Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

New developments in anti-Gram positive treatment

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La Hulpe, 06/11/2008

The anti-Gram(+) pipeline

recently brought on the Belgian market	on the market; not yet in Belgium	waiting for approval	investigational
moxifloxacin	synercid	telavancin	new β-lactams
linezolid	daptomycin	oritavancin	new oxazolidinones
tigecycline		dalbavancin	new ketolides
		ceftobiprole	new quinolones
		iclaprim	new lipopeptides
			FabI inhibitors
			antibact. peptides
			...

What will be your choice ?

Let’s travel together …

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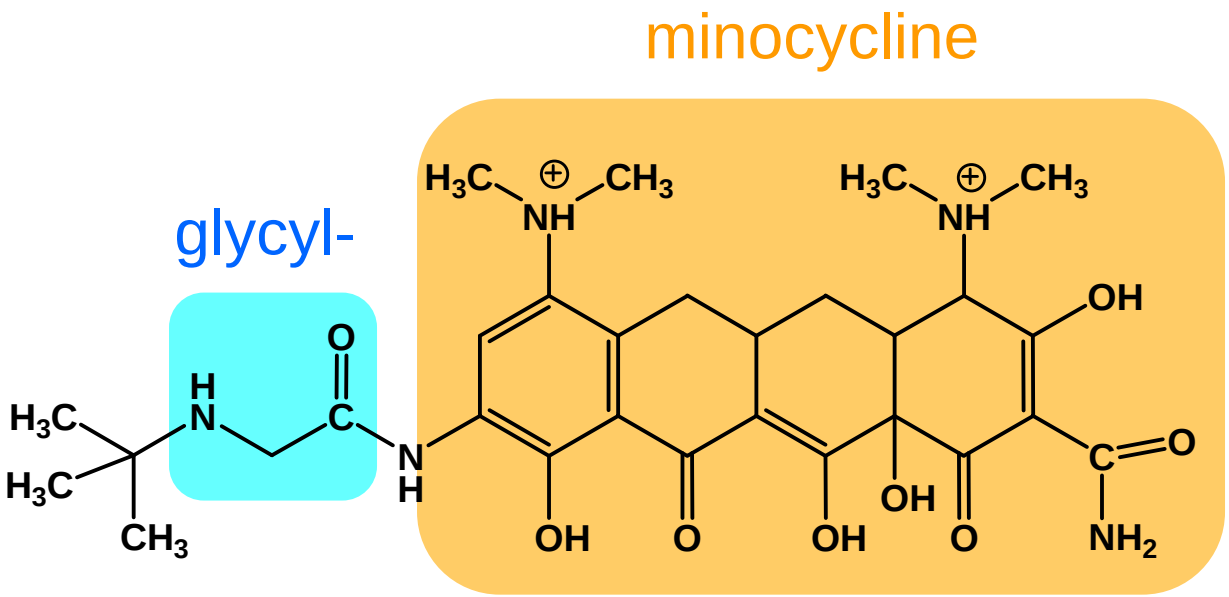
		ceftobiprole	new quinolones
		iclaprim	new lipopeptides
			FabI inhibitors
			...

The last introduced anti-MRSA: Tigecycline, a glycylcycline with XL spectrum

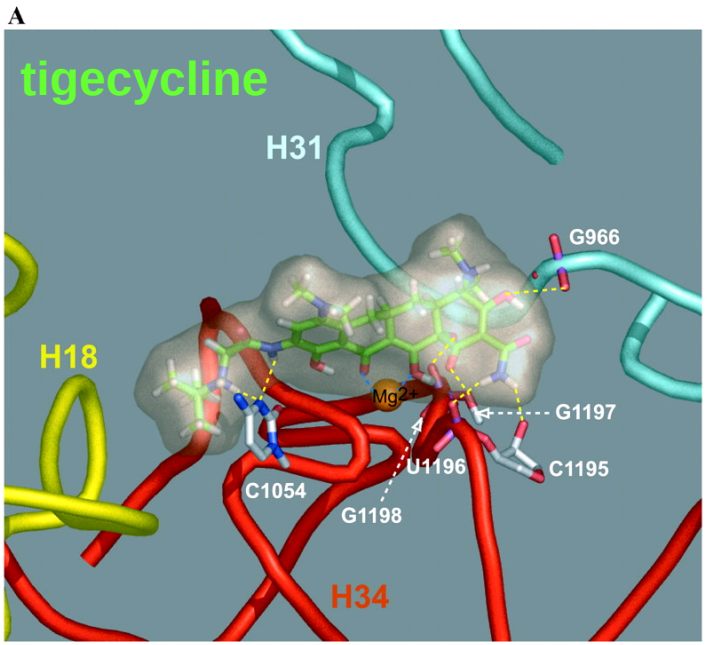
Tigecycline: a glycylcycline

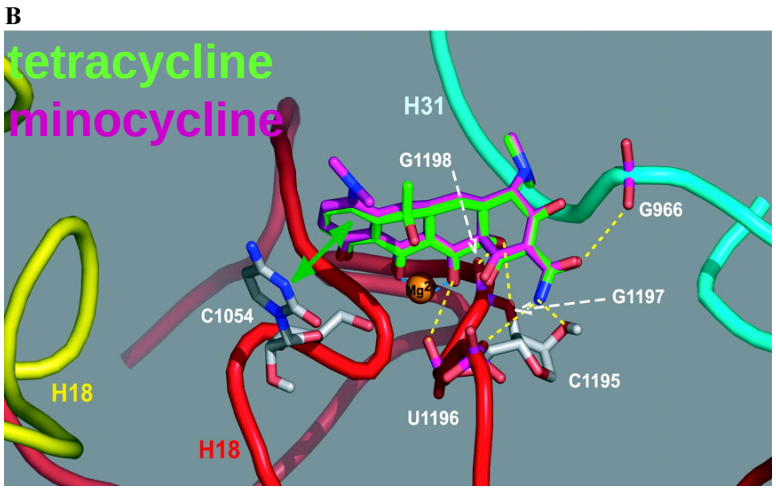


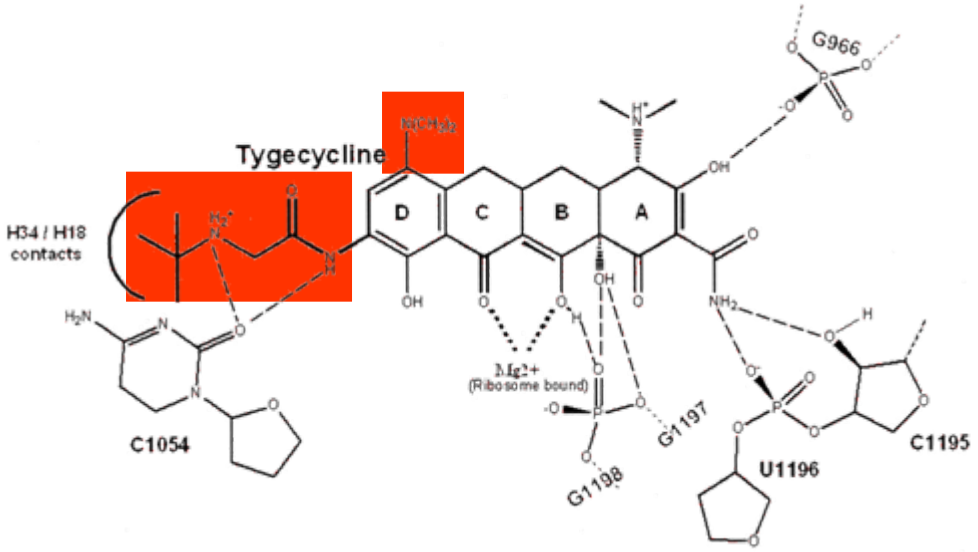
Wyeth

GAR936

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

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: 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

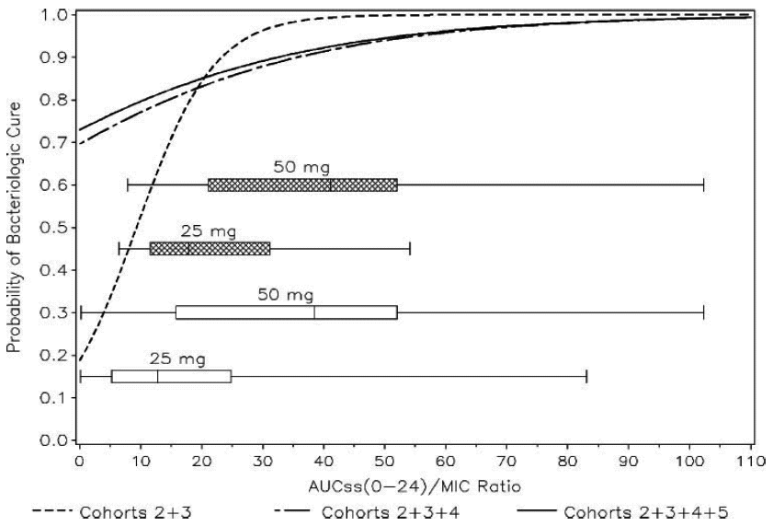
Rodvold, JAC (2006) 58:1221-9
Conte et al., Int J Antimicrob Agents (2005) 25:523-9

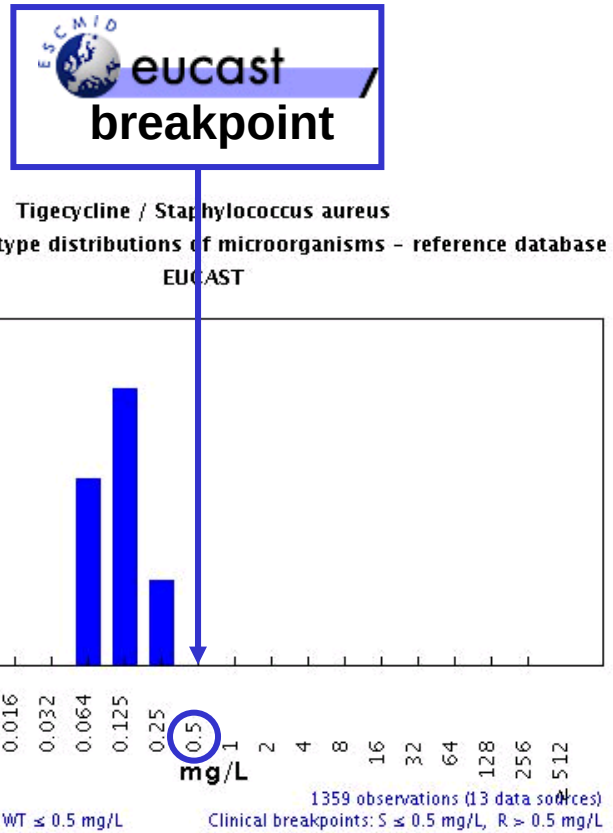
Tigecycline: setting up the breakpoint

Pharmacodynamic breakpoint for Gram(+) infections

AUC/MIC ≥ 18

MIC ≤ 18/5 = 0.25 mg/L



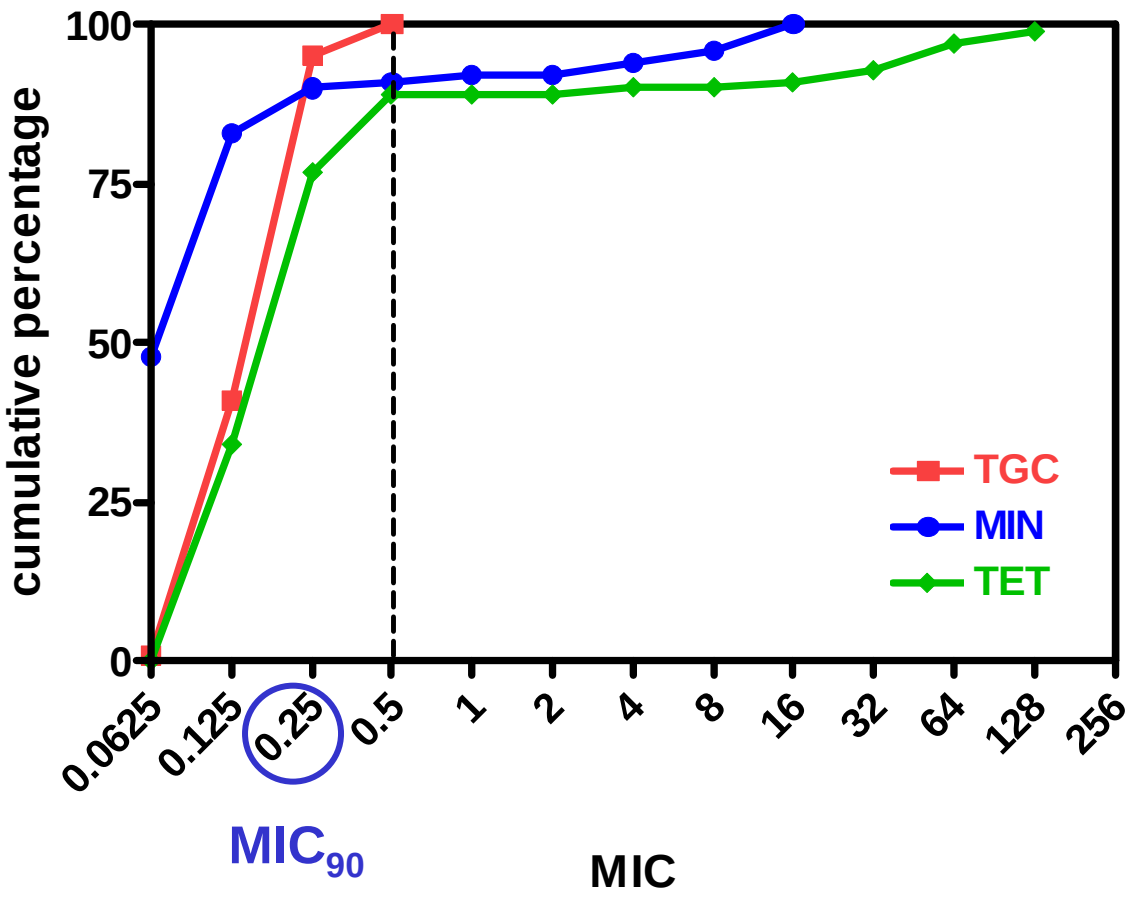


to avoid splitting the WT distribution …

Meagher et al., AAC (2007) 51:1939-45
McGowan, JAC (2008) 62: suppl.1 i11-i16

Tigecycline breakpoint: how does it fit with Belgian MICs ?

