	0.5	0.25	4.0
Bordetella pertussis	0.5	0.25	1.0
Gram positive			
Streptococcus pneumoniae			
Penicillin susceptible	0.008	0.016	0.008
Penicillin resistant	0.5	0.5	0.25
Staphylococcus aureus			
Methicillin susceptible	0.06	0.12	0.16–0.03
Methicillin resistant	8.0	8.0	8.0
Enterococcus faecalis	4.0	8.0	1.0
Enterococcus faecium	>32.0	>32.0	>32.0

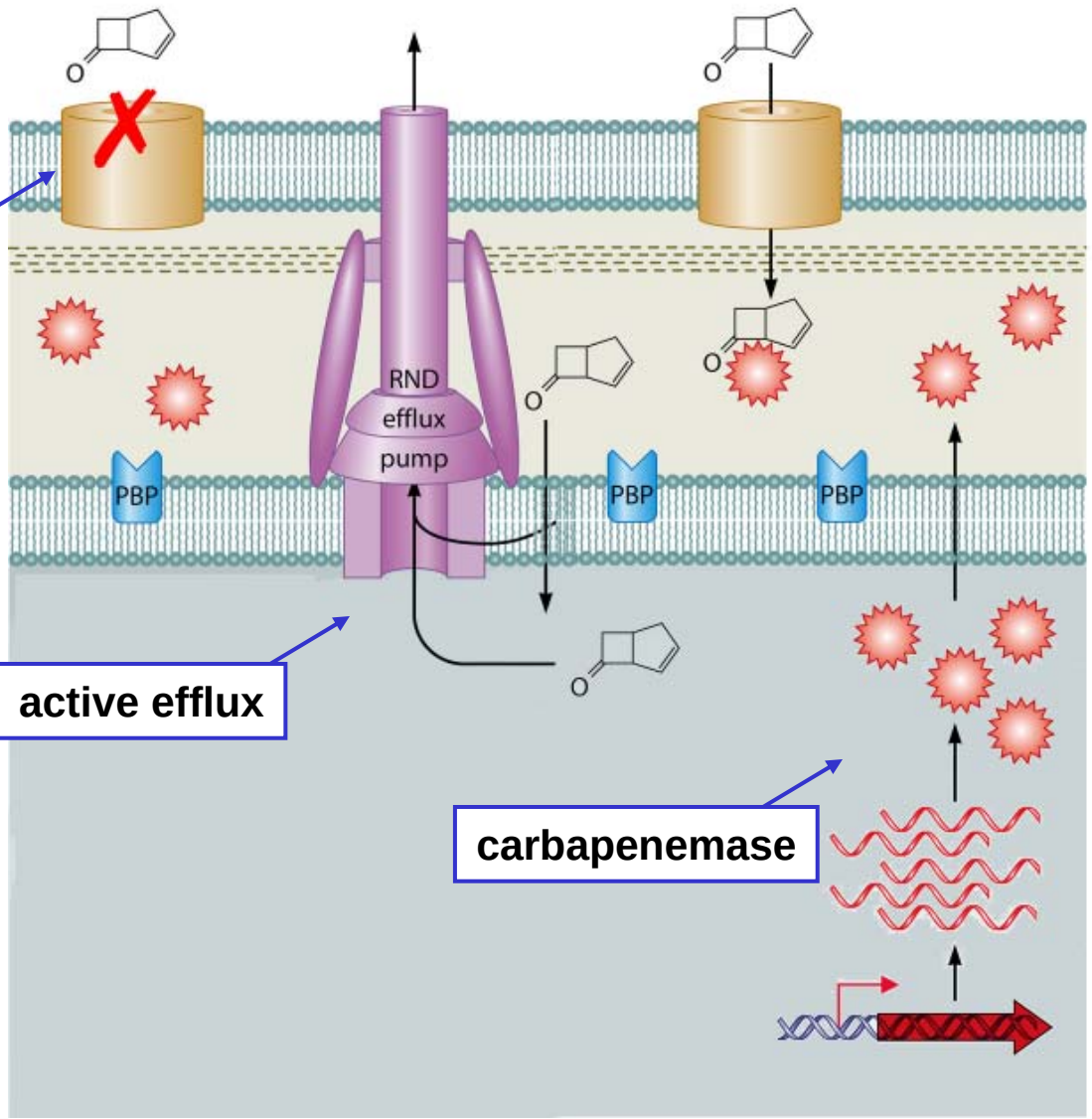
DOR vs IMI:
DOR MIC lower

DOR vs MEM:
1 (to 2) dilutions difference in MIC, most often in advantage to MEM,

except for *P. aeruginosa* and Gram (+)

Restrepo, CID (2009) 49:S11-16

Resistance mechanisms to carbapenems



Adapted from Lister et al., Clin. Microbiol. Rev. (2009) 22:582-610

Susceptibility to resistance mechanisms

Influence of resistance mechanisms in *Pseudomonas*

carbapenem	MexAB	MexEF	OprD	metallo β-lactamase
imipenem	S	r / R	R	R
meropenem	R	R	r	R
doripenem	R	nd	r	R

R : MIC > 8 mg/L
r : MIC < 8 mg/L

Dalhoff et al., Biochem. Pharmacol. (2006) 71:1085-95

Pharmacokinetics / Pharmacodynamics

Comparative PK profile in volunteers

Single dose PK

parameter	DOR	MEM	
	(500 mg)	(500 mg)	(1g)
C_{max} (mg/L)	20.2	26	50-60
Prot. binding (%)	8.9	2	
AUC (mg.h/L) – 8 h	44.1	27.2-32.4	66.9-77.5
$T_{½}$ (h)	0.93	1	

Elimination of doripenem is primarily via the renal route

- Dosage adjustment is necessary in patients with moderate and severe renal impairment; AUCs of doripenem and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require haemodialysis compared with healthy subjects
- the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