511 MRSA isolates from 112 Belgian hospitals



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

PK/PD of Tigecycline in different compartments

dose et voie d'administr.	compartiment	AUC	AUC/MIC (0.25 mg/L)	AUC/MIC (0.5 mg/L)
			MIC $_{90}$ in Belgium	*Breakpoint EUCAST*
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

PK/PD predicts success for AUC/MIC > 18

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

Tigecycline clinical experience

1. Phase 3 - Skin and skin structure infections

TGC 100 mg/ 50 mg q12h vs VAN/AZM 1g/2g q12h; up to 14 days

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

2. 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

3. 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)

Most are non-severe patients …

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

Only a few PenI/R isolates

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

Tigecycline clinical experience

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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

4. 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

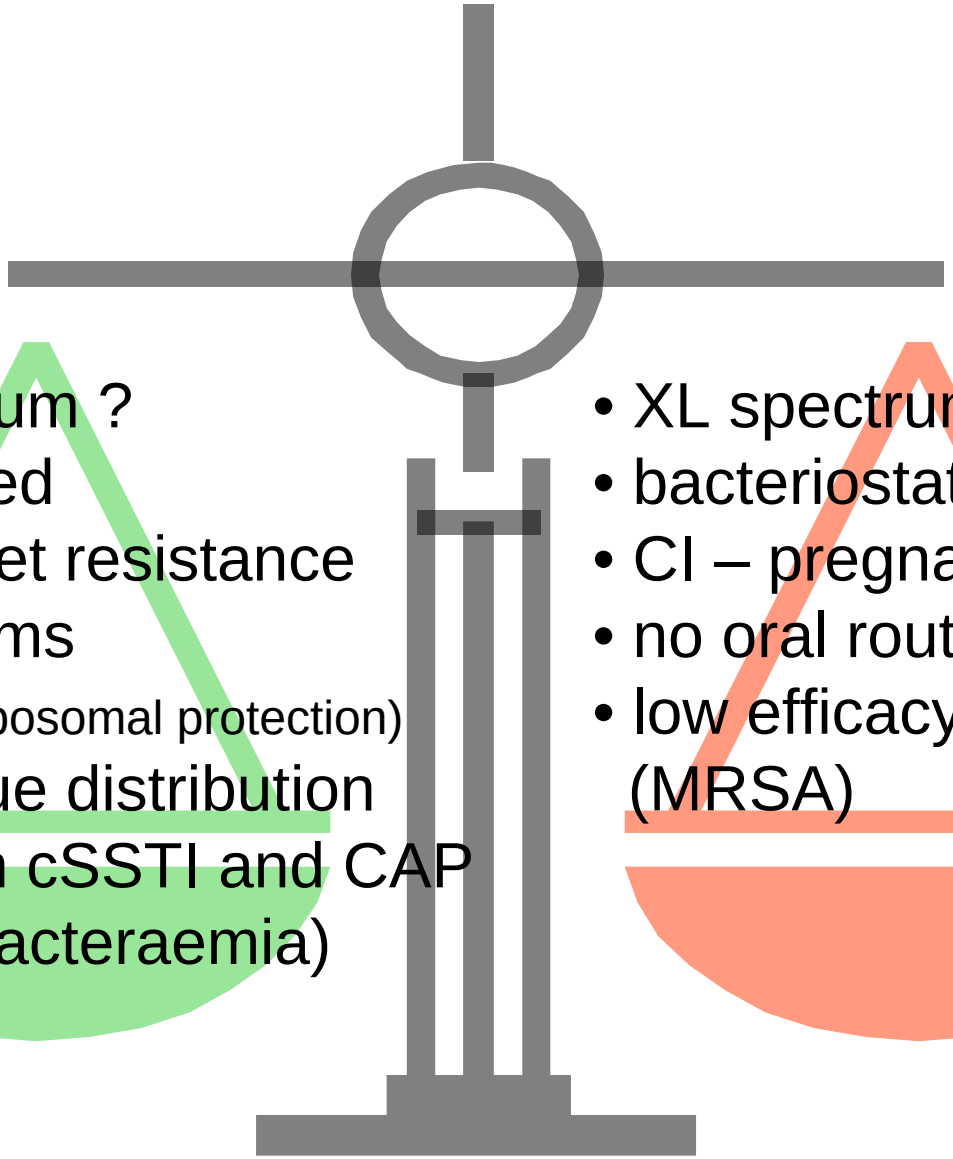
patients	population	tigecycline	imipenem/cilastatin
VAP/HAP	CE	67.9 %	78.2 %
	mITT	62.7 %	67.6 %
Non-VAP	CE	75.4 %	81.3 %
	mITT	69.3 %	71.2 %

microbiological response

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

EMEA/382036/2008

Tigecycline : pros and cons

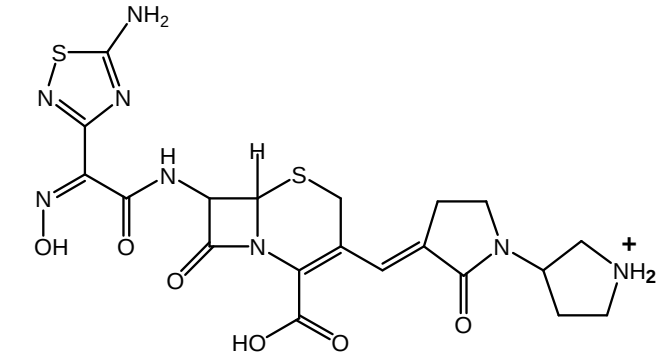


- XL spectrum ?
- not affected by some tet resistance mechanisms (Tet efflux, ribosomal protection)
- large tissue distribution
- efficient in cSSTI and CAP (MRSA; bacteraemia)

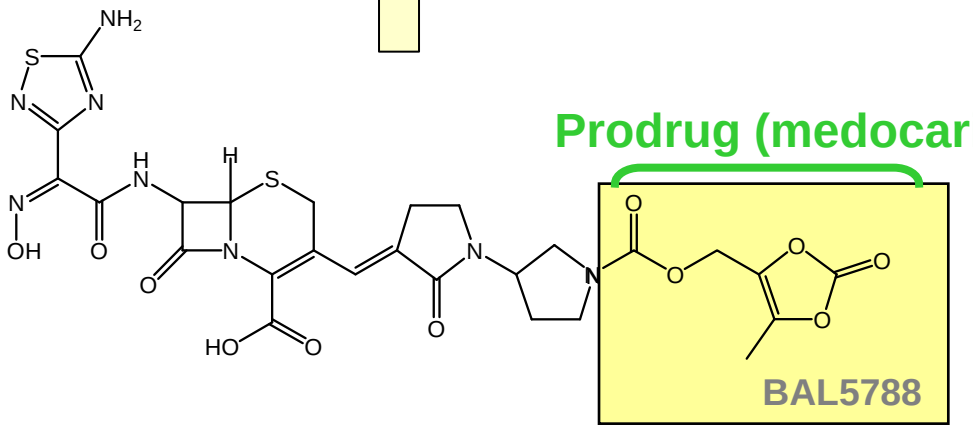
- XL spectrum ?
- bacteriostatic
- CI – pregnancy, children
- no oral route
- low efficacy in HAP/VAP (MRSA)

Ceftobiprole & Ceftaroline, two anti-MRSA *S. aureus* with improved binding capacity to PBP2a

Ceftobiprole



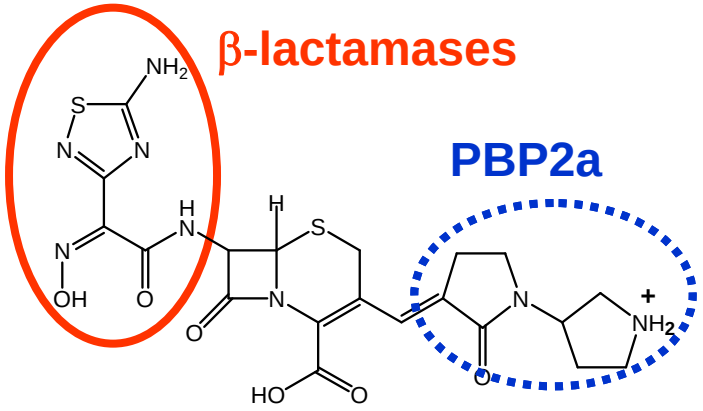
BAL9141



basilea PHARMACEUTICA J&JPRD

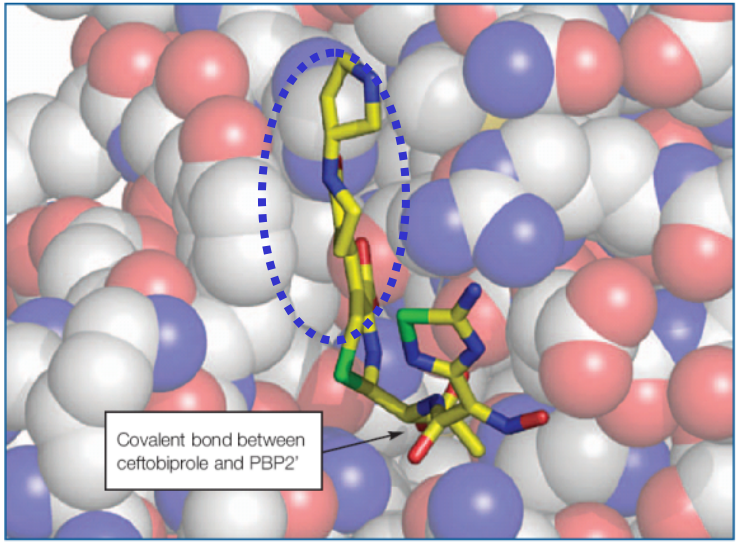
Ceftobiprole

Compound	Rates of hydrolysis by purified β-lactamases: Class A — *Staphylococcus aureus* PC 1
Ro 63-9141	0.93
Ceftriaxone	19
Cephalothin	200
Penicillin G	10,000



Compound	Affinity for PBPs: IC_{50} for competition with fluorescein-labeled ampicillin (μM) — *Staphylococcus epidermidis* PBP 2′
Ro 63-9141	0.87
Ceftriaxone	115
Imipenem	>500
Methicillin	>500

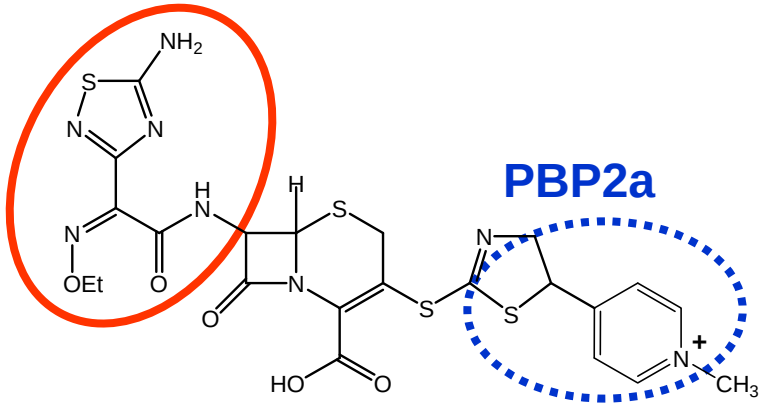
Model of the active site of SaPBP2' complexed with ceftobiprole.