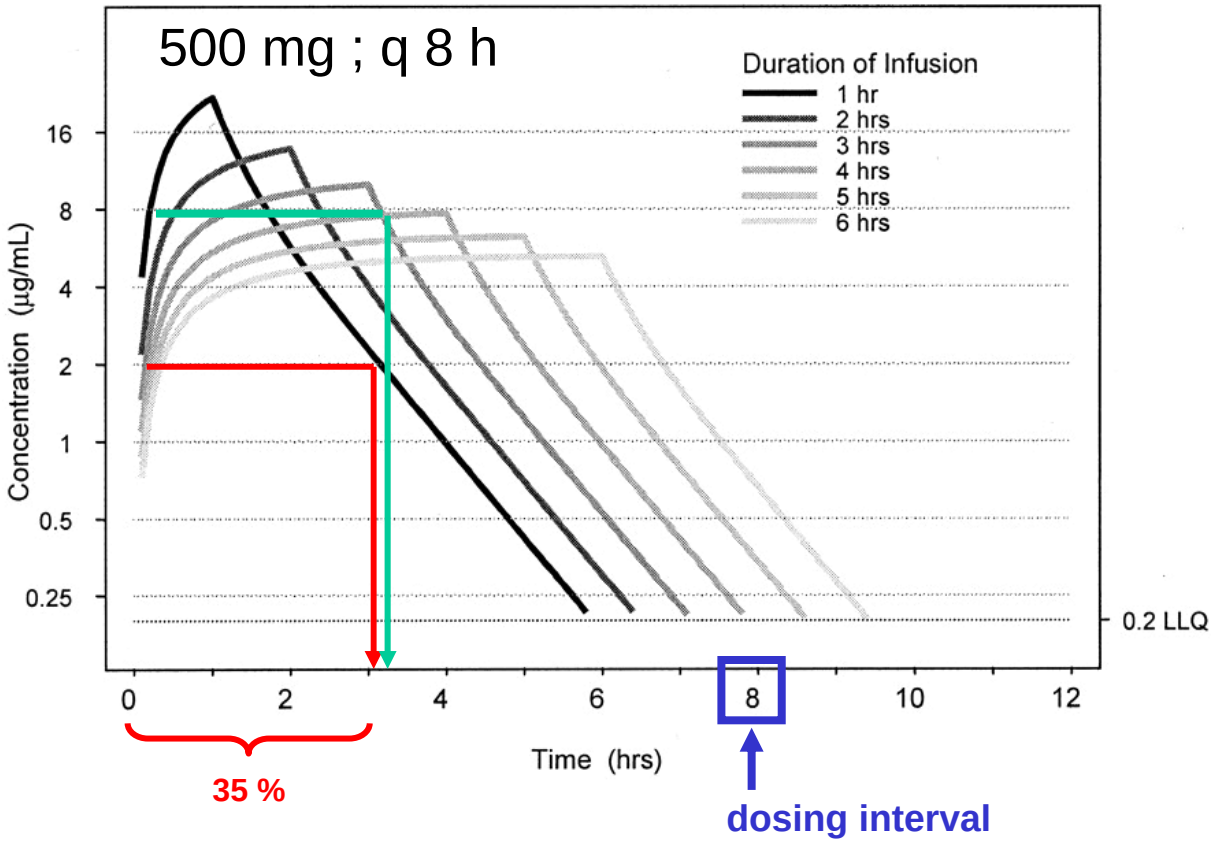
Zhanel et al., Drugs (2007) 67:1027-52

Doripenem: PK/PD modeling

PK/PD in support to dosing : *f* T > MIC ~ 35 %

4 h infusion :
MIC = 8

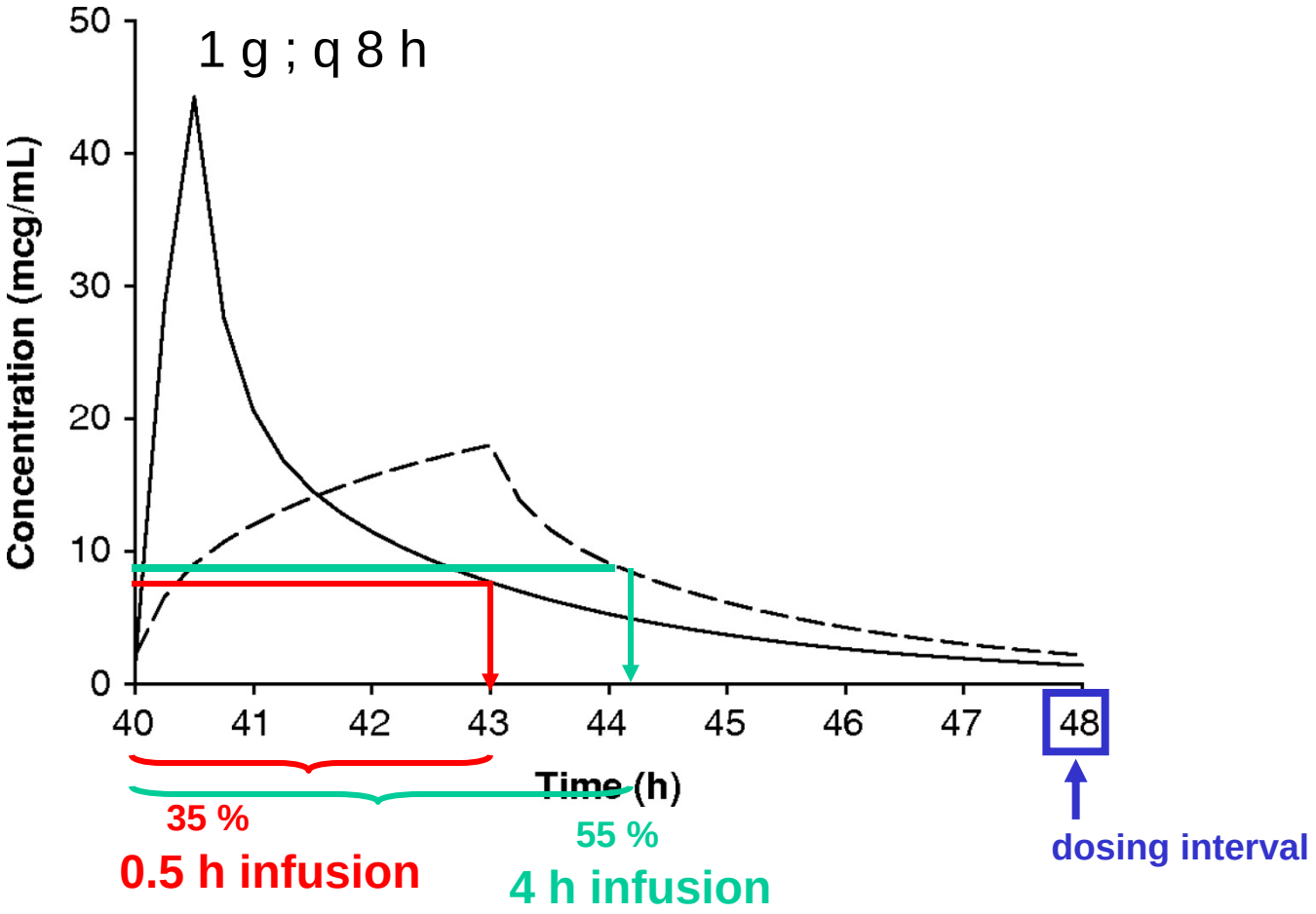
1 h infusion :
MIC = 2



Bhavnani et al., AAC (2005) 49:3944-47

Meropenem: PK/PD modeling

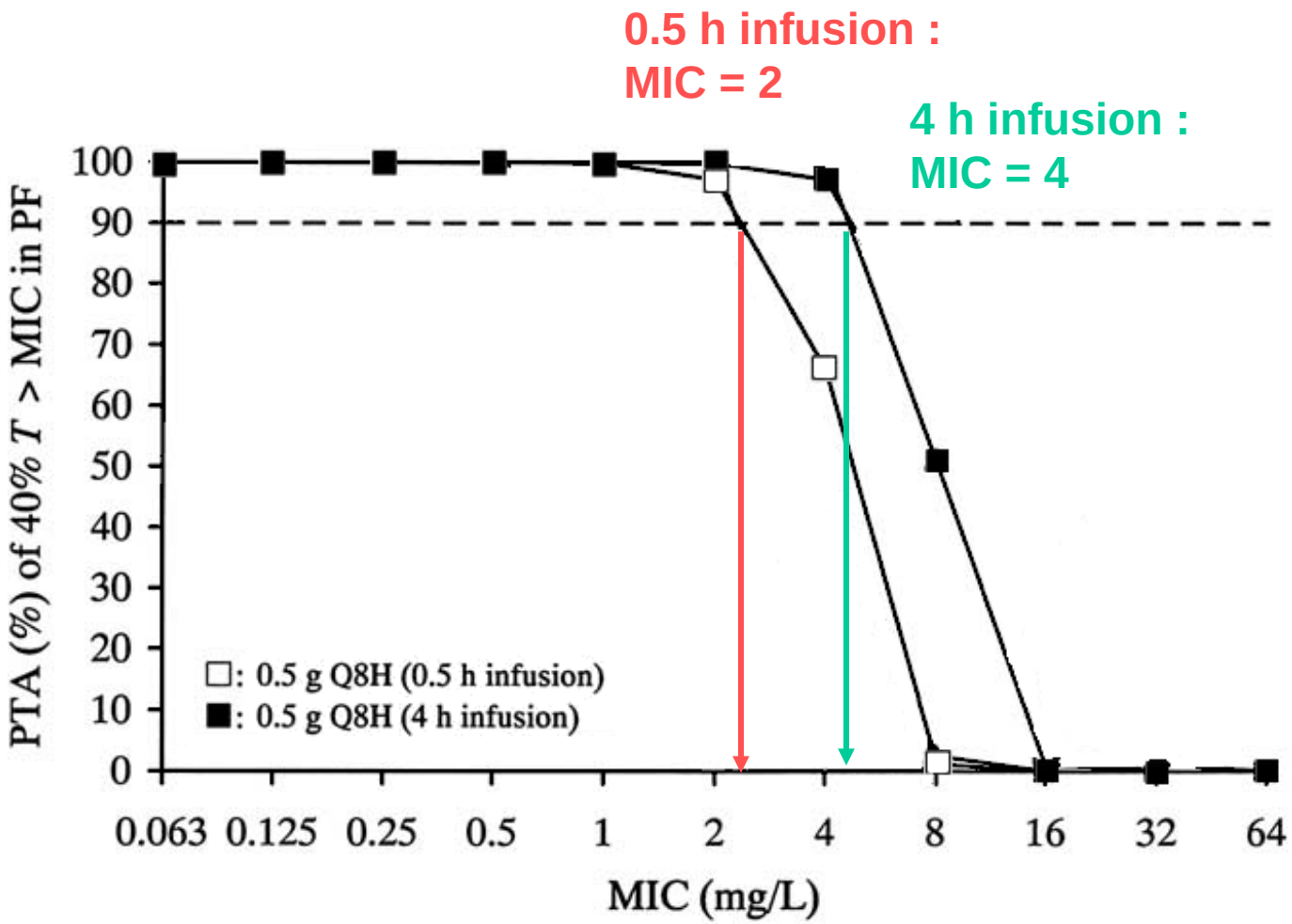
PK/PD in support to dosing : t > MIC ~ 35 %



Li et al. J Clin Pharmacol. (2006) 46:1171-8

Doripenem : PK/PD modeling

Probability of target attainment rate based on Monte Carlo simulation



Ikawa et al., Diagn Microbiol Infect Dis. (2008) 62:292-7

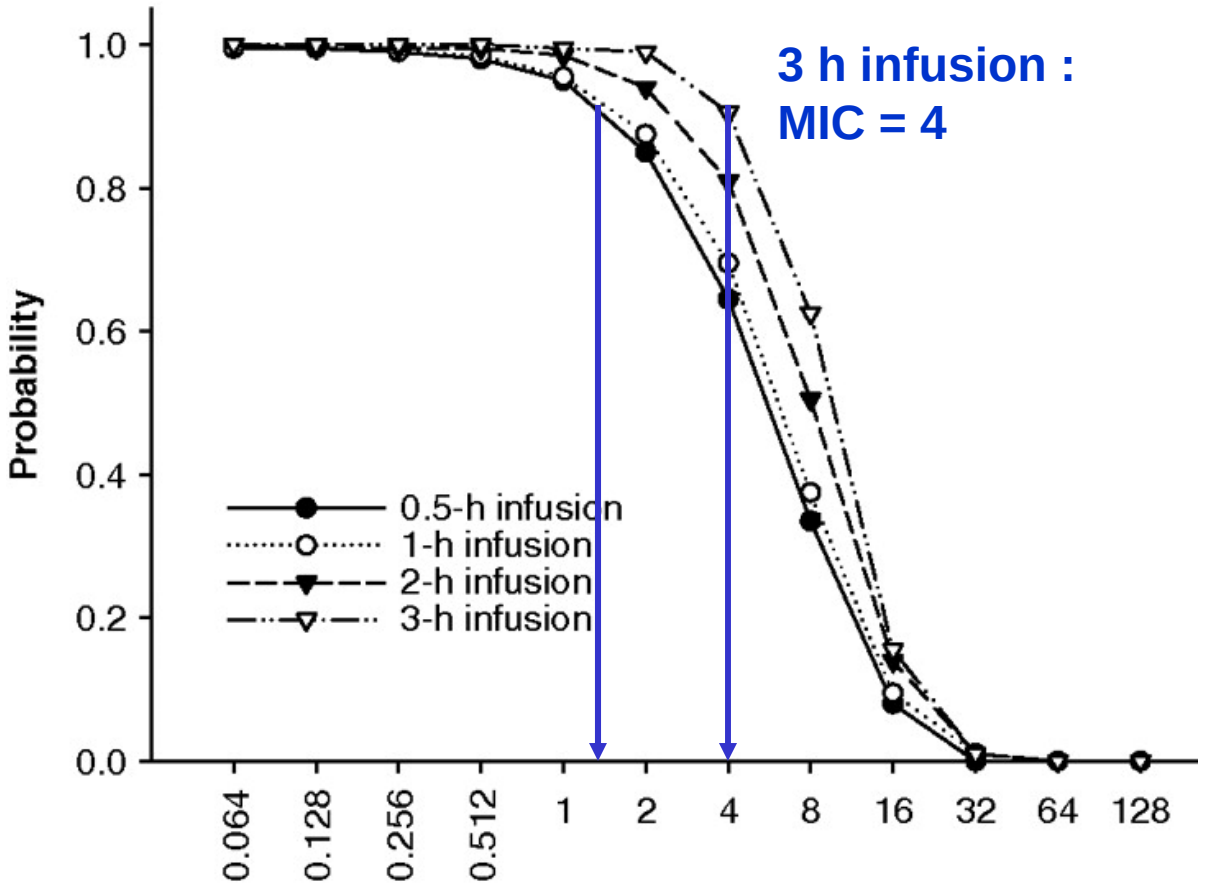
Meropenem : PK/PD modeling

Probability of target attainment rate based on Monte Carlo simulation

1 g ; q 8 h

0.5 h infusion :
MIC = 1.5

3 h infusion :
MIC = 4



Li et al., J. Clin. Pharmacol (2006) 46:1171-1178

Comparative PK profile

Bolus vs Prolonged infusion

parameter	DOR (500 mg)		MEM (1g)	
	(Bol)	(Prol)	(Bol)	(Prol)
Cmax (mg/L)	23	8	112	30
AUC (mg.h/L) – 8 h	36	17	136	186
T > CMI 1	55	80	75	98
T > CMI 4	27.5	55	57	73
T > CMI 8	17.5	-	46	58

anticipated success for organisms with MIC for which "*f* T > MIC" ~ 40 % *

anticipated failure for organisms with MIC for which "*f* T > MIC" < 40 % *

*** success/failure turn-out in animal models for a "*f* T > MIC" of 35 %**

Kim et al., AAC (2008) 52:2497-2502
Jaruratanasirikul et al., AAC (2005) 49:1337-39

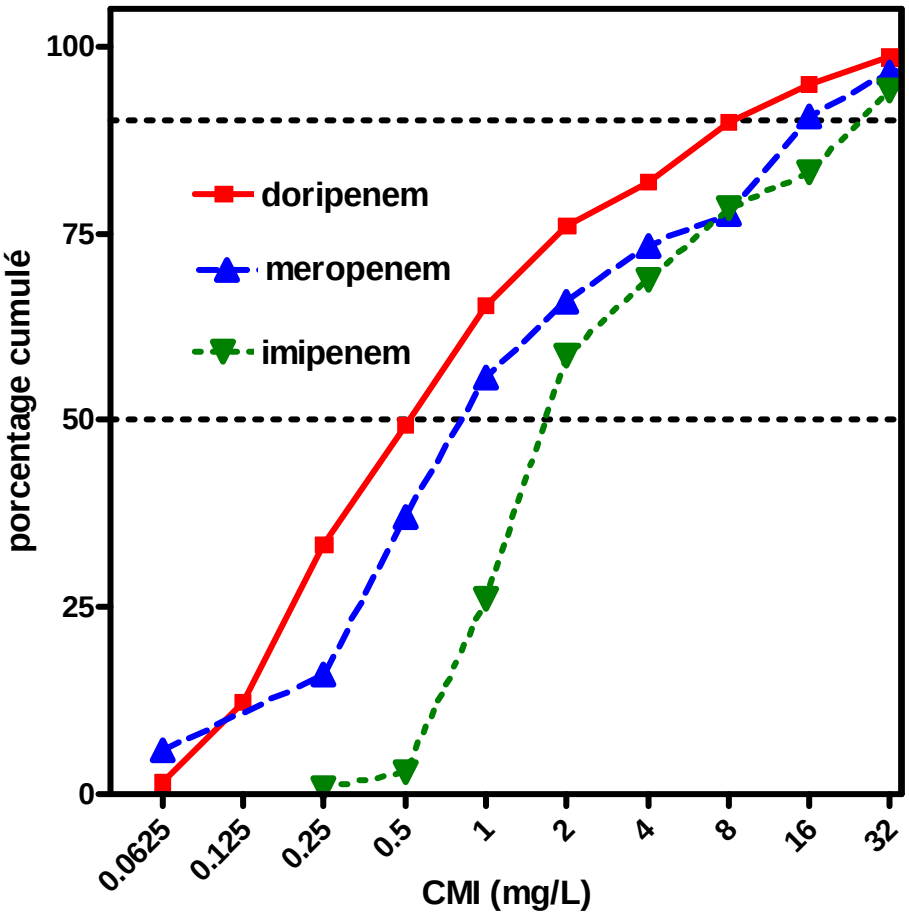
Meropenem vs Doripenem: PD vs EUCAST bkpts

	DOR (500 mg 3 x)	MEM (1 g 3 x)
EUCAST	1 / 4	2 / 8
PD short infusion	2	2
PD prolonged infusion	4	4

Li et al., J. Clin. Pharmacol (2006) 46:1171-1178

Carbapenems : Belgian MICs vs EUCAST bkpts

MIC distribution in *Pseudomonas* (Belgium; HAP or VAP isolates)



		DOR	MEM	IMI
EUCAST [a]	**S**	65.2	65.9	68.8
	I	16.7	11.6	9.4
	R	18.1	22.5	21.7

[a] ≤ S / R >: DOR: 1 / 4; MEM: 2 /8; IMI: 4 / 8

Riou et al. RICAI 2009 – poster 348

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST evaluation

Specific target attainment rates for organisms obtained <u>in the phase 3 clinical studies</u>

	Dosing regimens used					
	500 mg, q8h, 1 h infusion			500 mg, q8h, 4 h infusion		
Species specific target attainment	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**
Enterobacteriaceae	99.88	99.82	99.72	99.91	99.9	99.9
Non-Enterobacteriaceae	92.34	90.13	87.83	93.96	93.69	93.3
Pseudomonas aeruginosa	91.42	88.96	86.41	93.25	92.95	92.51
Acinetobacter spp.	82.13	80.95	78.99	82.26	82.2	82.16
Other gram-negative	99.43	98.01	96.06	100.02	100.02	100.01
Haemophilus spp.	100	99.97	99.88	100	100	100
Enterococcus faecalis	76.79	62.42	50.79	90.61	89.4	87.18
Staphylococcus aureus Oxa-S	100	100	99.99	100	100	100
Streptococcus pneumoniae	100	99.91	99.7	100.	100.	100.
Streptococcus spp. (other than *S. pneumoniae)*	99.81	99.66	99.54	99.96	99.96	99.93
Other gram-Positive	90.13	89.74	89.02	90.08	90.05	90.03
All Anaerobes	97.75	97.26	96.66	98.09	98	97.89

In press – not final

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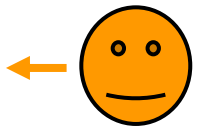

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In press – not final

EMEA registration

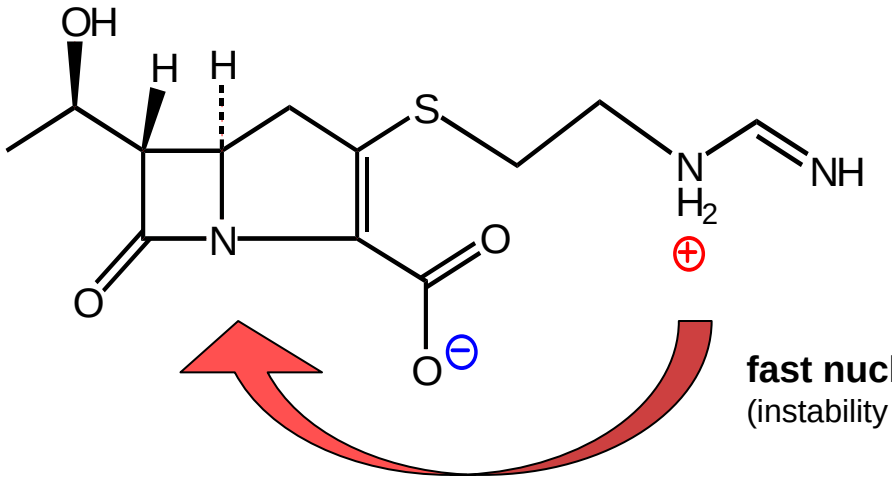
Pharmacokinetic/pharmacodynamic relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the MIC (%T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic (PK/PD) studies. Monte Carlo simulations using pathogen susceptibility results from completed phase 3 trials and population PK data indicated that the %T>MIC target of 35% was achieved in greater than 90% of patients with nosocomial pneumonia, complicated urinary tract infections and complicated intra-abdominal infections, for all degrees of renal function.

Extending the infusion time of Doribax to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

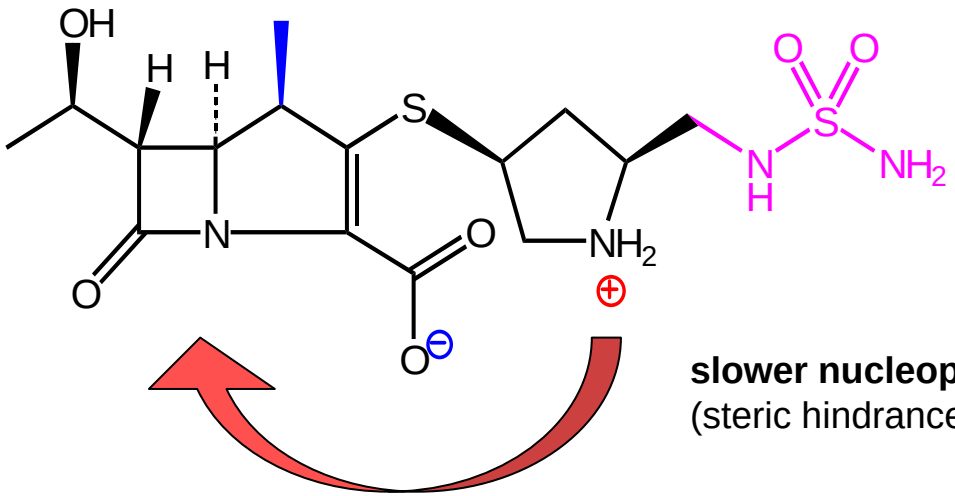
DORIBAX® Summary or Product Characteristics (EMEA)

But are carbapenems sufficiently stable for a 4 h infusion ?



imipenem

fast nucleophilic attack
(instability of the amidinium function)



doripenem *

slower nucleophilic attack
(steric hindrance)

Stability according to EMEA

Preparation of 500 mg dose of solution for infusion

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the vial and shake it to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 ml of either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection and mix to complete dissolution. Infuse all of this solution to administer a 500 mg dose of doripenem.

➔ **0.5 % solution… Intensive Care Units may like to put 500 mg in 48 mL (1.048 %)**

Time by which reconstitution, dilution and infusion must complete for Doribax infusion solutions

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
+dextrose 50 mg/ml (5%) solution for injection	4 hours	24 hours*

* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed refrigeration stability time.

+ Dextrose 50 mg/ml (5%) solution for injection should not be used for infusion durations greater than 1 hour.

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Stability according to EMEA

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* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time and room temperature and infusion time does not exceed refrig…

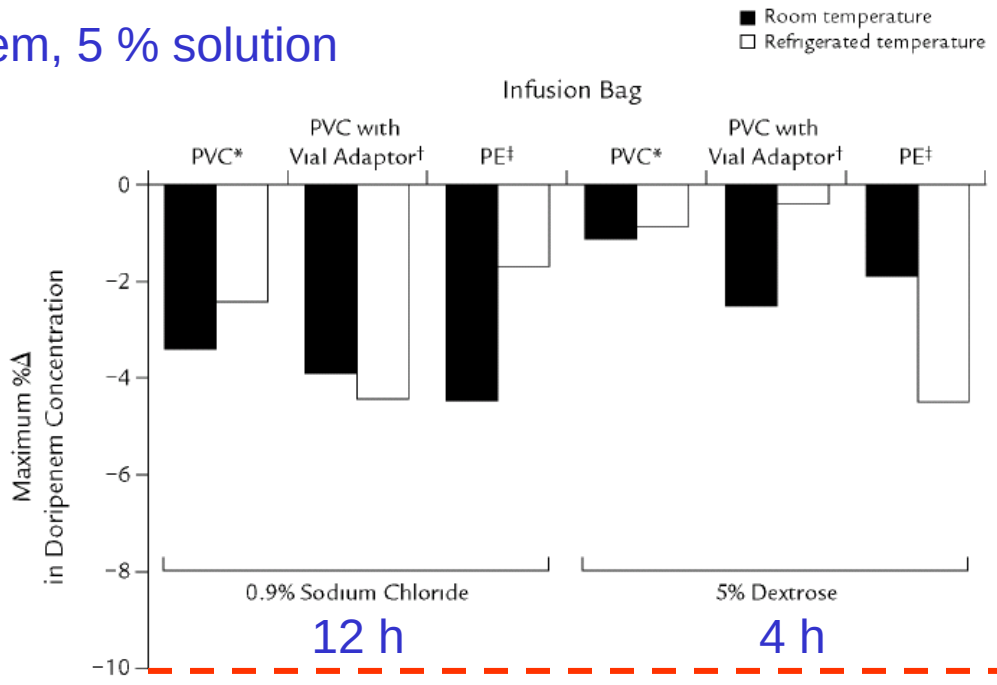
+ Dextrose 50 mg/m… for infusion durations greater than 1 hour.

glucose is a good nucleophilic attacker
(a lot of –OH groups…

DORIBAX® Summary or Product Characteristics (EMEA)

Stability according to EMEA

Doripenem, 5 % solution



acceptable limit of degradation

Figure 2. Maximum change in initial (0-hour) doripenem concentration after storage at room or refrigerated temperature. Infusion solutions prepared in 0.9% sodium chloride injection were stored at room temperature (25°C ± 2°C and 60% ± 5% relative humidity for 12 hours under fluorescent light) and at refrigerated temperature (5°C ± 3°C and 60% ± 5% relative humidity for 72 hours protected from light). Solutions prepared in 5% dextrose injection were stored at room and refrigerated temperatures for 4 and 48 hours, respectively. Changes at storage end point are shown. PVC = polyvinyl chloride; PE = polyethylene. *Trademark: Viaflex Mini-Bag (Baxter International Inc., Deerfield, Illinois). †Trademark: Mini-Bag Plus (Baxter International Inc.). ‡Trademark: Viaflo Mini-Bag (Baxter International Inc.).

Psathas et al. Clin. Ther. (2008) 30:2075-87

Stability according to EMEA

TABLE 3. Time during which β-lactams remains >90% stable at the highest concentration tested (see Table 1)

Drug(s)	Time (h, min)[a] at:	
	37°C	25°C
Aztreonam	>24	ND
Piperacillin	21, 40	~30
Piperacillin + tazobactam	>24	⩾72[b]
Azlocillin	>24	⩾72[b]
Mezlocillin	14	46, 30
Ceftazidime	8	24
Cefepime	13	20, 30
Cefpirome	7, 15	23, 40
Imipenem + cilastatin	2, 45	3, 30
Meropenem	1, 50	5, 15
Faropenem	>24	~80

[a] Decays were monitored for 24 h; the slope was calculated by linear regression and used to determine the 90% stability time point. All data were rounded to the closest 15-min value. ND, not determined.