open conformation

Lovering et al., ECCMID (2006) P1586
Hebeisen et al., AAC (2001) 45:825-31

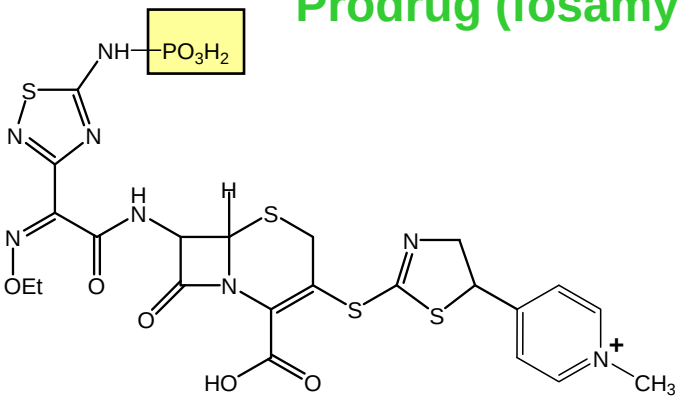
Ceftaroline



β-lactamases

PBP2a

Prodrug (fosamyl) TAK-599



TAK-91825

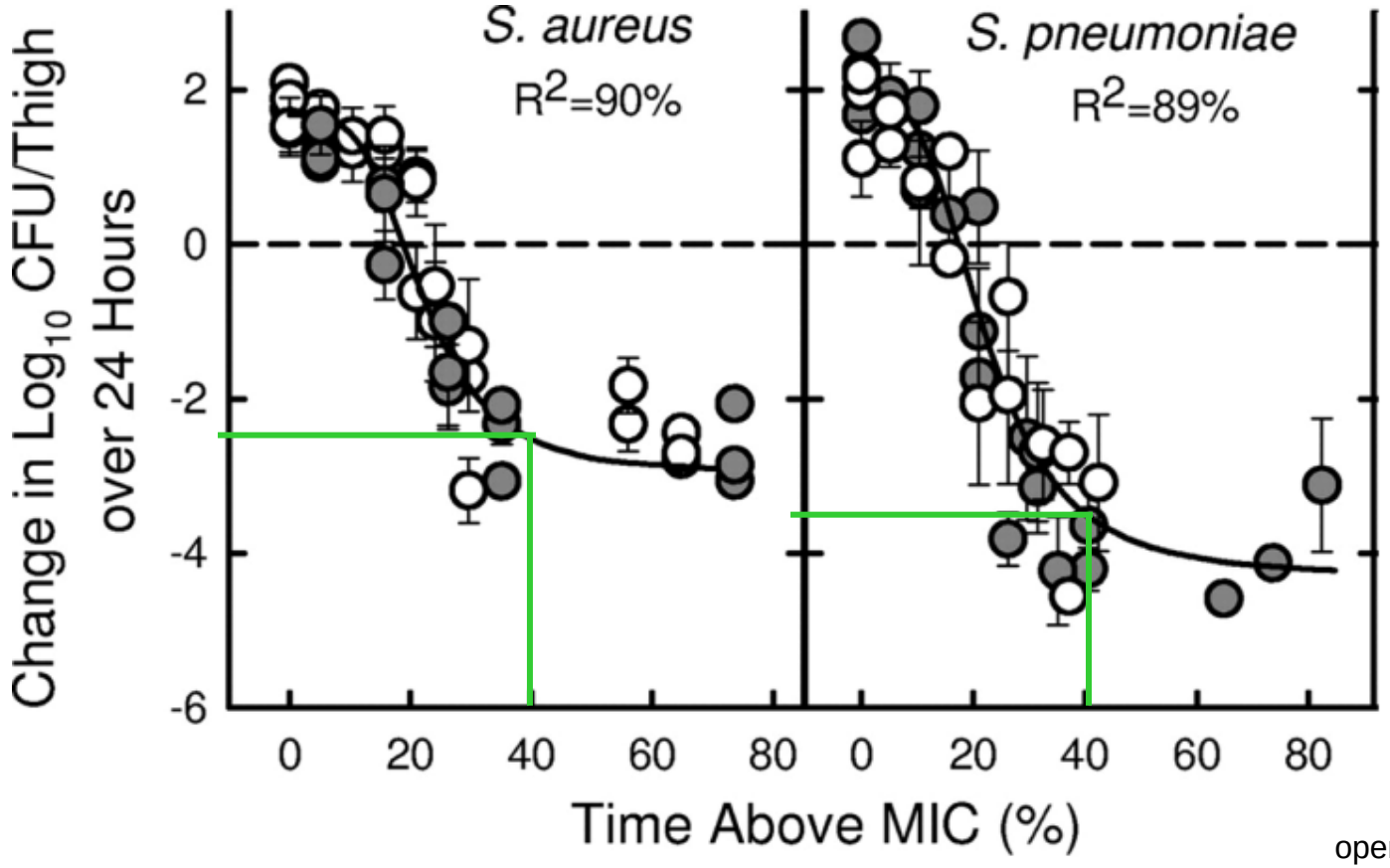
Ishikawa et al., Bioorg Med Chem. (2003) 11:2427-37

Ceftobiprole & Ceftaroline: in vitro activity

strain	ceftobiprole			ceftaroline		
	MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range
MSSA	0.25	0.5	0.12-1	0.25	0.25	≤ 0.03-1
MRSA	1	2	0.25-4	0.5	1	0.12-2
S. pneumo PenS	0.008	0.015	≤ 0.002-0.06	≤ 0.008	0.015	≤ 0.008-0.25
S. pneumo PenI	0.06	0.25	0.008-0.5	0.015	0.06	≤ 0.008-0.5
S. pneumo PenR	0.5	0.5	0.25-1	0.12	0.12	≤ 0.008-0.5

Pillar et al., JAC (2008)61:595-602
Ge et al., AAC (2008) 52:3398-404

Ceftobiprole : pharmacodynamics in animals

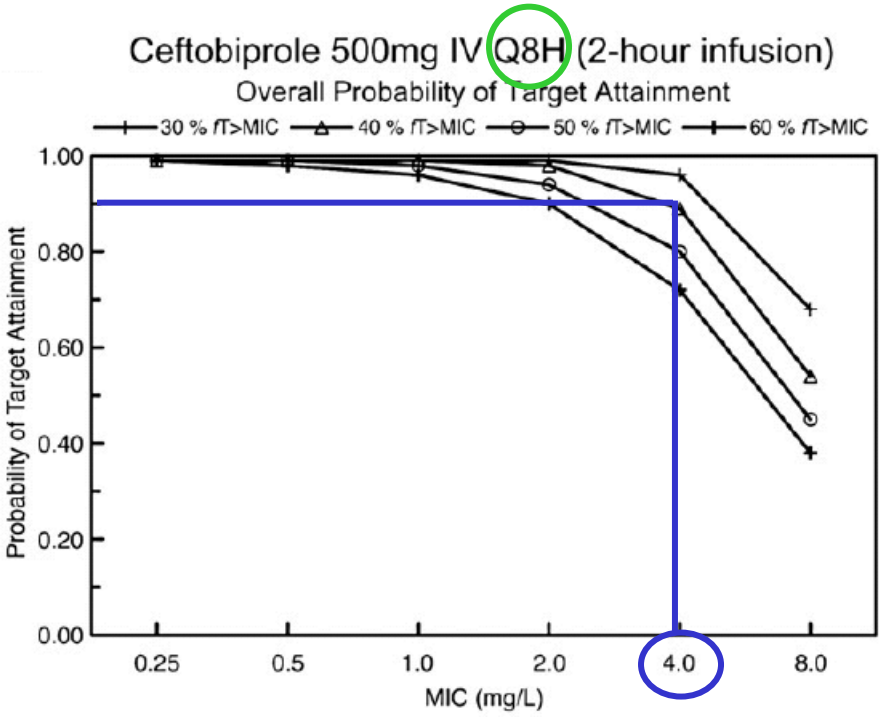


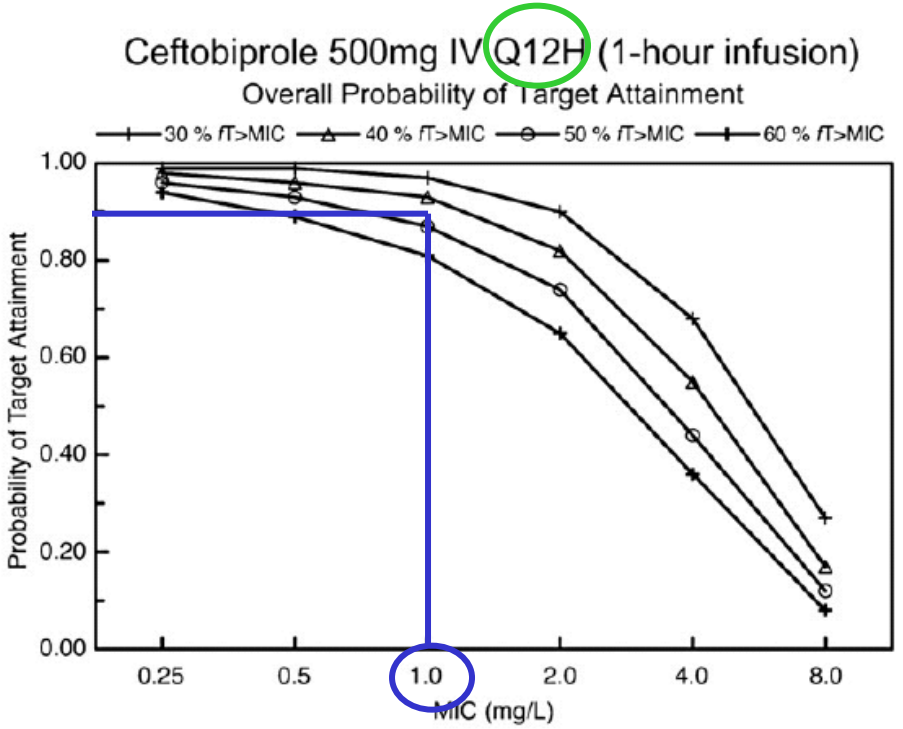
open: S; closed: R

Maximal effect for conc > MIC for 40 % of time

Craig and Andes, AAC (2008) 52:3492-6

Ceftobiprole : setting up PK/PD breakpoints



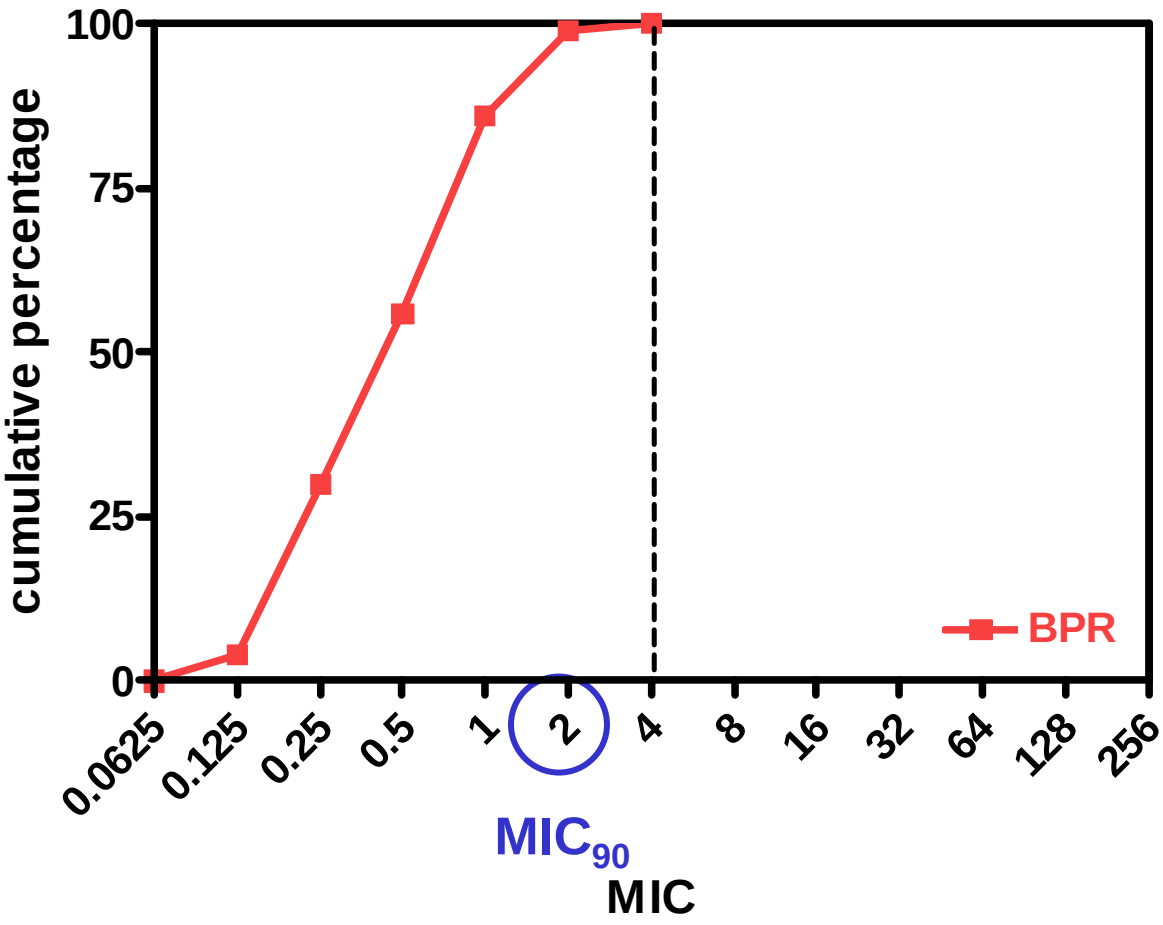


provisional breakpoint
Mouton *et al*, AAC (2004) 48:1713-8.

Lodise et al., AAC (2007) 51:2378–2387

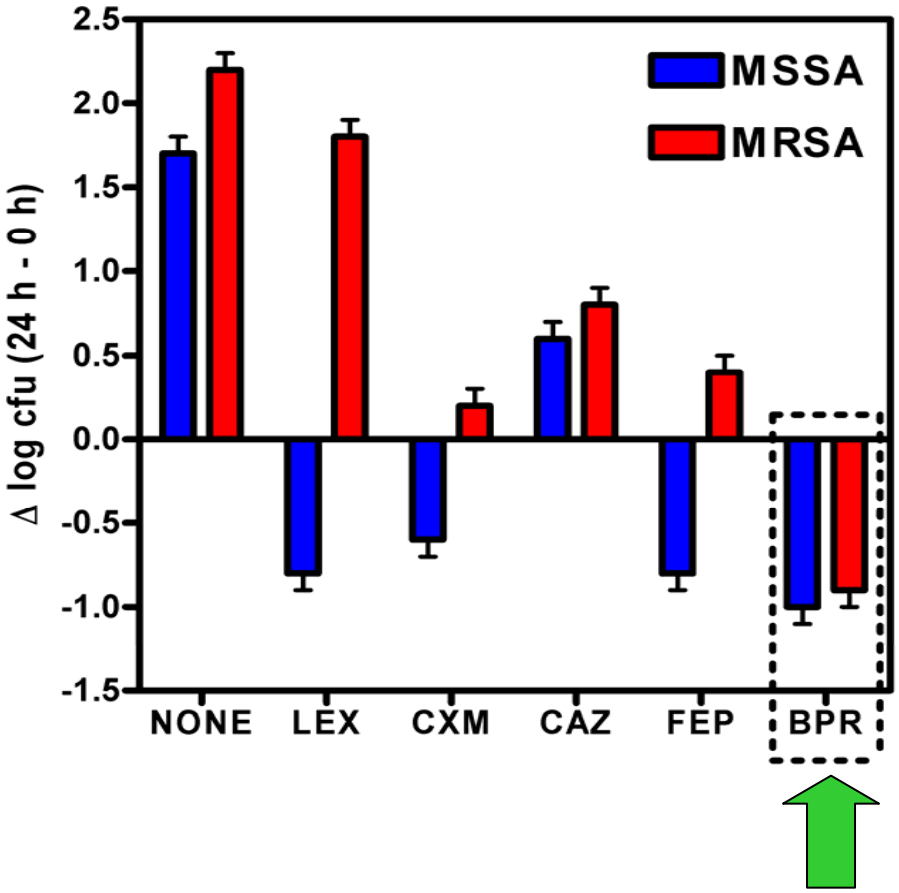
Ceftobiprole « breakpoint »: how does it fit with Belgian MICs ?

511 MRSA isolates from 112 Belgian hospitals



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

Ceftobiprole intracellular activity



Similar activity against intracellular MSSA and MRSA

Lemaire et al., ICAAC (2007) A1438

Ceftobiprole & Ceftaroline: pharmacokinetics

parameter	Ceftobiprole (500 mg)	Ceftaroline (600 mg q12h)
Cmax (mg/L)	40.6	23.5
Cmin (mg/L)		0.46
$T_{½}$ (h)	3.6	2.6
Prot. binding (20%)	< 20 %	< 20 %
T > MIC 4 mg/L	~ 6 h	

Schmitt-Hoffmann, AAC (2004) 48:2576-80
Ge et al. ICAAC (2007): A34

Ceftobiprole: clinical experience

1. Phase 3 - Skin and skin structure infections

BPR 500 mg **q12h** vs VAN 1g q12h ; 7-14 days

(+ metronidazole or aztreonam before identification)

Clinical cure rates in trial populations

Population	Cure rate (no. of patients cured/total no. of patients [%])		95% CI of difference in cure rates
	Ceftobiprole group	Vancomycin group	
ITT	309/397 (77.8)	300/387 (77.5)	−5.5, 6.1
mITT			
Only gram-positive bacteria isolated at the baseline	225/276 (81.5)	219/267 (82.0)	−7.0, 6.0
Only gram-negative bacteria isolated at the baseline	27/36 (75)	17/34[a] (50)	3.0, 47.0
CE with:	263/282 (93.3)	259/277 (93.5)	−4.4, 3.9
Wound infections	77/80 (96.3)	78/87 (89.7)	−1.0, 14.2
Abscess	142/152 (93.4)	129/134 (96.3)	−7.9, 2.2
Cellulitis	44/50 (88.0)	52/56 (92.9)	−16.2, 6.4
ME	213/226 (94.2)	203/217 (93.5)	−3.8, 5.2

[a] Cures occurred in 3 of 4 subjects who received aztreonam with vancomycin and 14 of 30 subjects who received vancomycin alone.

Clinical cure rates at TOC visit for patients in ME population with *S. aureus* infections

Cause of infection	Cure rate (no. of patients cured/total no. of patients [%])		95% CI of difference
	Ceftobiprole group	Vancomycin group	
All *S. aureus* isolates	177/187 (94.6)	162/172 (94.2)	−0.4 (−4.3, 5.2)
MSSA	121/126 (96.0)	108/112 (96.4)	−0.4 (−5.2, 4.4)
MRSA	56/61 (91.8)	54/60 (90.0)	1.8 (−8.4, 12.1)
PVL positive + MRSA	27/29 (93.1)	22/26 (84.6)	
MRSA and CRP[a] >50 mg/dl	20/23 (86.9)	21/24 (87.5)	
MRSA infections extending to fascia or muscle	19/21 (90.5)	18/21 (85.7)	

[a] CRP, C-reactive protein.

Noel et al., AAC (2008) 52:37-44

Ceftobiprole: clinical experience

1. Phase 3 - Skin and skin structure infections [Gram(+)]

BPR 500 mg **q12h** vs VAN 1g q12h ; 7-14 days
(+ metronidazole or aztreonam before identification)

Incidence of treatment-emergent AEs occurring in at least 3% of patients in either treatment group

AE or characteristic	No. (%) of patients	
	Ceftobiprole group (n = 389)	Vancomycin group (n = 382)
Nausea	55 (14)	29 (8)
Vomiting	27 (7)	15 (4)
Dysgeusia	30 (8)	2 (1)
Diarrhea	21 (5)	15 (4)
Constipation	14 (4)	11 (3)
Headache	27 (7)	24 (6)
Dizziness	14 (4)	8 (2)
Rash	9 (2)	11 (3)
Pruritus	12 (3)	22 (6)
At least one AE	203 (52)	193 (51)
At least one serious AE	24 (6)	23 (6)
Discontinuation due to AE	17 (4)	22 (6)

« caramel-like »

But is this an adverse effect ?

Noel et al., AAC (2008) 52:37-44

Ceftobiprole: clinical experience

2. Phase 3 - Skin and skin structure infections [mixed]

BPR 500 mg **q8h** vs VAN 1g q12h/CAZ 1g q8h ; 7-14 days

Clinical cure rates at the test-of-cure visit in clinically evaluable patients for the 4 leading infecting organisms.

Organism	Clinical cure rate, proportion (%) of cured patients		95% CI
	Ceftobiprole arm	Vancomycin plus ceftazidime arm	
Staphylococcus aureus			
All	228/247 (92.3)	117/128 (91.4)	−5.0 to 7.7
Methicillin resistant	78/87 (89.7)	31/36 (86.1)	−8.0 to 19.7
Methicillin susceptible	150/160 (93.8)	84/90 (93.3)	−5.8 to 8.2
Escherichia coli	33/37 (89.2)	24/26 (92.3)	−19.0 to 15.9
Pseudomonas aeruginosa	26/30 (86.7)	9/9 (100)	−30.2 to 18.5
Streptococcus pyogenes	18/20 (90.0)	11/12 (91.7)	−25.0 to 30.0

Noel et al., CID (2008) 46:647–655

Ceftobiprole: clinical experience

3. Phase 3 – community acquired pneumonia

BPR vs CRO +/- LZD

	ceftobiprole	comparator
Clinical cure	86 %	87 %
If *S. pneumoniae*	93 %	89 %

Basilea press release, Sept. 2007

Ceftobiprole: clinical experience

4. Phase 3 – Nosocomial pneumonia

BPR 500 mg **q8h** vs CAZ 2g q8h/LZD 600 mg q12h

	Cure rates % (CRs; cured/total)		Diff.	95% CI
	BPR	CAZ/LZD		
Clinically Evaluable (CE)	69.3 (174/251)	71.6 (179/250)	-2.3	(-10.3;5.7)
Non-VAP	77.4 (154/199)	76.3 (145/190)	1.1	(-7.3;9.5)
VAP	38.5 (20/52)	56.7 (34/60)	-18.2	(-36.4;0.0)
Intent-to-Treat (ITT)	49.9 (195/391)	52.8 (206/390)	-2.9	(-10.0;4.1)
Non-VAP	59.2 (171/289)	58.9 (168/285)	0.2	(-7.8;8.3)
VAP	23.5 (24/102)	36.2 (38/105)	-12.7	(-25.0;-0.3)

Noel et al., ICAAC (2008) K486

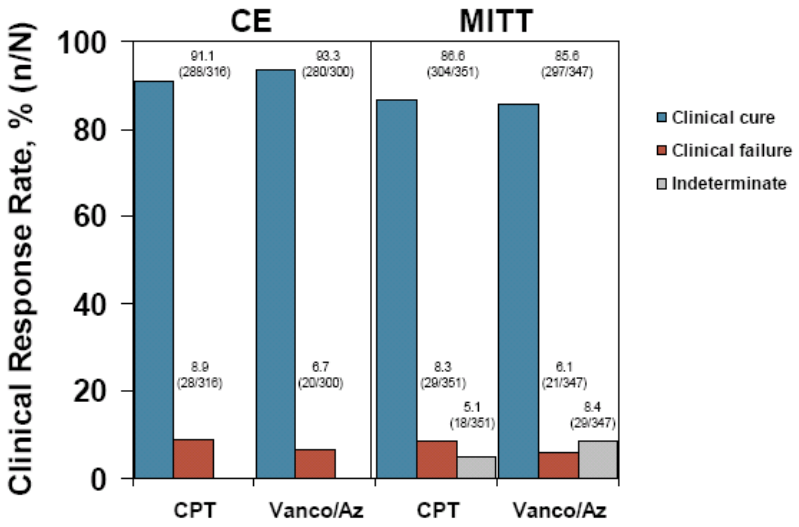
Ceftaroline: clinical experience

1. Phase 3 - Skin and skin structure infections

CPT 600 mg q12h vs VAN/AZM 1 g/1g q12h ; 5-14 days

Clinical Cure

- Clinical cure rates similar between treatment groups at TOC for CE and MITT populations
- Ceftaroline noninferior to combination of vancomycin/aztreonam for CE and MITT populations

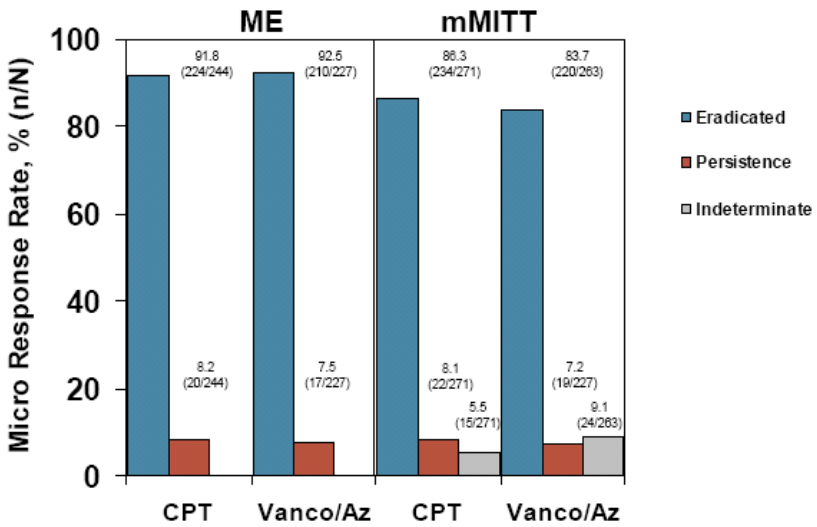


CE Population: 95% CI -2.2 (-6.6, 2.1)

MITT Population: 95% CI 1.0 (-4.2, 6.2)

Microbiological Eradication

Microbiological response exceeded 91% in both treatment groups for ME Population



ME Population: 95% CI -0.7 (-5.7, 4.4)

mMITT Population: 95% CI 2.7 (-3.4, 8.9)