[b] 90% stability for at least 72 h, but the slope was too weak to calculate the 90% intercept value with accuracy from the 24-h decay data.

Viaene et al. AAC (2002) 46:2327-32

Clinical efficacy

Clinical trials

Table 1. Overview of doripenem clinical trials.

Study	Indication	Study design	Doripenem dosage	Comparator drug (dosage)	No. of patients randomized	Outcome evaluated
Naber et al. [13]	cUTI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Levofloxacin (250 mg every 24 h by 1-h IV infusion)	753	Microbiological cure rate
Ortho-McNeil-Janssen Pharmaceuticals (unpublished data)	cUTI	Phase 3, open-label, single-arm, multicenter	500 mg every 8 h by 1-h IV infusion	…	426	Microbiological cure rate
Lucasti et al. [14]	cIAI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Meropenem (1 g every 8 h by IV bolus)	476	Clinical cure rate
Malafaia et al. [15]	cIAI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Meropenem (1 g every 8 h by IV bolus)	486	Clinical cure rate
Rea-Neto et al. [16]	NP[a]	Phase 3, randomized, open-label, multicenter	500 mg every 8 h by 1-h IV infusion	Piperacillin-tazobactam (4.5 g every 6 h by 30-min IV infusion)	448	Clinical cure rate
Chastre et al. [17]	VAP[b]	Phase 3, randomized, open-label, multicenter	500 mg every 8 h by 4-h IV infusion	Imipenem (500 mg every 6 h by 30-min IV infusion or 1 g every 8 h by 1-h IV infusion)	531	Clinical cure rate

NOTE. cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

[a] Including early-onset (but not late-onset) VAP.

[b] Early onset or late onset.

Restrepo, CID (2009) 49:S17-27

Respiratory tract infections

Table IX. Efficacy of intravenous doripenem (DOR) in serious bacterial lower respiratory tract infections. Results of randomized trials that compared DOR with imipenem/cilastin (IPM),[129] meropenem (MEM)[127] or piperacillin/tazobactam (TZP)[126] in patients (pts) with nosocomial pneumonia (including one trial[129] in pts with ventilator-associated pneumonia [VAP][126,129] or other serious lower respiratory tract infections.[127] Study drugs were administered intravenously

Study	No. of pts randomized	Treatment regimen	Planned treatment duration (d)	Response rates (% pts) [evaluable pts]			
				clinical response	between-group difference (95% CI)	bacteriological response	between-group difference (95% CI)
Nosocomial pneumonia, including VAP							
Chastre et al.[129]	264	DOR 500 mg q8h infused over 4h	7–14	68.3[a] [126]	3.5 (−9.1, 16.1)[b]	73.3[c] [116]	6.0 (−6.8, 18.8)
	267	IPM 500 mg q6h or 1000 mg q8h infused over 30 or 60 min	7–14	64.8[a] [122]		67.3[c] [110]	
Réa-Neto et al.[126]	225	DOR 500 mg q8h infused over 60 min[d]	7–14	81.3[a] [134]	1.5 (−9.1, 12.1)[e]	84.5[c] [84]	3.8 (−8.9, 16.5)
	223	TZP 4.5 g q6h infused over 30 min[d]	7–14	79.8[a] [119]		80.7[c] [83]	
Other serious lower respiratory tract infections							
Saito et al.[127]	112	DOR 250 mg bid infused over 30–60 min	7	92.7[f] [96]	2.0 (−5.8, 9.8)[g]	86.0 [43]	−9.8 (−21.6, 2.0)
	107	MEM 500 mg bid infused over 30–60 min	7	90.7[f] [97]		95.8 [48]	

Keam, Drugs (2008) 68:2021-2057

Respiratory tract infections

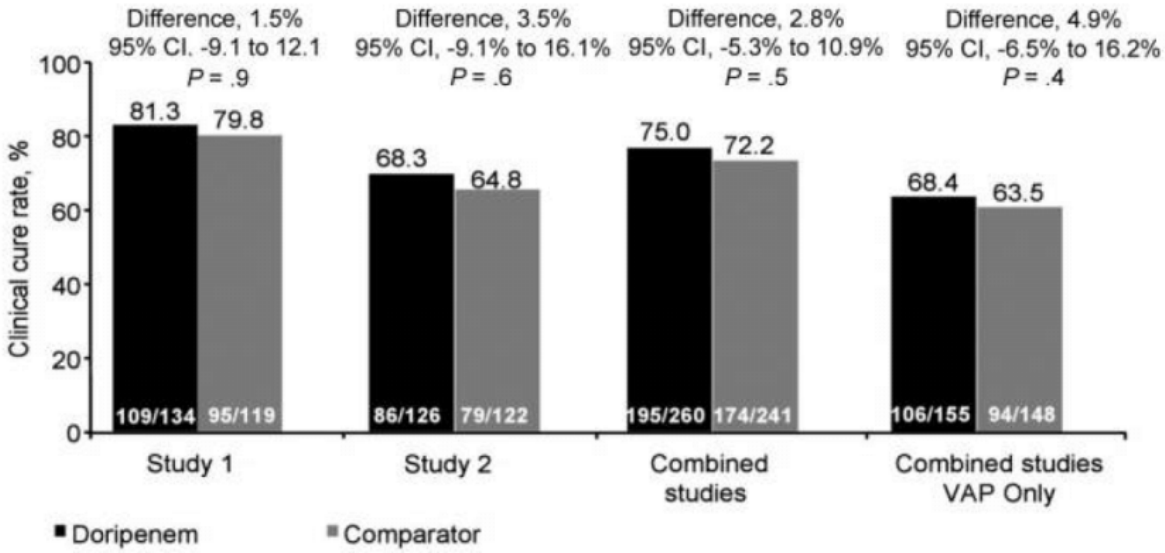


Figure 1. Clinical cure rates among clinically evaluable patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP). In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data for combined studies are from Chastre et al. [20]. All data are from Ortho-McNeil-Janssen Pharmaceuticals. CI, confidence interval.

Restrepo, CID (2009) 49:S17-27

Respiratory tract infections

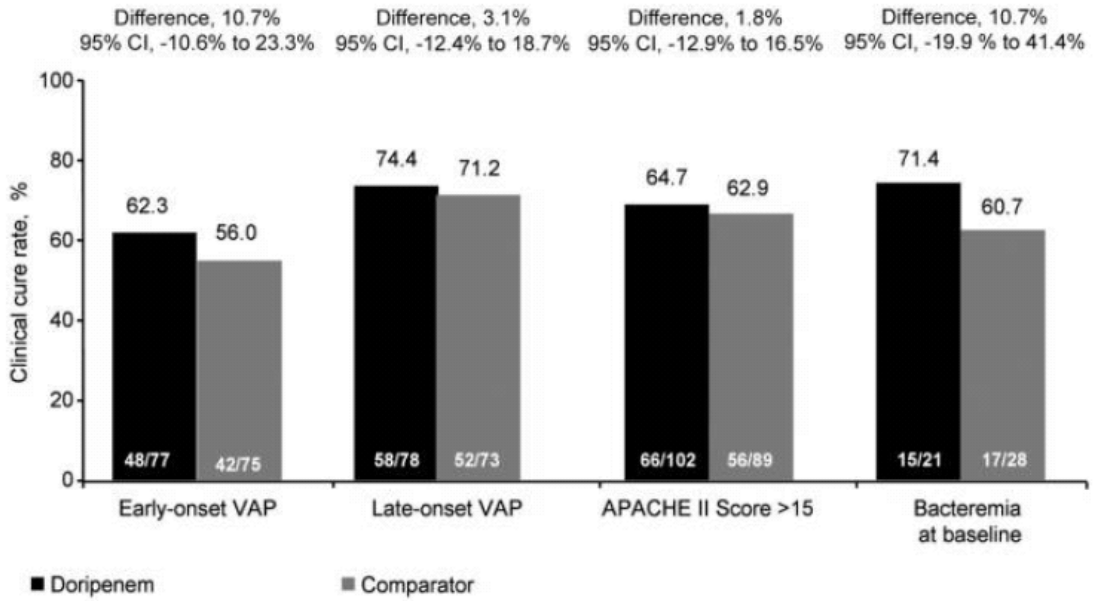


Figure 2. Clinical cure rates among clinically evaluable patients with serious nosocomial pneumonia, including ventilator-associated pneumonia (VAP), in combined studies. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data are from Ortho-McNeil-Janssen Pharmaceuticals. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval.

Restrepo, CID (2009) 49:S17-27

Respiratory tract infections

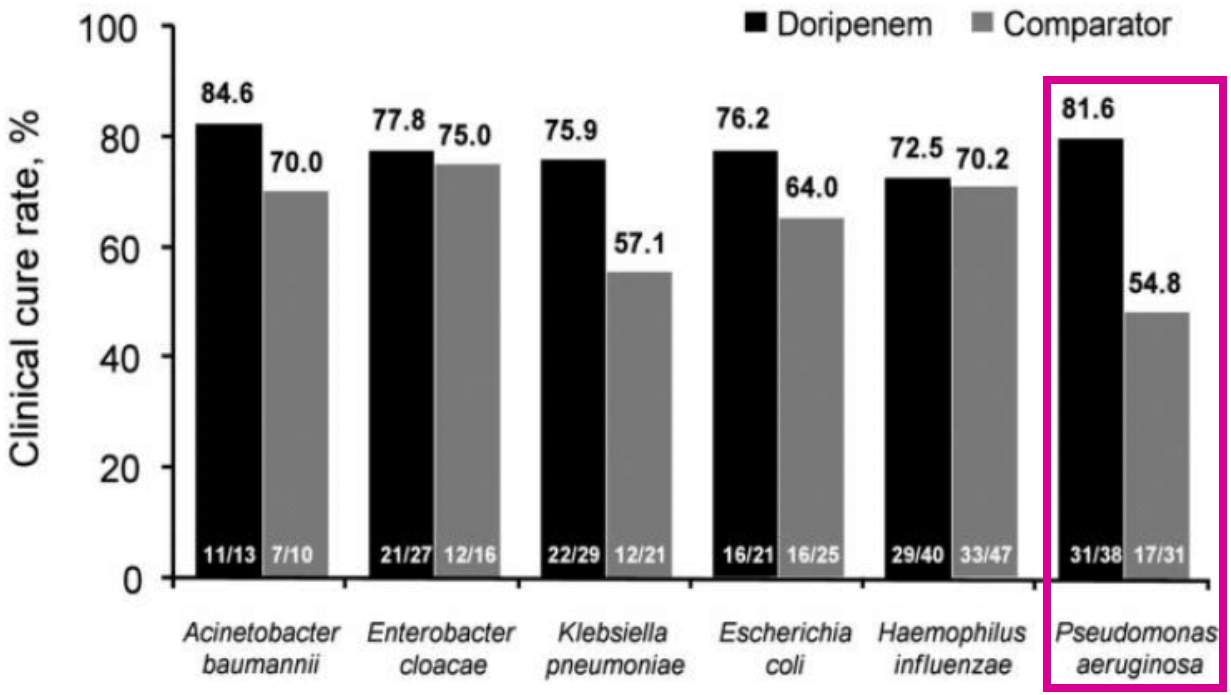


Figure 3. Pooled clinical cure rates, by pathogen, among microbiologically evaluable patients with nosocomial pneumonia, including ventilator-associated pneumonia, in the combined studies. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data are from Ortho-McNeil-Janssen Pharmaceuticals.