Corey et al., ICAAC (2008) L1515a

Ceftaroline: clinical experience

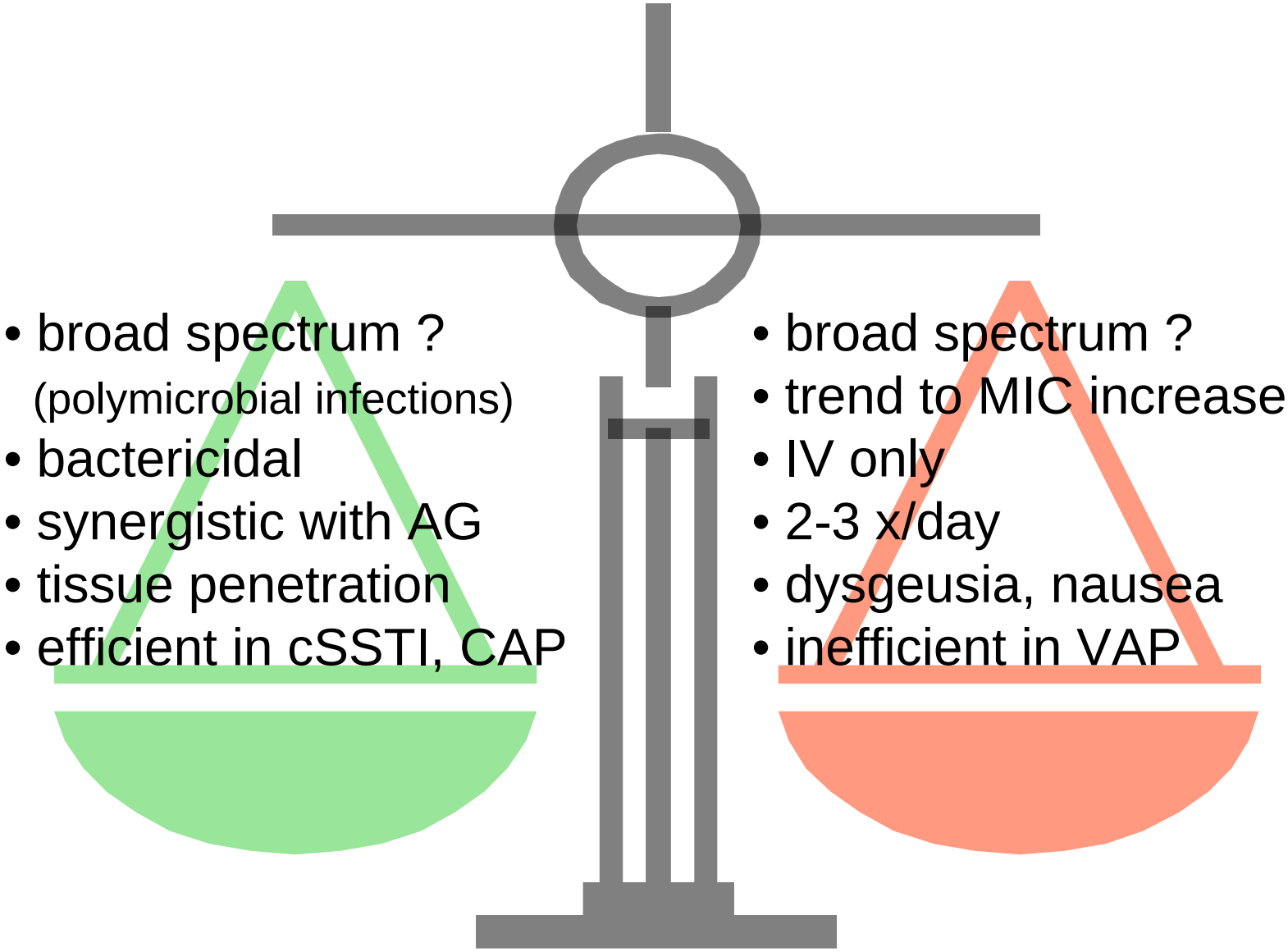
1. Phase 3 - Skin and skin structure infections

CPT 600 mg q12h vs VAN/AZM 1 g/1g q12h ; 5-14 days

Organisms	Clinical Cure % (n/N)		Microbiological Eradication % (n/N)		MIC_{90} µg/mL		
	Ceftaroline N = 244	Vanco/Az N = 227	Ceftaroline N = 244	Vanco/Az N = 227	Ceftaroline N = 244	Vancomycin N = 227	Aztreonam N = 227
Gram-positive							
S. aureus	92.9 (169/182)	94.7 (162/171)	94.0 (171/182)	92.4 (158/171)	0.5	1	
MRSA	94.9 (75/79)	95.1 (58/61)	94.9 (75/79)	91.8 (56/61)	1	1	
MSSA	91.3 (94/103)	94.5 (104/110)	93.2 (96/103)	92.7 (102/110)	0.25	1	
S. pyogenes	100 (23/23)	100 (32/32)	100 (23/23)	100 (32/32)	≤ 0.004	0.5	
S. agalactiae	92.9 (13/14)	100 (13/13)	85.7 (12/14)	100 (13/13)	0.015	0.5	
E. faecalis	92.9 (13/14)	91.7 (11/12)	92.9 (13/14)	91.7 (11/12)	8	2	

Corey et al., ICAAC (2008) L1515a

Ceftobiprole: pros and cons



- broad spectrum ?
  (polymicrobial infections)
- bactericidal
- synergistic with AG
- tissue penetration
- efficient in cSSTI, CAP

- broad spectrum ?
- trend to MIC increase
- IV only
- 2-3 x/day
- dysgeusia, nausea
- inefficient in VAP

Ceftobiprole: current status

Seeked indication : cSSTI including diabetic foot infections

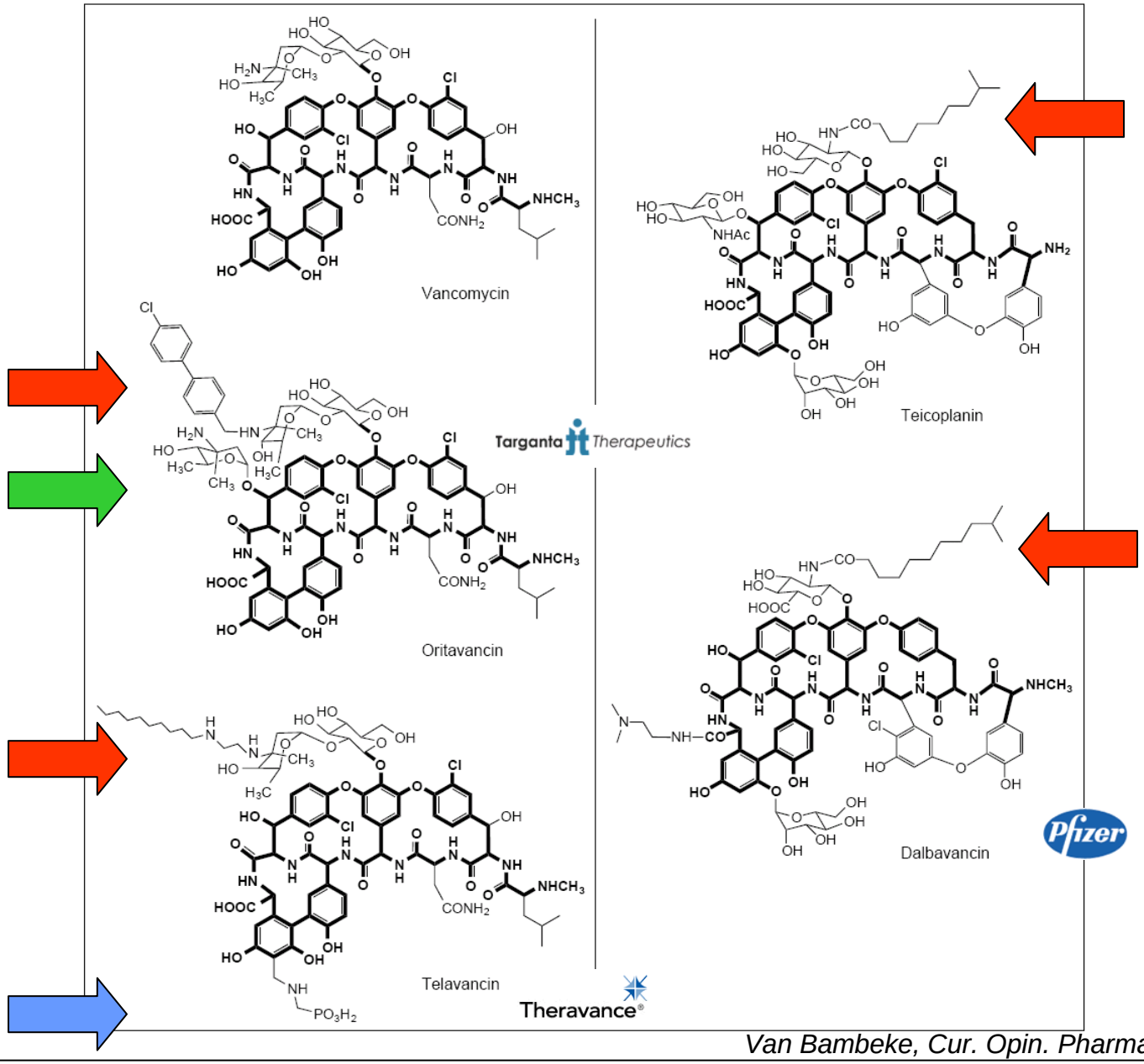
- Regulatory approvement from Health Canada authorizing the marketing of ZEFTERA (TM) for the treatment of complicated skin and skin structure infections including diabetic foot infections

- New Drug Application submitted to the FDA; response to queries considered completed

- Marketing Authorization Application submitted; currently under review by EMEA.

Lipoglycopeptides, bactericidal glycopeptides with multiple modes of action (membrane destabilization)

New glycopeptides



Van Bambeke, Cur. Opin. Pharmacol. (2004) 4:471-8

New glycopeptides: structure-activity relationship

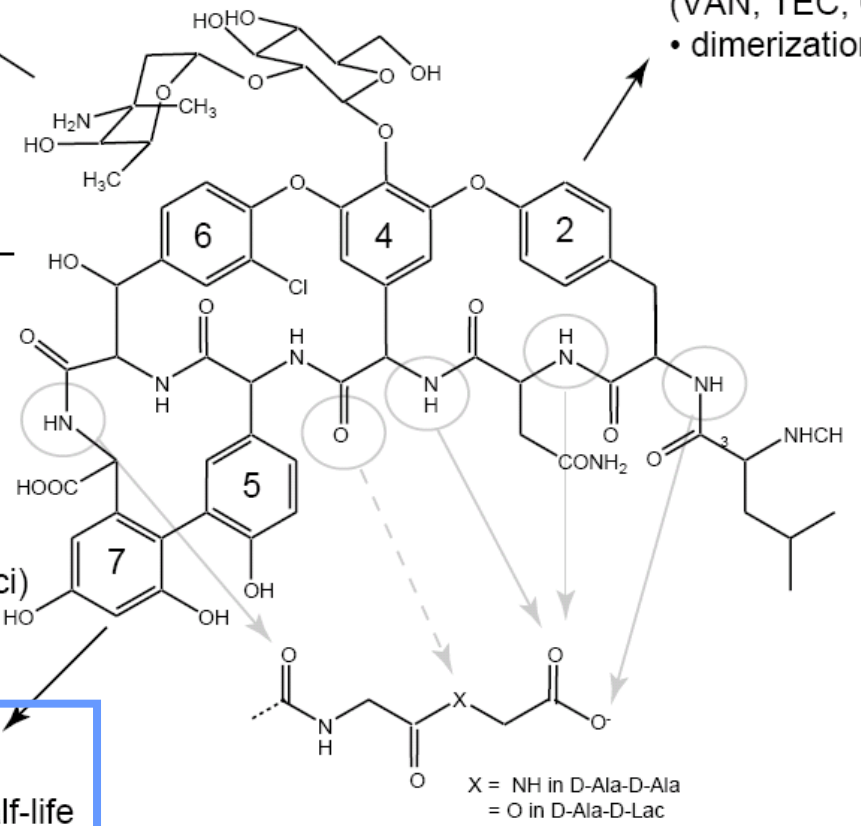
Lipophilic side chain
(TEC, ORI, TEL, DAL)
- membrane anchoring
- prolonged half-life
- increased activity (enterococci)

Sugar
(ORI)
- dimerization

Basic amide
(DAL)
- increased activity (staphylococci)

Polar group
(TEL)
- decreased half-life

Cl
(VAN, TEC, ORI, TEL)
- dimerization



Van Bambeke, Cur. Opin. Pharmacol. (2004) 4:471-8

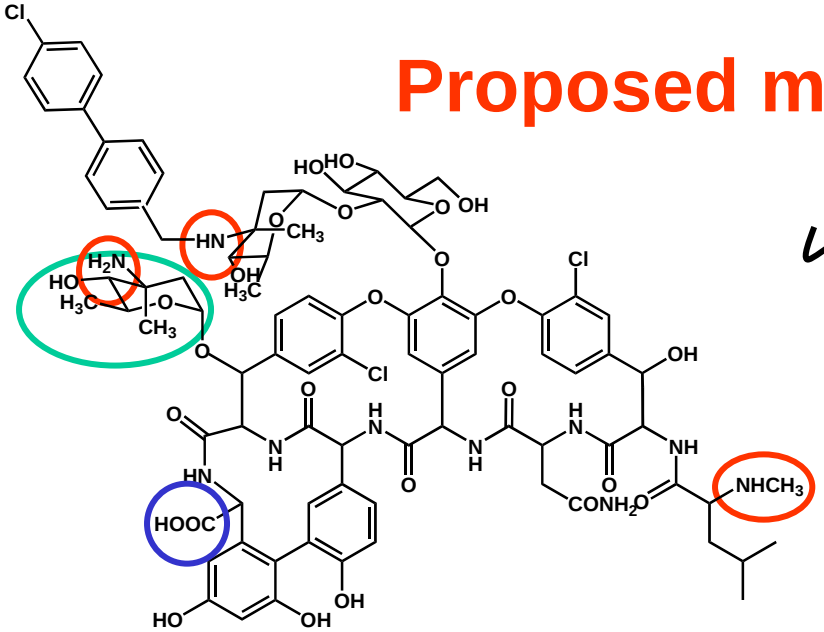
In vitro activity

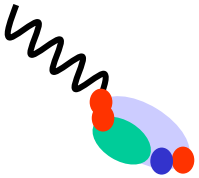
species	phenotype	ORI	TLV	DAL	VAN
S. aureus	MSSA	0.25/0.5	0.25/0.5	0.06/0.06	1/1
	MRSA	0.25/0.5	0.25/0.25	0.06/0.06	1/1
	VISA	1/1	0.5-1	0.25/2	4/4
	VRSA	0.5*	2-4	16*	16*
S. pneumo	PenS	≤ 0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.03/≤ 0.03	≤ 0.25/≤ 0.25
	Pen nonS	≤0.002/0.004	≤ 0.06/≤ 0.06	≤ 0.03/≤ 0.03	≤ 0.25/≤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

* Median value

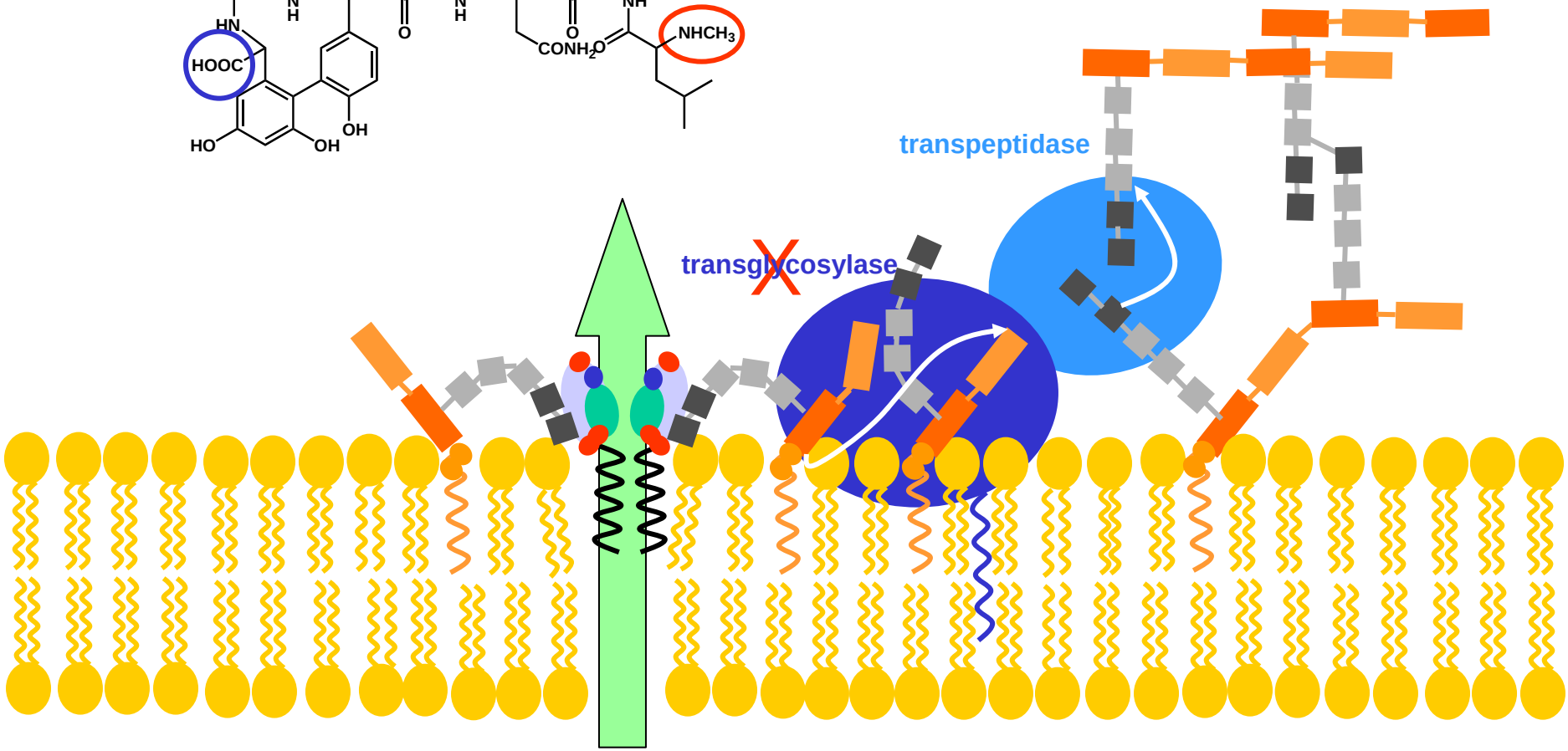
Draghi et al.,AAC (2008) 52:2383-2388
ICAAC (2008) C1-146,150,151

Proposed mode of action



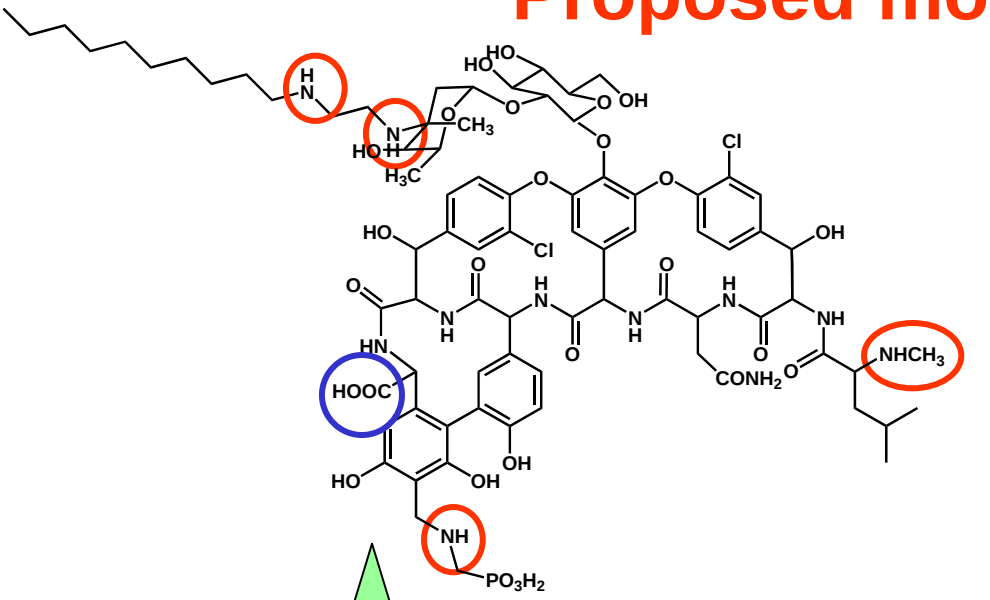


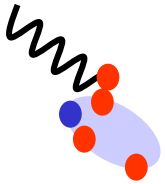
oritavancin



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

Proposed mode of action

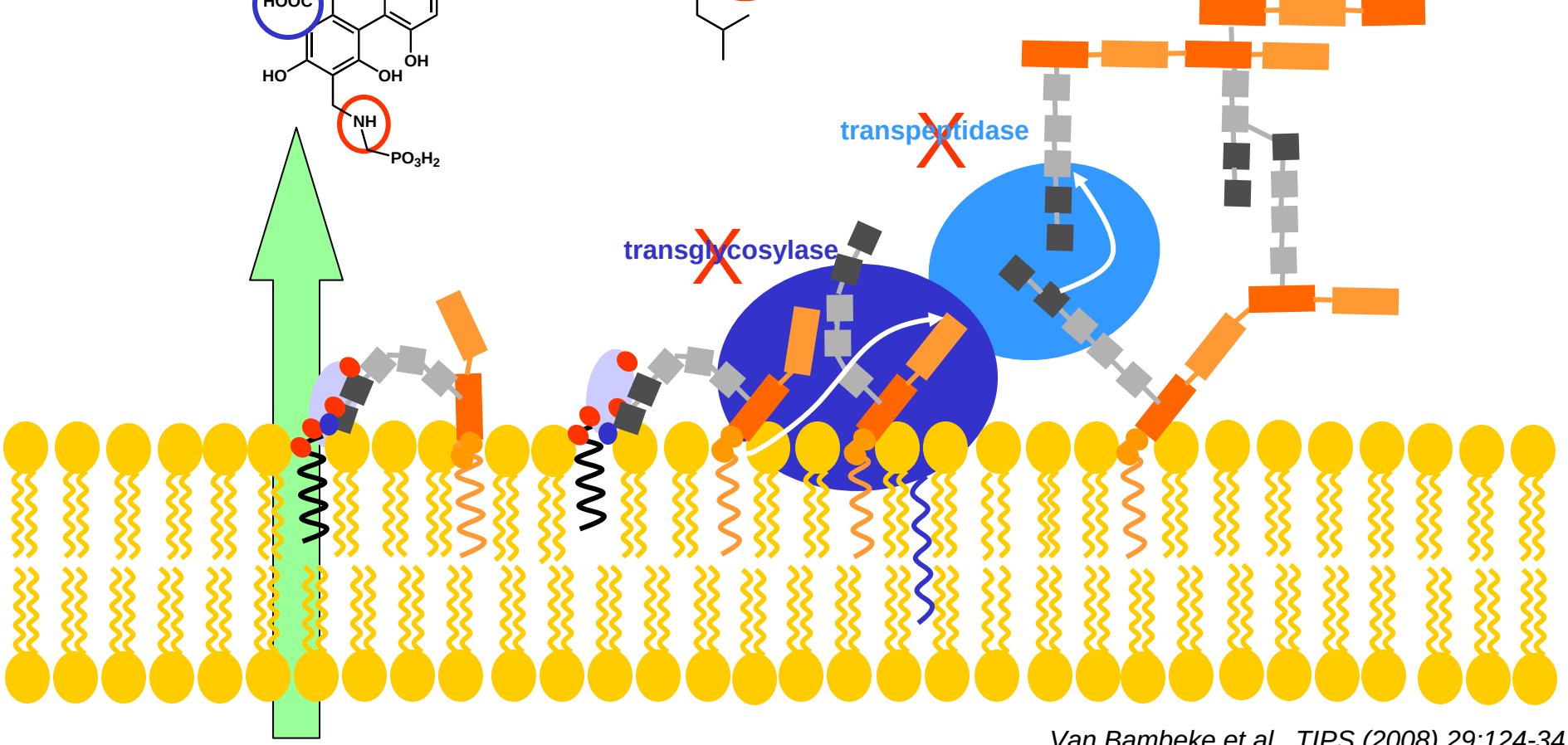




telavancin

transpeptidase

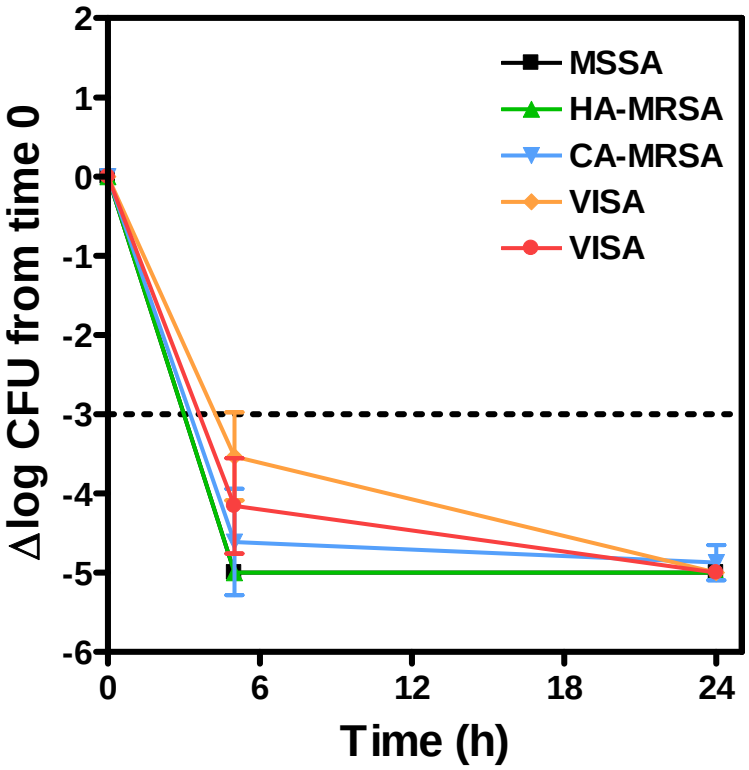
transglycosylase



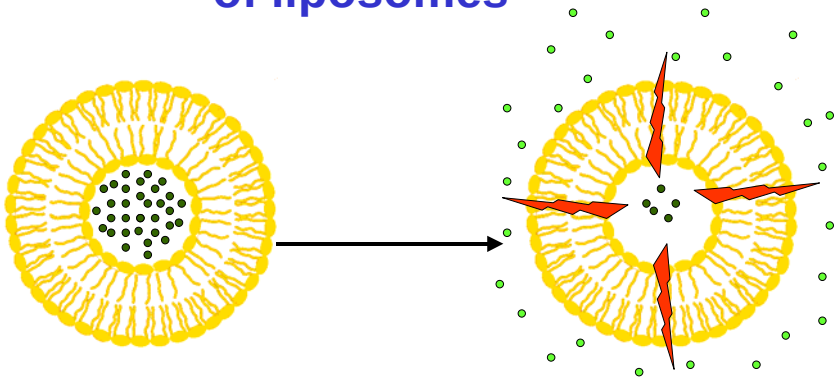
Van Bambeke et al., TIPS (2008) 29:124-34