Restrepo, CID (2009) 49:S17-27

Respiratory tract infections

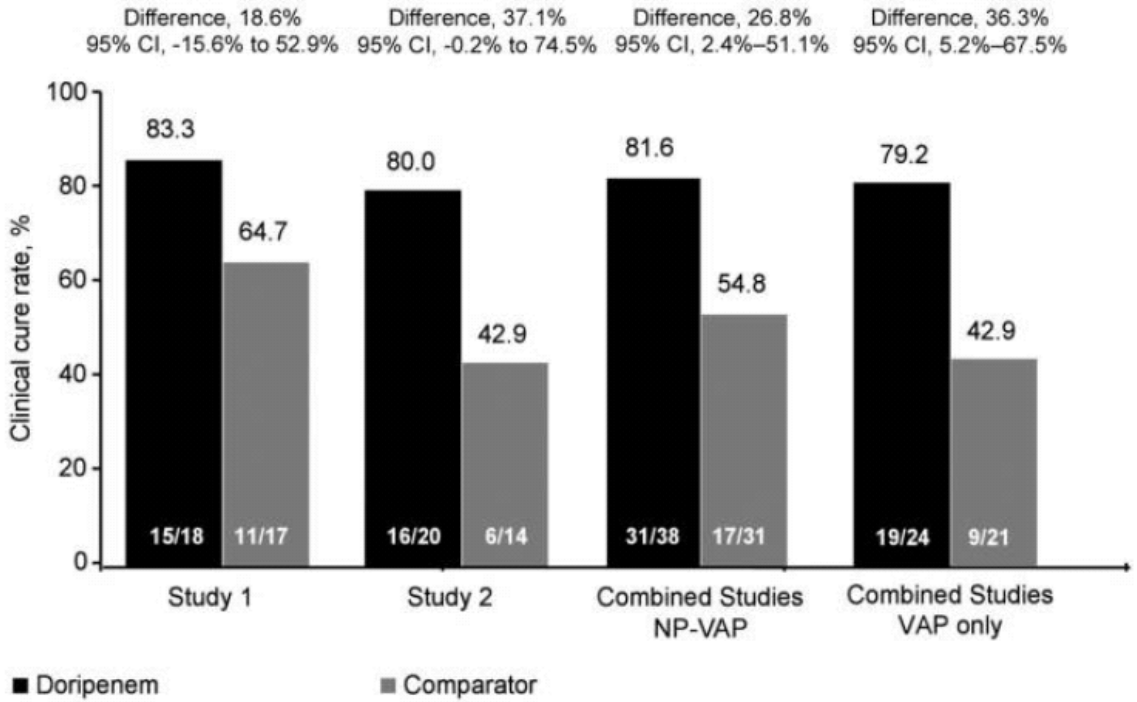


Figure 4. Clinical cure rates among microbiologically evaluable patients infected with *Pseudomonas aeruginosa*. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data for combined studies are from Chastre et al. [20]. All data are from Ortho-McNeil-Janssen Pharmaceuticals. CI, confidence interval; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

Restrepo, CID (2009) 49:S17-27

Intra-abdominal infections

Design

Patients with IAI, surgical intervention < 24 h + AB needed

exclusion :
- uncomplicated infections
- APACHE II > 30
- life-threatening illness
- necrotizing pancreatitis / pancreatic abcess
- infection by pathogen R to one of the studied drugs

Patients profile

91 % APACHE II < 10
60 % appendix; 20 % colon
10 % post-operative

Treatment

DOR 500 mg x 3; 1h ***vs*** MEM 1 g x 3 ; 5 minutes

Lucasti et al., Clin. Ther (2008) 30:868-83

Intra-abdominal infections

Microbiology

Table III. Microorganisms isolated from microbiological modified intent-to-treat patients in this noninferiority study of IV doripenem versus meropenem in adults with complicated intra-abdominal infection. Values are no. (%) of patients.

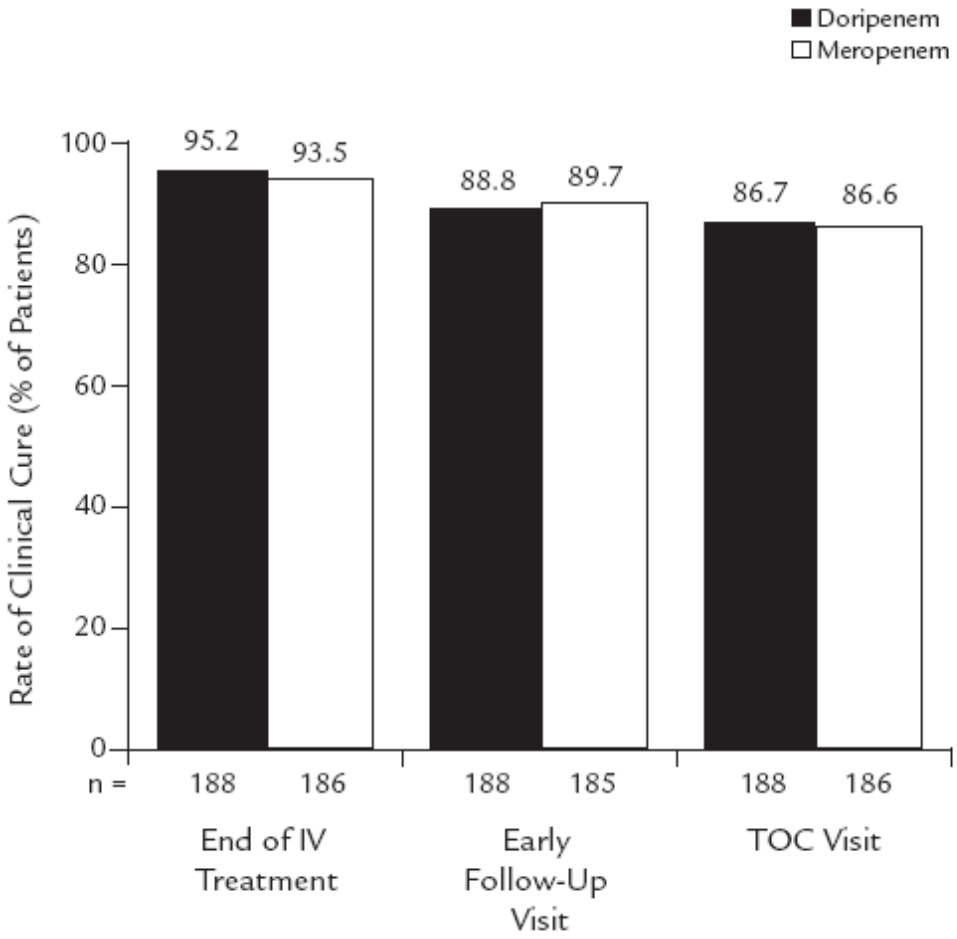
Microorganism	Doripenem (n = 195)	Meropenem (n = 190)
Gram-negative aerobes		
Escherichia coli	121 (62.1)	115 (60.5)
Pseudomonas aeruginosa	22 (11.3)	21 (11.1)
Klebsiella pneumoniae	18 (9.2)	14 (7.4)
Citrobacter spp	18 (9.2)	6 (3.2)
Enterobacter spp	9 (4.6)	10 (5.3)
Proteus spp	8 (4.1)	13 (6.8)
Other *Klebsiella* spp	6 (3.1)	6 (3.2)
Other *Pseudomonas* spp	2 (1.0)	4 (2.1)
Other	13 (6.7)	13 (6.8)
Gram-negative anaerobes		
Bacteroides fragilis	33 (16.9)	28 (14.7)
Other *Bacteroides* spp	20 (10.3)	39 (20.5)
Bacteroides thetaiotaomicron	20 (10.3)	22 (11.6)
Prevotella spp	19 (9.7)	18 (9.5)
Bacteroides caccae	15 (7.7)	8 (4.2)
Bacteroides uniformis	11 (5.6)	15 (7.9)

Microorganism	Doripenem (n = 195)	Meropenem (n = 190)
Gram-negative anaerobes (continued)		
Fusobacterium spp	9 (4.6)	7 (3.7)
Other	5 (2.6)	7 (3.7)
Gram-positive aerobes		
Other *Streptococcus* spp	43 (22.1)	49 (25.8)
Streptococcus viridans group	22 (11.3)	15 (7.9)
Streptococcus intermedius	21 (10.8)	15 (7.9)
Enterococcus faecalis	20 (10.3)	14 (7.4)
Other *Enterococcus* spp	11 (5.6)	16 (8.4)
Staphylococcus aureus	8 (4.1)	12 (6.3)
Other *Staphylococcus* spp	8 (4.1)	10 (5.3)
Enterococcus faecium	6 (3.1)	12 (6.3)
Other	4 (2.1)	2 (1.1)
Gram-positive anaerobes		
Peptostreptococcus spp	13 (6.7)	16 (8.4)
Clostridium spp	10 (5.1)	9 (4.7)
Other	18 (9.2)	16 (8.4)

Lucasti et al., Clin. Ther (2008) 30:868-83

Intra-abdominal infections

Clinical success



Lucasti et al., Clin. Ther (2008) 30:868-83

Intra-abdominal infections

Microbiological evaluation

Table V. Favorable microbiological outcomes for selected baseline intra-abdominal pathogens in the microbiologically evaluable patients in this noninferiority study of IV doripenem versus meropenem in adults with complicated intra-abdominal infection.

	No. (%)		
Pathogen	Doripenem	Meropenem	Difference, %*
Gram-positive aerobes			
Viridans group streptococci	50/54 (92.6)	35/41 (85.4)	7.2
Streptococcus intermedius	15/16 (93.8)	8/10 (80.0)	13.8
Other	27/33 (81.8)	32/38 (84.2)	−2.4
Enterococcus fecalis	9/12 (75.0)	8/9 (88.9)	−13.9
Gram-positive anaerobes	27/33 (81.8)	30/37 (81.1)	0.7
Gram-negative aerobes			
Enterobacteriaceae	140/157 (89.2)	122/141 (86.5)	2.6
Escherichia coli	91/104 (87.5)	84/100 (84.0)	3.5
Klebsiella pneumoniae	14/15 (93.3)	9/9 (100)	−6.7
Nonfermenters	22/23 (95.7)	17/24 (70.8)	24.8
Pseudomonas aeruginosa	18/19 (94.7)	15/19 (78.9)	15.8
Gram-negative anaerobes			
Bacteroides fragilis group	67/75 (89.3)	75/89 (84.3)	5.1
B fragilis	23/27 (85.2)	16/22 (72.7)	12.5
Bacteroides thetaiotaomicron	14/16 (87.5)	19/20 (95.0)	−7.5
Bacteroides caccae	11/12 (91.7)	8/8 (100)	−8.3
Bacteroides uniformis	10/11 (90.9)	8/11 (72.7)	18.2
Other	21/27 (77.8)	28/30 (93.3)	−15.6

Lucasti et al., Clin. Ther (2008) 30:868-83

Safety profile

Safety profile – clinical studies

6 phase III and 1 phase II studies

Table 2. Adverse drug reactions in phase 2 and 3 clinical trials of doripenem.