Bactericidal effect and membrane permeabilization

Bactericidal effect on bacteria

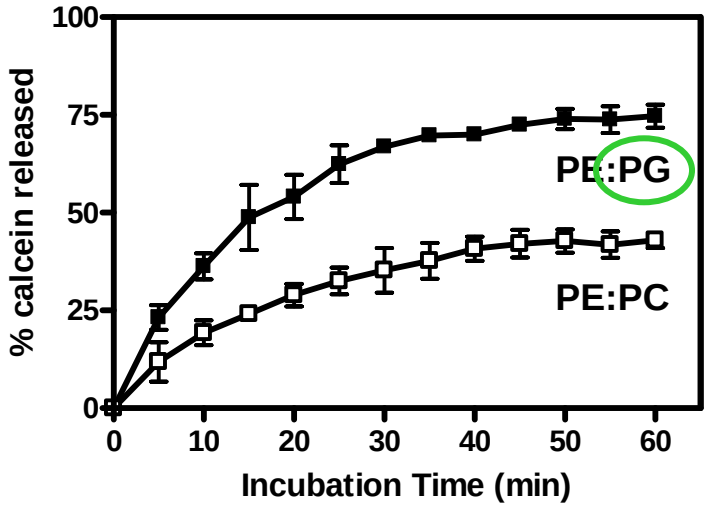


Permeabilization of liposomes



calcein entrapped at a self-quenching concentration

increase in fluorescence signal upon release and dilution in the external medium

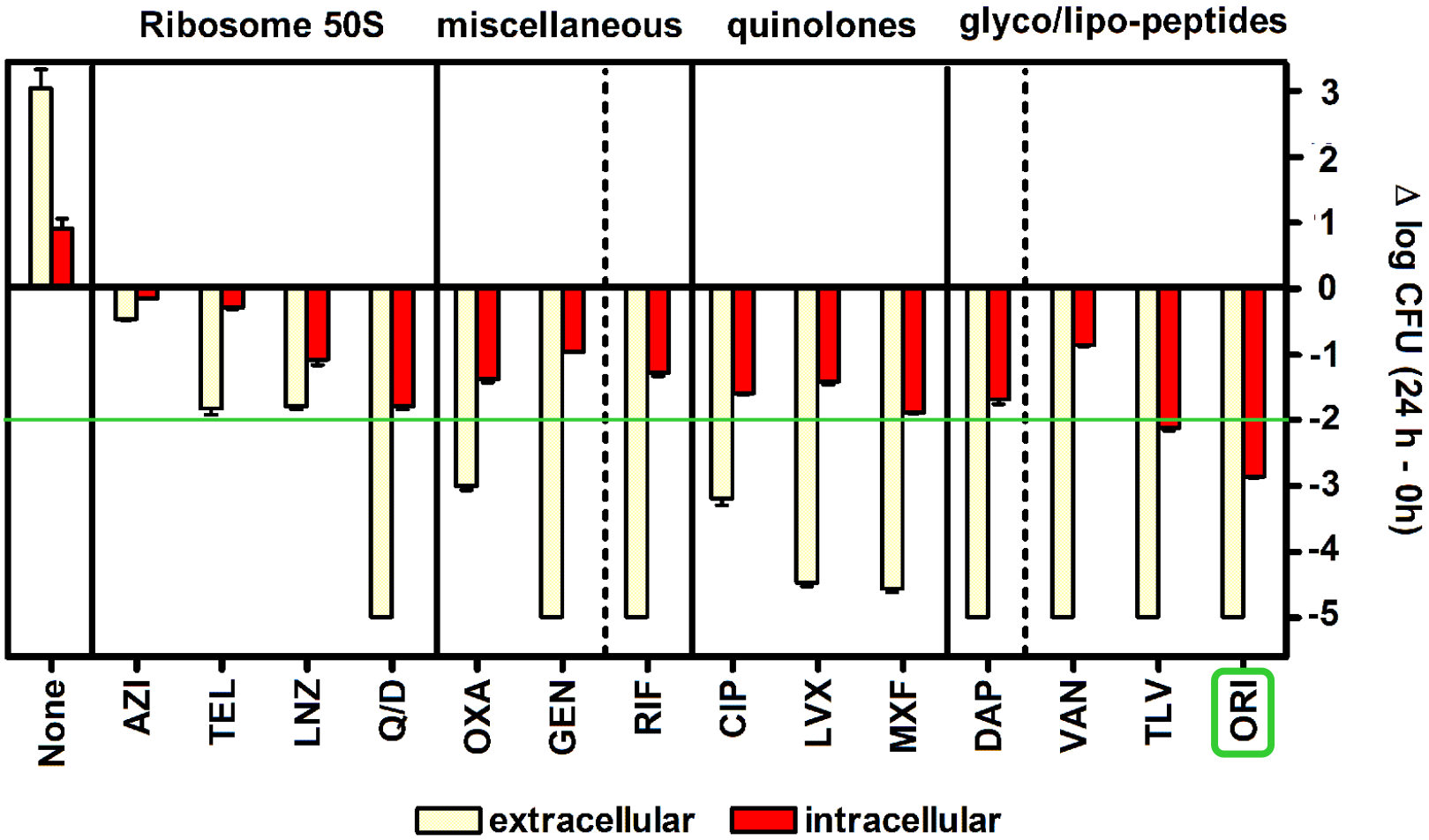


abundant in bacterial membranes

Baudoux et al., ICAAC (2008) A971
Domenech et al., ICAAC (2008) C1-199

Intracellular activity

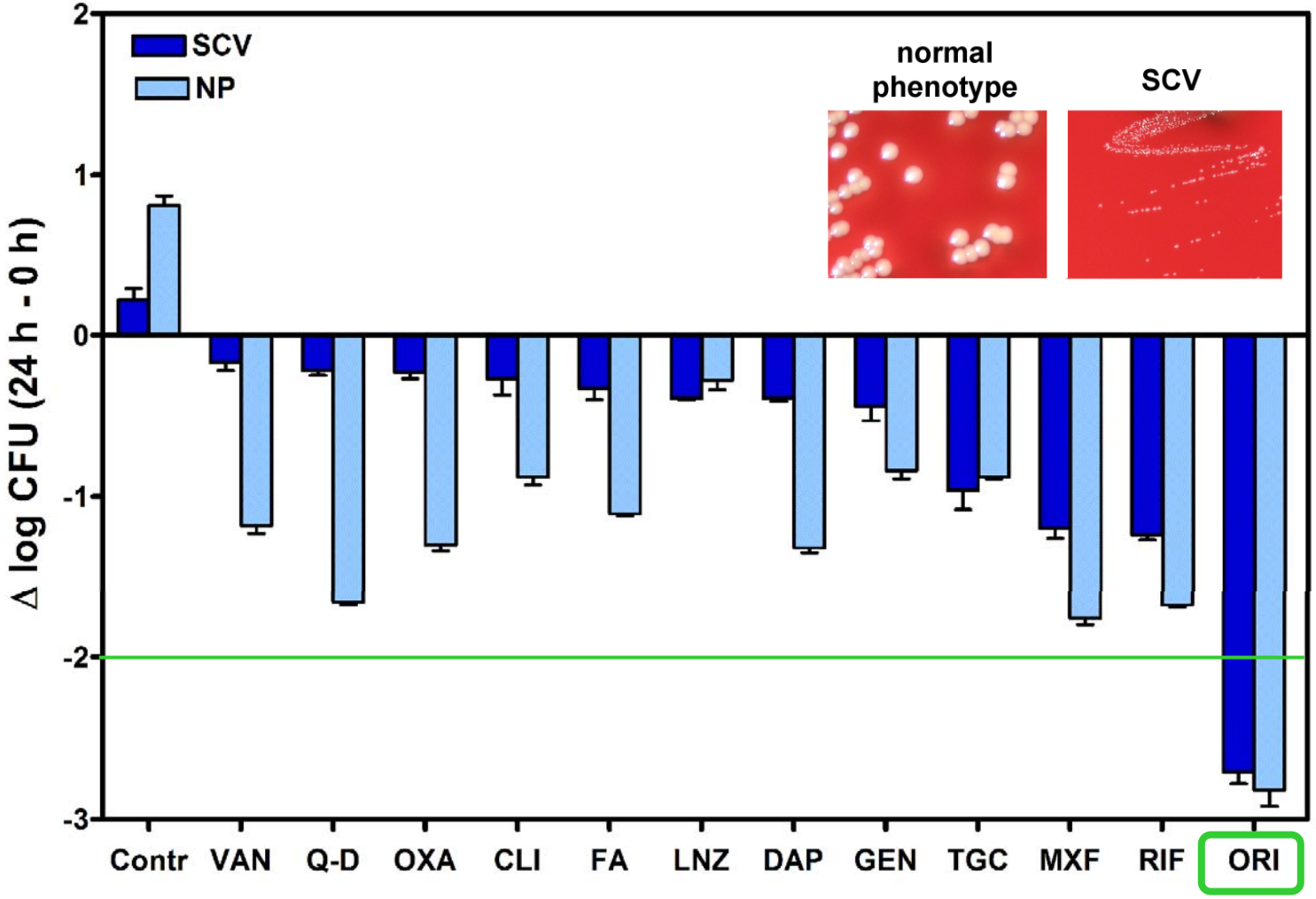
THP-1; 24 h, MSSA ATCC25923, antibiotics at Cmax



Barcia-Macay et al., AAC (2006) 50:841-51

Extra- and Intracellular activity against SCVs

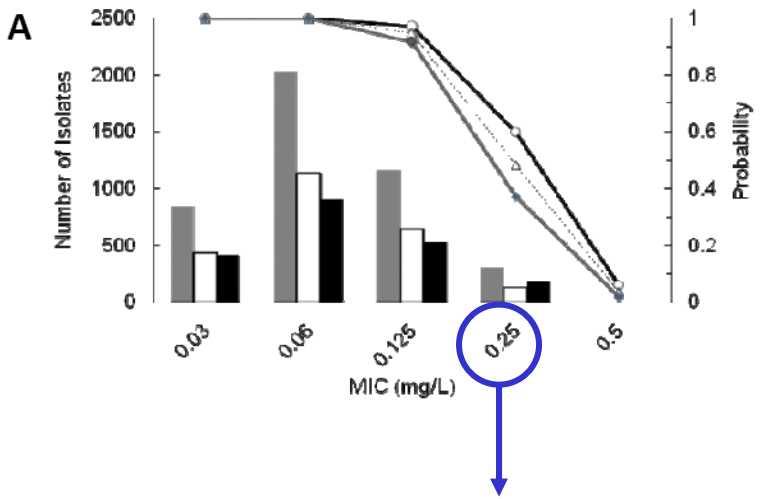
THP-1; 24 h, antibiotics at Cmax



Nguyen et al., RICAI 2007, poster 325

Oritavancin tentative PK/PD breakpoint

Probability of PK/PD target attainment for different MIC targets at 48 h for 200 mg once-daily oritavancin against *S. aureus* according to oxacillin susceptibility status



S. aureus oxaS oxaR	Static - 1 log - 2 log

proposed PK/Pd Bkpt

MIC_{90} MRSA

Bhavnani et al., ICAAC (2008) A994

Pharmacokinetics

parameter	VAN	ORI	TLV	TEC	DAL
Dosage (mg/kg)	15	3	7.5	6	16
Cmax (mg/L)	20-50	46	90	43	312
Cmin (mg/L)	5-12 (12 h)	10 (24 h)	~ 8 (24 h)	5 (24 h)	40 (168 h)
AUC (mg.h/L)	260	457	668	600	27100
(%) prot. binding	55	90	95	88-94	95
T ½ (h)	1 (β) 3-9 (γ)	18 (β) 360 (γ)	8	10 (β) 168 (γ)	149-321 (β)

Van Bambeke ICAAC (2006)

New glycopeptides: clinical experience

oritavancin (5-10 mg/kg 1x day ~ 10 days)
- skin and soft tissue infection
- bloodstream infections (Phase II)

withdrawn Oct. 2008

telavancin (10 mg/kg 1x day ~ 10 days)
- skin and soft tissue infection

➔ fast track designation by the FDA for the treatment of
  - hospitally-acquired pneumonia (MRSA or multiresistant *S. pneumoniae)*
  - MRSA-associated complicated skin and skin structure infection

dalbavancin (1 g followed by 500 mg 1 week later)
- skin and skin structure infections
- catheter-related bloodstream infections (Phase II)