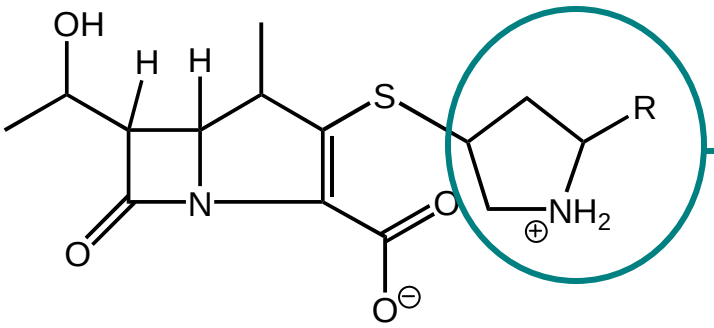
Adverse reaction	Doripenem (*n* = 1817)	Levofloxacin (*n* = 372)	Meropenem (*n* = 469)	Piperacillin-tazobactam (*n* = 221)	Imipenem (*n* = 263)	Comparator agents combined (*n* = 1325)	OR (95% CI)[a]
Clostridium difficile colitis	9 (0.5)	0 (0)	0 (0)	2 (0.9)	6 (2.3)	8 (0.6)	0.8 (0.3–2.4)
Diarrhea	163 (9.0)	38 (10.2)	52 (11.1)	24 (10.9)	45 (17.1)	159 (12.0)	0.7 (0.6–0.9)
Headache	183 (10.1)	54 (14.5)	24 (5.1)	5 (2.3)	8 (3.0)	91 (6.9)	1.5 (1.2–2.0)
Hypersensitivity	12 (0.7)	3 (0.8)	2 (0.4)	1 (0.5)	0 (0)	6 (0.5)	1.5 (0.5–4.8)
Nausea	142 (7.8)	22 (5.9)	44 (9.4)	7 (3.2)	28 (10.6)	101 (7.6)	1.0 (0.8–1.4)
Oral candidiasis	23 (1.3)	0 (0)	8 (1.7)	1 (0.5)	6 (2.3)	15 (1.1)	1.1 (0.6–2.3)
Phlebitis	103 (5.7)	15 (4.0)	26 (5.5)	5 (2.3)	2 (0.8)	48 (3.6)	1.6 (1.1–2.3)
Pruritis	33 (1.8)	4 (1.1)	9 (1.9)	1 (0.5)	5 (1.9)	19 (1.4)	1.3 (0.7–2.4)
Rash	67 (3.7)	3 (0.8)	11 (2.3)	7 (3.2)	16 (6.1)	37 (2.8)	1.3 (0.9–2.1)
Vulvomycotic infection	14 (0.8)	4 (1.1)	2 (0.4)	0 (0)	1 (0.4)	7 (0.5)	1.5 (0.6–4.3)

NOTE. Data are no. (%) of patients, unless otherwise specified. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5-min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Patients from the phase 2 trial who received doripenem at a dosage of 250 mg are not included in the calculations. CI, confidence interval; OR, odds ratio. Data are from Ortho-McNeil-Janssen Scientific Affairs.

[a] Pairwise comparison for doripenem vs. comparators combined, by exact estimate of OR.

Redman & File, CID (2009) 49:S28-35

Neurotoxicity



binding affinity for GABA receptors
depending of (+) charge
of the side chain

drug	IC 50 (mM)
imipenem	0.5
meropenem	27.6
doripenem	50.0

X 55

X 1.8

Dalhoff et al., Biochem. Pharmacol. (2006) 71:1085-95

Neurotoxicity

Table 3. Treatment-emergent seizures in doripenem clinical trials.

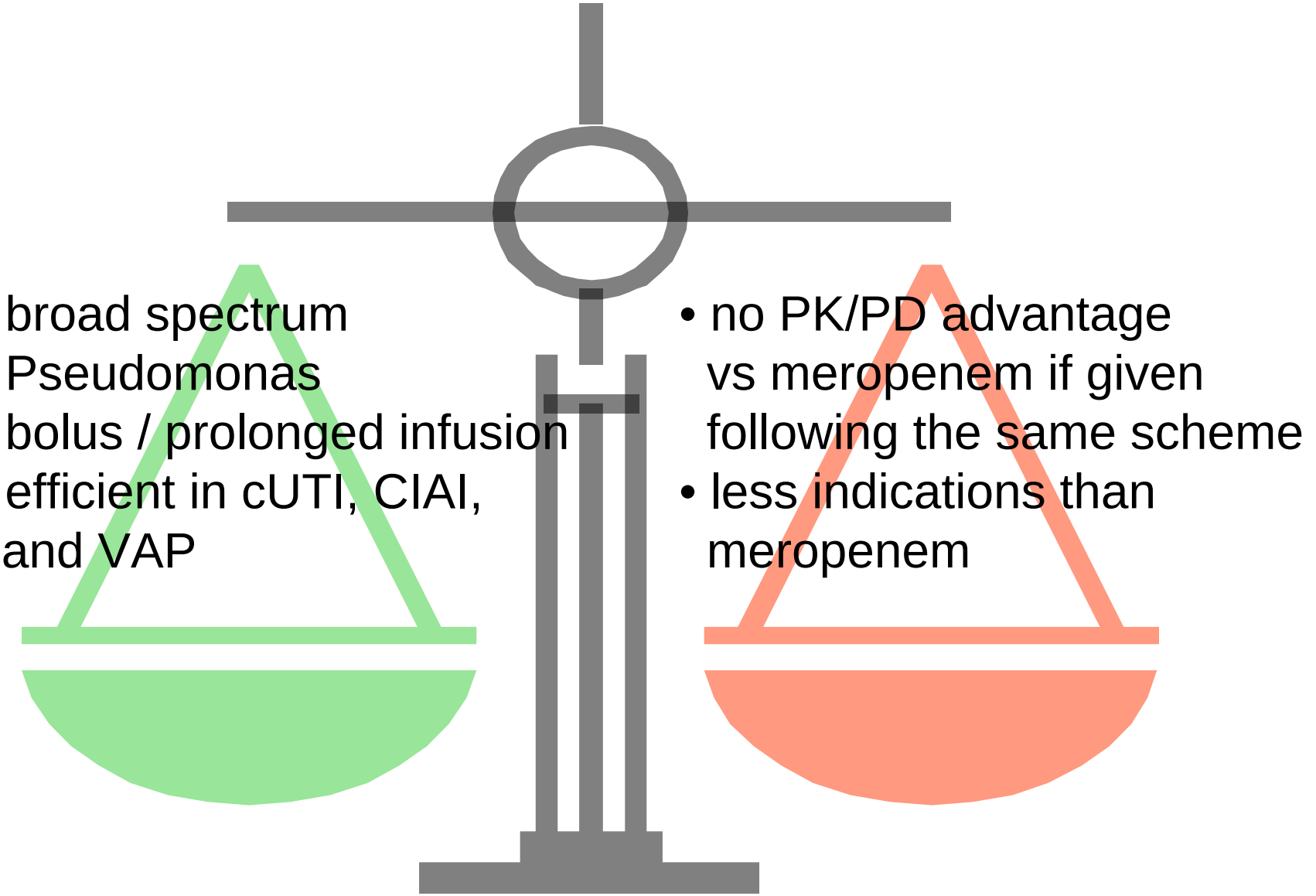
Seizure	Doripenem (n = 1817)	Levofloxacin (n = 372)	Meropenem (n = 469)	Piperacillin-tazobactam (n = 221)	Imipenem (n = 263)	Comparator agents combined (n = 1325)	OR (95% CI)[a]
Any seizure event	6 (0.3)	1 (0.3)	0 (0)	6 (2.7)	10 (3.8)	17 (1.3)	0.3 (0.1–0.7)
Convulsion	5 (0.3)	0 (0)	0 (0)	5 (2.3)	7 (2.7)	12 (0.9)	0.3 (0.1–0.9)
Epilepsy	1 (0.1)	0 (0)	0 (0)	1 (0.5)	2 (0.8)	3 (0.2)	0.2 (0.0–3.0)
Grand mal convulsion	0 (0)	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.1)	0.0 (0.0–13.9)
Status epilepticus	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	1 (0.1)	0.0 (0.0–13.9)

NOTE. Data are no. (%) of patients, unless otherwise specified. Dosages were as follows: doripenem, 500 mg every 8 h via 1-h or 4-h infusion; levofloxacin, 250 mg every 24 h via 1-h infusion; meropenem, 1 g every 8 h via 3–5 min bolus injection; piperacillin-tazobactam, 4.5 g every 6 h via 30-min infusion; and imipenem, 500 mg every 6 h via 30-min infusion or 1 g every 8 h via 1-h infusion. Patients from the phase 2 trial who received doripenem at a dosage of 250 mg are not included in the calculations. At each level of summarization, a patient was counted once if the patient reported ⩾1 event. Seizures were adverse events designated with the Medical Dictionary for Regulatory Activities high-level group term of "seizures (including subtypes)." Seizure events were reported for the subtypes convulsion, epilepsy, grand mal convulsion, and status epilepticus only. CI, confidence interval; OR, odds ratio. Data are from Ortho-McNeil-Janssen Scientific Affairs.

[a] OR for doripenem vs. comparators combined.

Redman & File, CID (2009) 49:S28-35

Doripenem : pros and cons



- broad spectrum
- Pseudomonas
- bolus / prolonged infusion
- efficient in cUTI, CIAI, and VAP

- no PK/PD advantage vs meropenem if given following the same scheme
- less indications than meropenem

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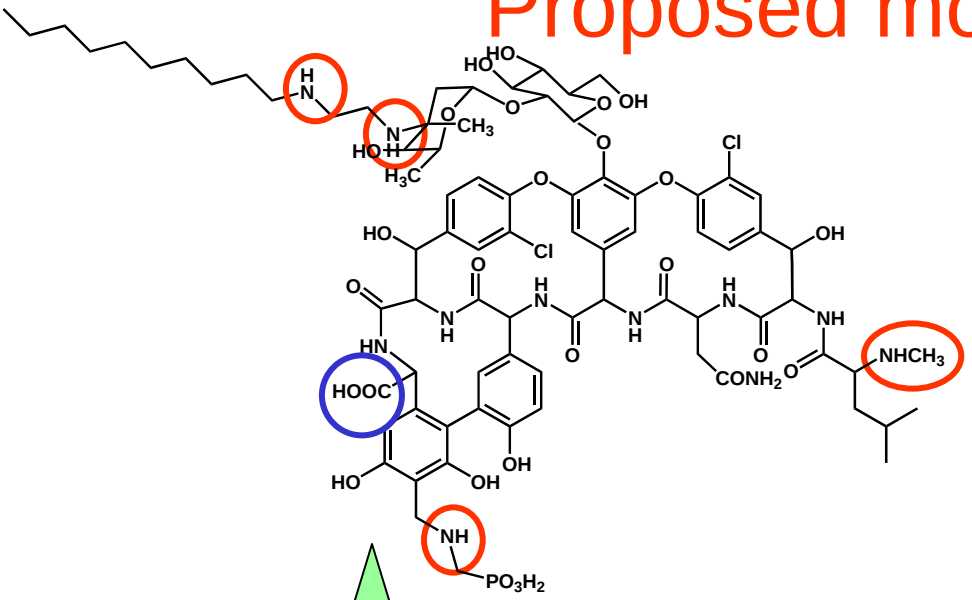
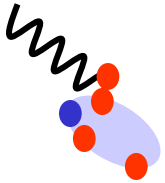
  - *Streptococcus pyogenes*
  - *Streptococcus agalactiae*
  - *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius* and *S. constellatus*)
  - *Enterococcus faecalis* (vancomycin-susceptible isolates only)

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative organisms.

Important Safety Information

Proposed mode of action

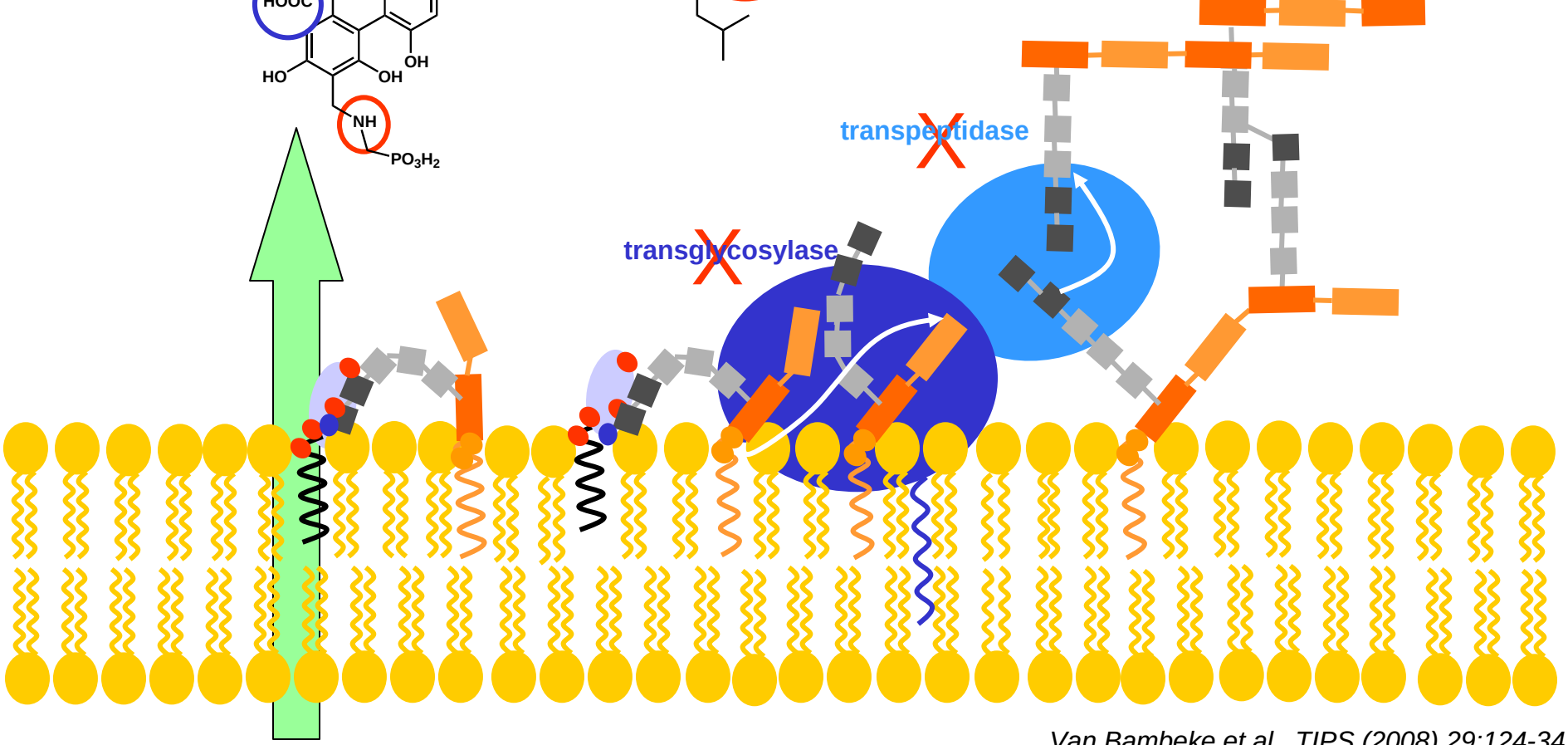




telavancin

transpeptidase

transglycosylase



Van Bambeke et al., TIPS (2008) 29:124-34

In vitro activity

In vitro activity

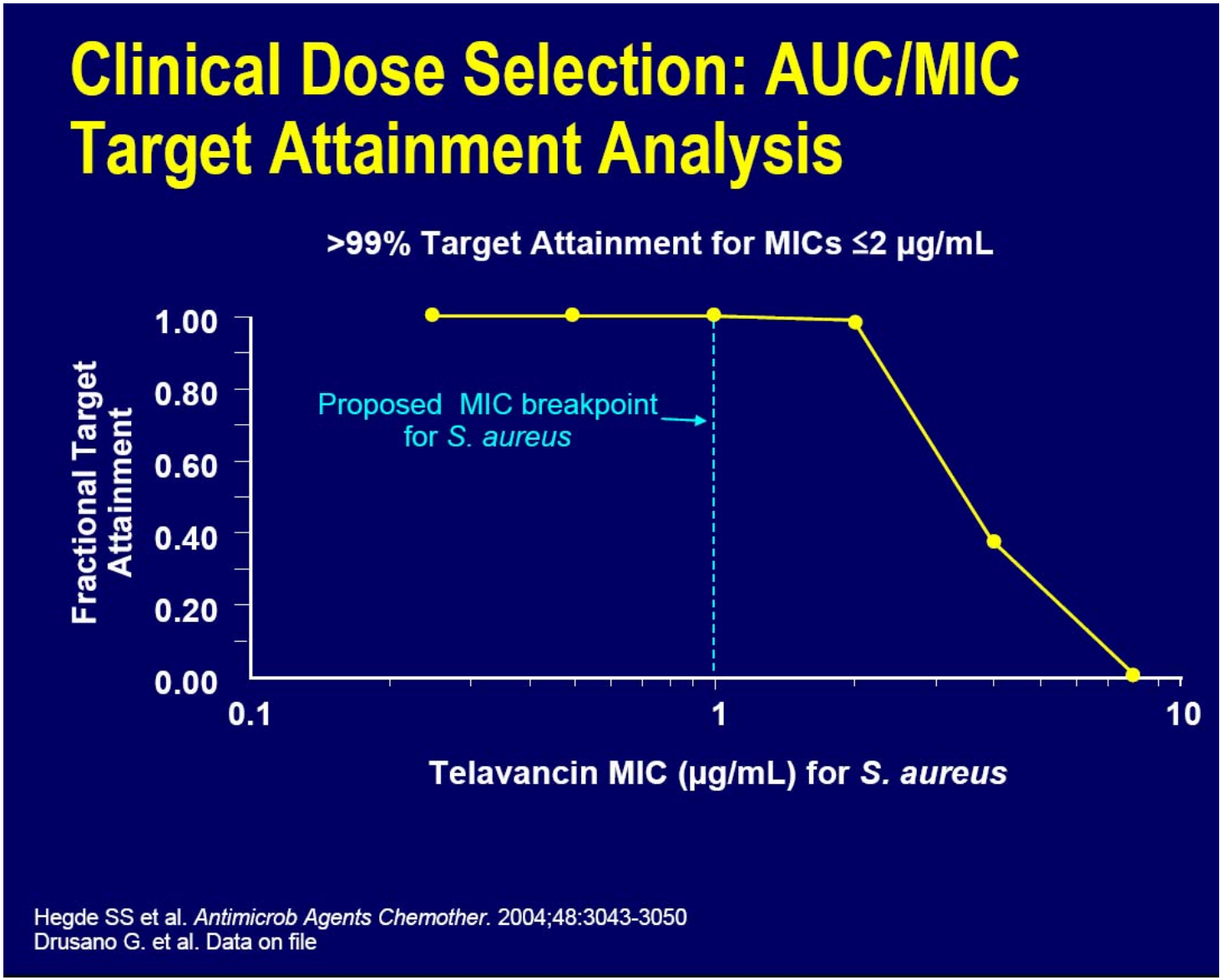
species	phenotype	ORI	TLV	VAN
S. aureus	MSSA	0.25/0.5	0.25/0.5	1/1
	MRSA	0.25/0.5	0.25/0.25	1/1
	VISA	1/1	0.5-1	4/4
	VRSA	0.5*	2-4	16*
S. pneumo	PenS	≤ 0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.25
	Pen nonS	≤0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.25/≤ 0.5
Enterococci	VanS	0.12/0.5	0.12/0.5	1/2
	VanR	0.03*	4-16	16*

* Median value

Draghi et al.,AAC (2008) 52:2383-2388
ICAAC (2008) C1-146,150,151

Pharmacokinetics / Pharmacodynamics

Telavancin tentative PK/PD breakpoint



Barriere- FDA meeting (2009)

Pharmacokinetics

parameter	VAN	ORI	TLV	TEC
Dosage (mg/kg)	15	3	10	6
Cmax (mg/L)	20-50	46	93	43
Cmin (mg/L)	5-12 (12 h)	10 (24 h)	~ 8 (24 h)	5 (24 h)
AUC (mg.h/L)	260	457	668	600
(%) prot. binding	55	90	95	88-94
T ½ (h)	1 (β) 3-9 (γ)	18 (β) 360 (γ)	8	10 (β) 168 (γ)

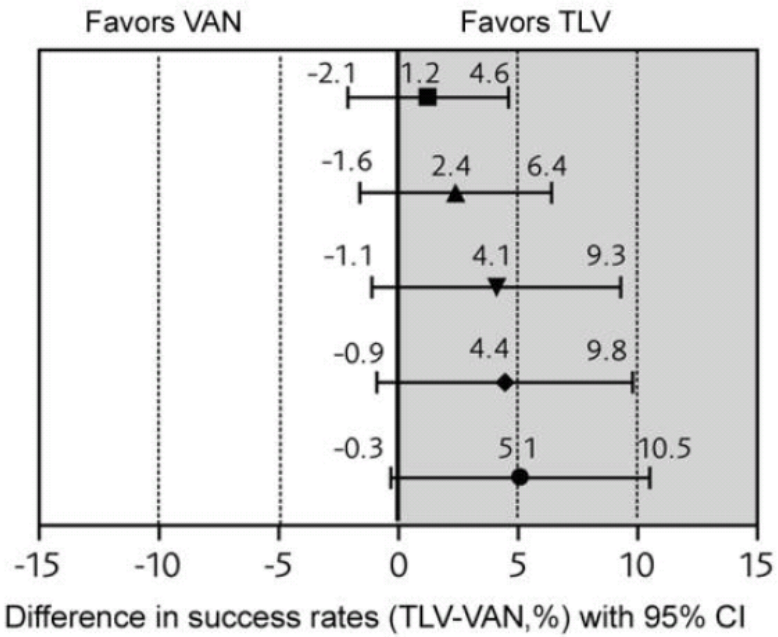
Clinical efficacy

Clinical studies: efficacy

Phase 3 - Skin and skin structure infections

TLV 10 mg/kg q24h vs VAN 1 g q12h ; 7-14 days

Clinical outcome



	TLV % success (N)	VAN % success (N)
Clinical cure in CE patients	88.3% (745)	87.1% (744)
Overall therapeutic response[a] in ME patients	88.6% (527)	86.2% (536)
Clinical cure in ME patients with MRSA infection	90.6% (278)	86.4% (301)
Microbiological eradication in ME patients with MRSA infection	89.9% (278)	85.4% (301)
Overall therapeutic response[a] in ME patients with MRSA infection	89.9% (278)	84.7% (301)

Stryjewski et al., CID (2008) 46:1683-93

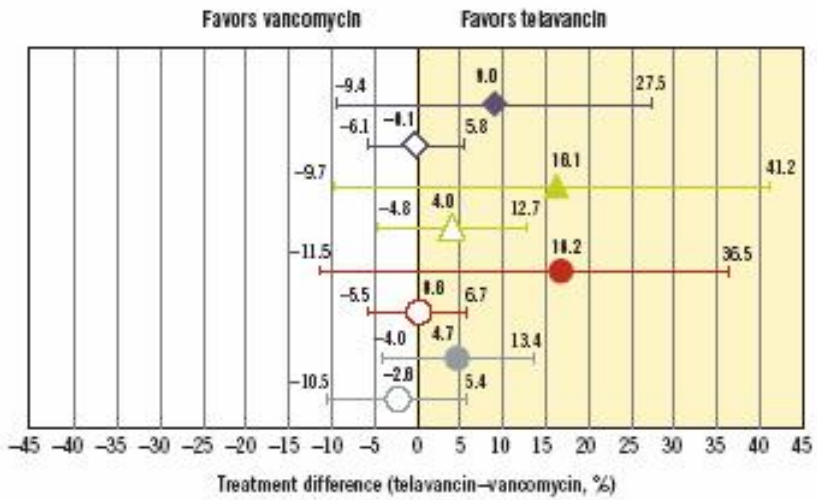
Clinical studies: efficacy

Phase 3 - HAP

TLV 10 mg/kg q24h vs VAN 1 g q12h ; 7-21 days

Clinical outcome

2 Clinical cure rates in different severity subgroups at TOC (pooled clinically evaluable population).



Subgroup	Clinical cure rates at TOC % (n/N) Telavancin	Vancomycin
APACHE II ≥20	67.9 (36/53)	56.9 (33/58)
APACHE II <20	85.3 (221/259)	85.6 (243/284)
ALI or ARDS	83.9 (26/31)	68.8 (11/16)
No ALI or ARDS	82.7 (115/139)	78.5 (139/177)
Bacteremia	85.0 (17/20)	69.2 (18/26)
No bacteremia	82.2 (240/292)	81.6 (258/316)
Age ≥65 years	80.6 (125/155)	76.0 (146/192)
Age <65 years	84.1 (132/157)	86.7 (130/150)

TOC, test-of-cure; APACHE, Acute Physiology and Chronic Health Evaluation; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Rubinstein et al., ICAAC/IDSA (2008) K529

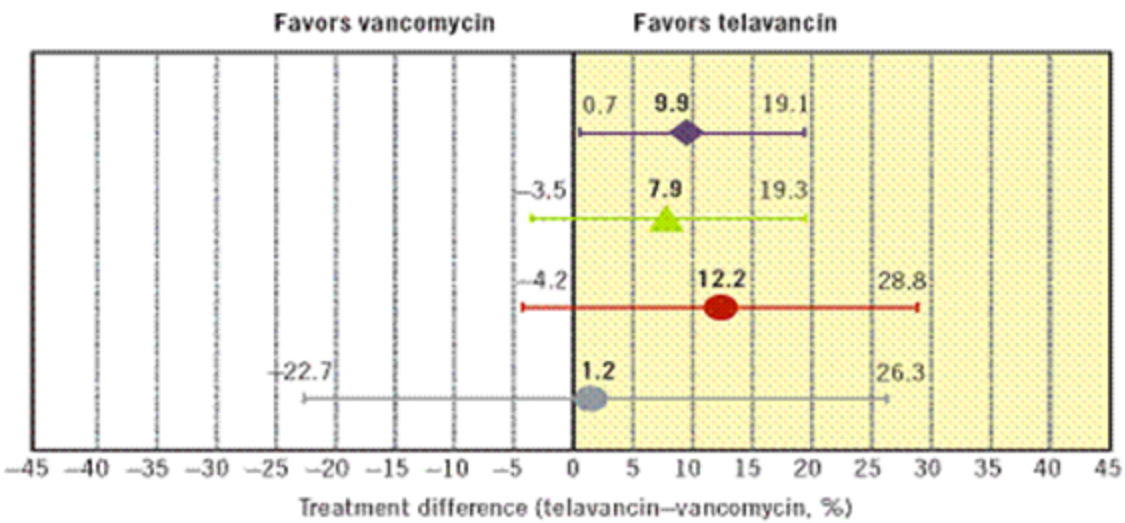
Clinical studies: efficacy

Phase 3 - HAP

TLV 10 mg/kg q24h vs VAN 1 g q12h ; 7-21 days

Microbiological outcome

2 **Pooled clinical cure rates at TOC (microbiologically evaluable patients with monomicrobial infection) by baseline pathogen.**



	Clinical cure rates at TOC, % (n/N)	
	Telavancin	Vancomycin
S. aureus	84 (123/146)	74 (113/152)
MRSA	82 (72/88)	74 (86/116)
MSSA	88 (51/58)	75 (27/36)
S. pneumoniae	93 (13/14)	92 (11/12)

TOC, test of cure; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

Rubinstein et al., ICAAC/IDSA (2008) K530

Safety profile

Clinical studies: safety

« metallic/soapy »

this is not so nice …

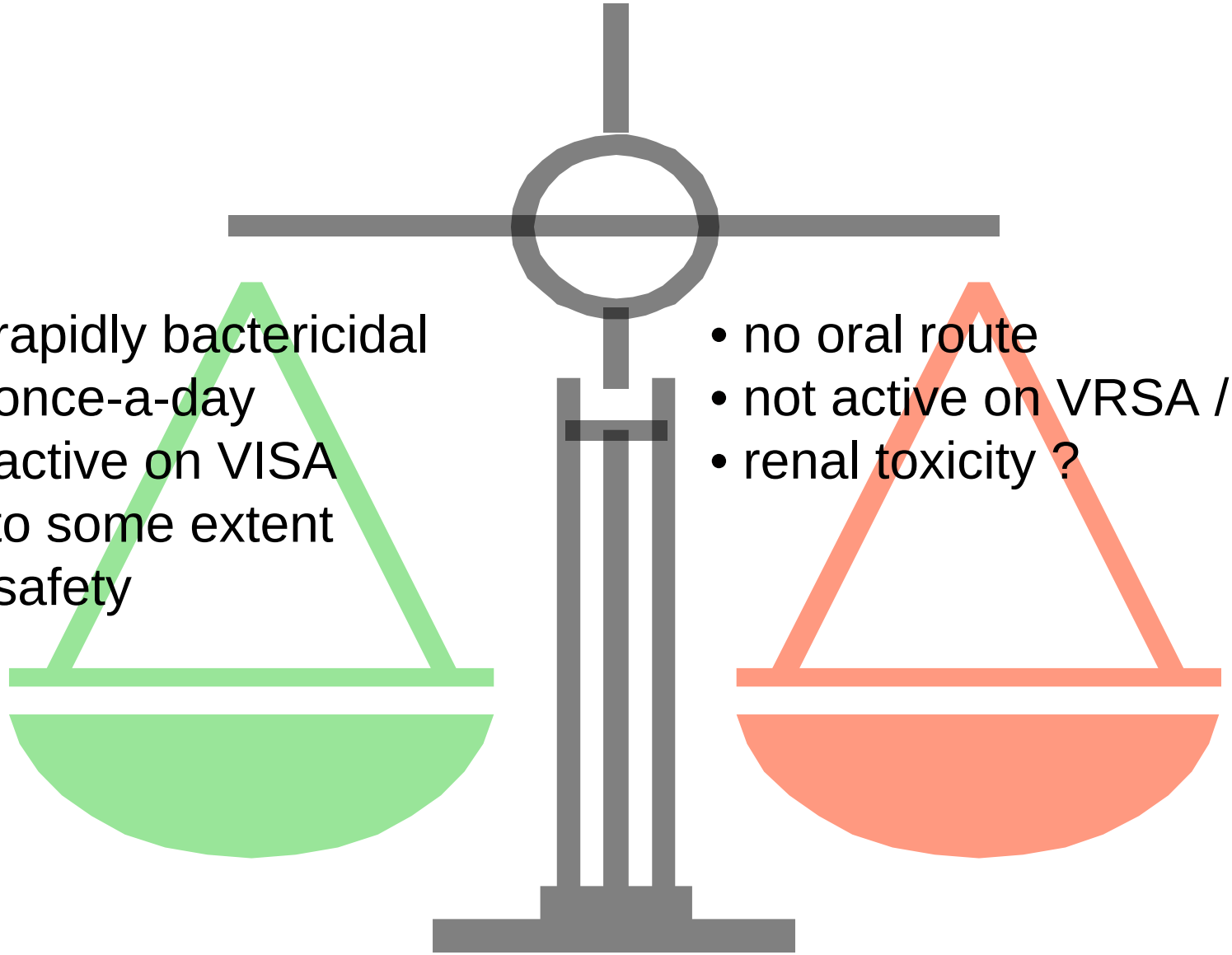
Adverse events reported in ⩾3% of patients in any group in the all-treated population: pooled analysis (studies 0017 and 0018).

Variable	No. (%) of patients	
	Telavancin treatment arm (n = 929)	Vancomycin treatment arm (n = 938)
Any adverse event	735 (79)	676 (72)
Serious adverse event	69 (7)	42 (4)
Discontinued treatment because of an adverse event	73 (8)	53 (6)
Adverse event term		
Taste disturbance	311 (33)	62 (7)
Nausea	249 (27)	142 (15)
Headache	130 (14)	120 (13)
Vomiting	127 (14)	69 (7)
Urine abnormality (foamy urine)	122 (13)	27 (3)
Insomnia	90 (10)	86 (9)
Constipation	96 (10)	61 (7)
Diarrhea	67 (7)	76 (8)
Dizziness	55 (6)	53 (6)
Rash	35 (4)	43 (5)
Infusion site pain	41 (4)	40 (4)
Fatigue	41 (4)	31 (3)
Chills	41 (4)	21 (2)
Generalized pruritus	28 (3)	60 (6)
Infusion site erythema	24 (3)	24 (3)
Decreased appetite	25 (3)	19 (2)
Anxiety	26 (3)	22 (2)
Renal dysfunction	27 (3)	10 (1)
Abdominal pain	17 (2)	26 (3)

reason for withdrawal from EMEA

Stryjewski et al., CID (2008) 46:1683-93

Telavancin : pros and cons



- rapidly bactericidal
- once-a-day
- active on VISA to some extent
- safety

- no oral route
- not active on VRSA / VISA
- renal toxicity ?

Conclusions

- Linezolid useful alternative to vancomycin in poorly accessible compartments, but take care of toxicity …
- Tigecycline useful in polymicrobial infections, but take care of Pseudomonas …
- Doripenem is a meropenem-like drug registered for use by prolonged infusion, but has less indications …
- Telavancin is promizing for MRSA but take care of renal toxicity ….
- Can we hope something better for the future ?

What about the future ?

- most of the recent drugs are new in existing classes, with improved properties

- new classes in pre-clinical development ; will they go further ?

- new molecules coming on the market are (too) scarce in view of the rapidly evolving resistance….

  Rejected by FDA in 2009:
  - oritavancin (more clinical data; fear of toxicity)
  - iclaprim (lack of efficacy)
  - ceftobiprole (dossier to revise)

- new strategies under investigation (targeting virulence)

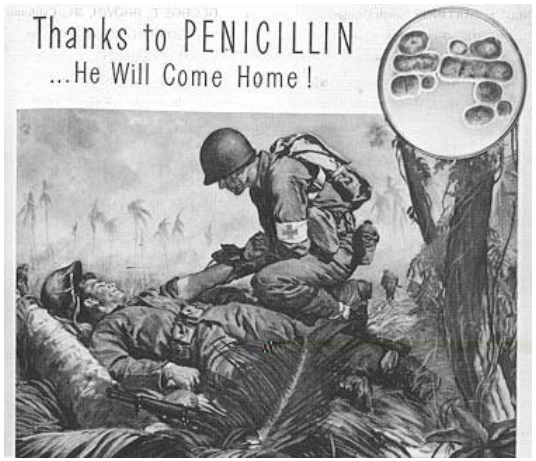
What about the future ?

1945 2000

the pre-antibiotic era | antibiotic gold period | the post-antibiotic age

« avant la découverte de la pénicilline »

De Konk – Le Monde 1975



« après la découverte de la pénicilline »

De Konk – Le Monde 1975

What about the future ?