➔ priority review status by the FDA for the treatment of MRSA complicated skin and soft tissue infections.

withdrawn Sept. 2008

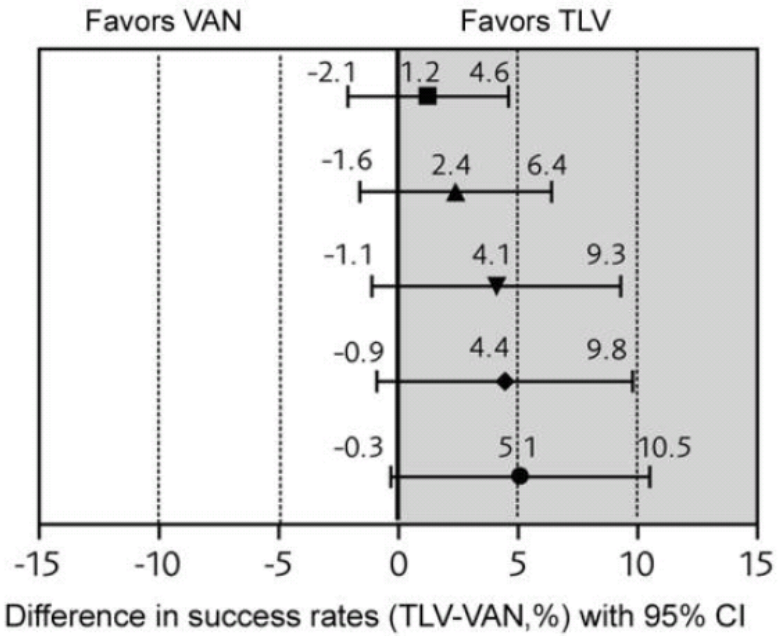
Van Bambeke, Curr. Opin. Investig. Drugs (2006) 7:740-9

Telavancin withdrawal: why ?

Phase 3 - Skin and skin structure infections

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

Clinical outcome



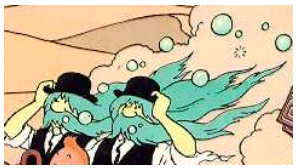
	TLV % success (N)	VAN % success (N)
Clinical cure in CE patients	88.3% (745)	87.1% (744)
Overall therapeutic response[a] in ME patients	88.6% (527)	86.2% (536)
Clinical cure in ME patients with MRSA infection	90.6% (278)	86.4% (301)
Microbiological eradication in ME patients with MRSA infection	89.9%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

Telavancin withdrawal: why ?

Safety profile

« metallic/soapy »



this is
less 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)

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

Oritavancin: clinical experience

Phase 3 - Skin and skin structure infections

ORI 1.5-3 mg/kg q24h (3-7 days)
vs VAN 15 mg/kg q12h followed by oral cephalexin (10-14 days)

Clinical outcome

Outcome at Test-of-Cure

Study population	Oritavancin All doses	Oritavancin 180 – 330 mg	Vancomycin 15 mg/kg	95% CI (Oritavancin 180 – 330mg – Vancomycin)
	% (n of patients/total)			
CLINICAL CURE				
Intent-to-treat	76.6 (787/1027)	77.6 (662/853)	75.6 (385/509)	-2.7, 6.6
Clinically evaluable	76.9 (722/939)	77.7 (597/768)	75.8 (347/458)	-2.9, 6.9
Disease Category (CE Population)				
Wound infection	75.9 (214/282)	75.8 (185/244)	71.0 (103/145)	-4.3, 13.9
Major abscess	79.5 (299/376)	80.7 (255/316)	78.5 (139/177)	-5.3, 9.6
Cellulitis	74.4 (209/281)	75.5 (157/208)	77.2 (105/136)	-10.9, 7.4
MICROBIOLOGICAL SUCCESS				
Microbiological evaluable	78.2 (448/615)	74.0 (378/511)	72.5 (232/320)	-4.7, 7.7

Hartman et al., ICAAC (2008) L1514

Oritavancin: clinical experience

Safety profile

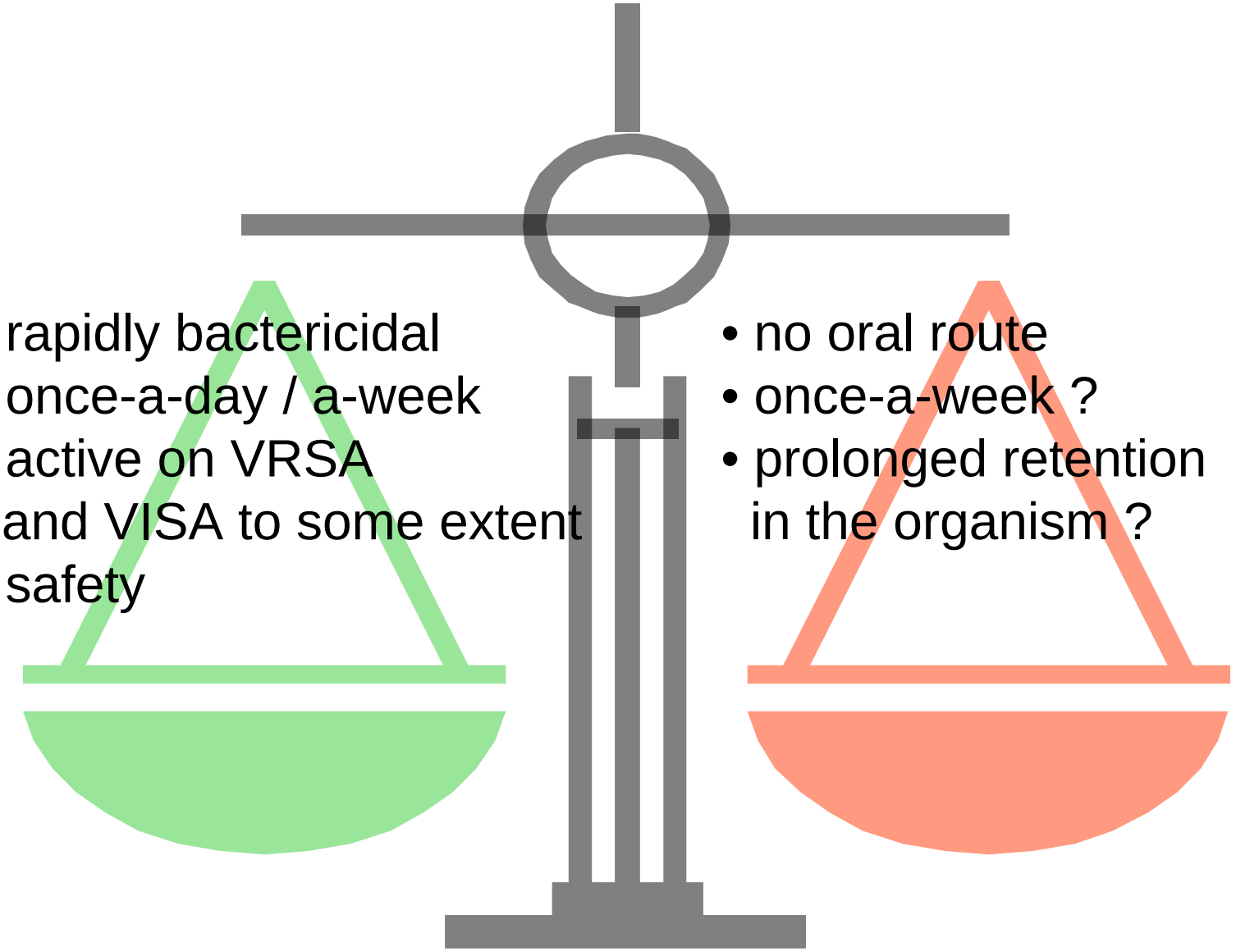
Adverse Event	Oritavancin All doses N=1173	Oritavancin 180 – 330 mg N=956	Vancomycin 15 mg/kg N=590	p-value Oritavancin All doses vs. Vancomycin	p-value Oritavancin 180 – 330 mg vs. Vancomycin
	n (%) of patients				
Adverse event					
Any	628 (53.5)	478 (50.0)	368 (62.4)	<0.001	<0.001
Serious event	107 (9.1)	71 (7.4)	67 (11.4)	0.150	0.010
Adverse event during IV administration phase	495 (42.2)	374 (39.1)	295 (50.0)	0.002	<0.001
Medication-related adverse event					
Any	211 (18.0)	165 (17.3)	149 (25.3)	<0.001	<0.001
Serious	10 (0.9)	4 (0.4)	7 (1.2)	0.606	0.117
Adverse events leading to discontinuation of study medication	35 (3.0)	25 (2.6)	33 (5.6)	0.009	0.004

HLIR Patient Population – Results of Subgroup Analyses

Percentage of Patients with HLIRs who	Oritavancin N=36 % (n)	Vancomycin N=65 % (n)	p-value[a]
Received Concomitant Medications Due to an HLIR	25.0 (9)	44.6 (29)	0.057
Discontinued Study Drug Due to HLIR-related event	8.3 (3)	16.9 (11)	0.368
Discontinued Study Due to HLIR-related event	0.0 (0)	7.7 (5)	0.155

ICAAC (2008) L1514, L1515

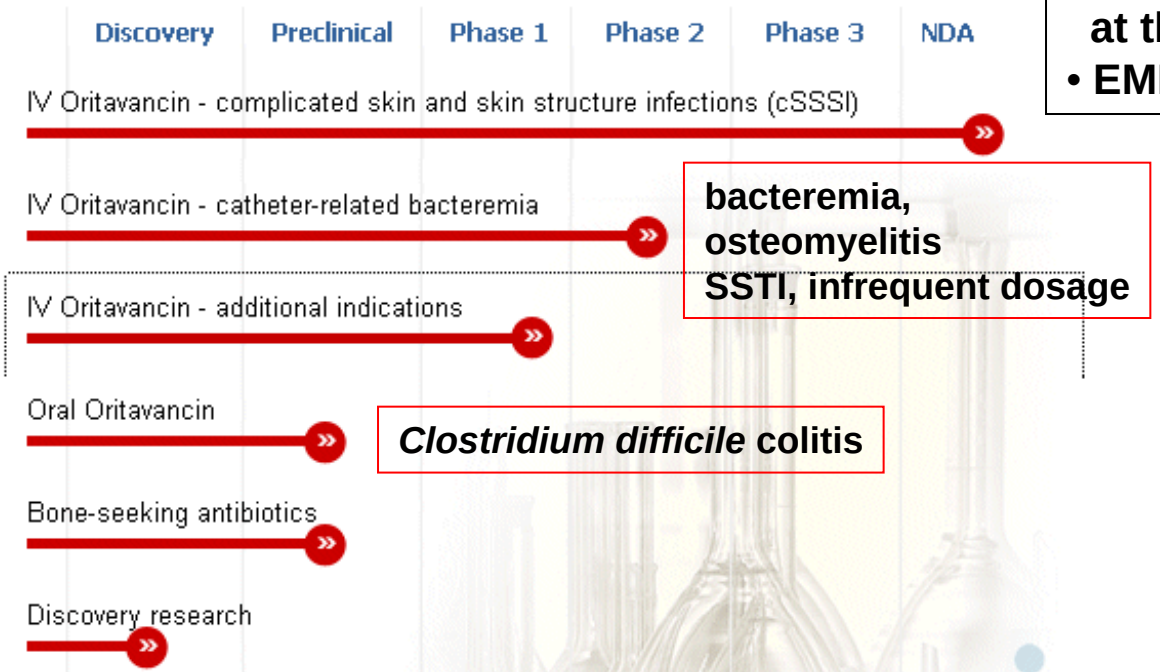
Oritavancin : pros and cons



- rapidly bactericidal
- once-a-day / a-week
- active on VRSA and VISA to some extent
- safety

- no oral route
- once-a-week ?
- prolonged retention in the organism ?

Oritavancin: current status



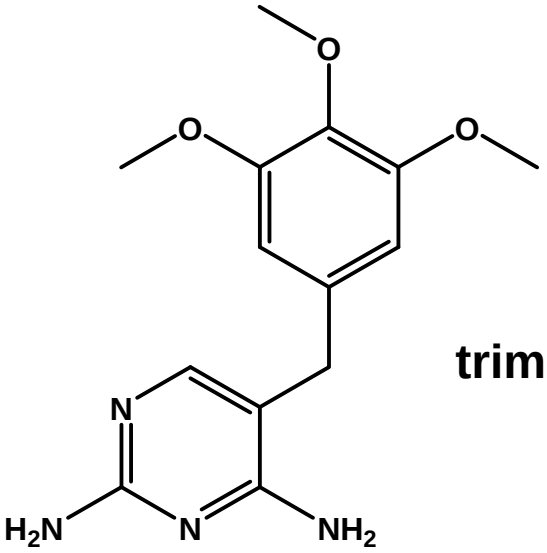
- **FDA; to be discussed at the end of November**
- **EMEA**

bacteremia, osteomyelitis SSTI, infrequent dosage

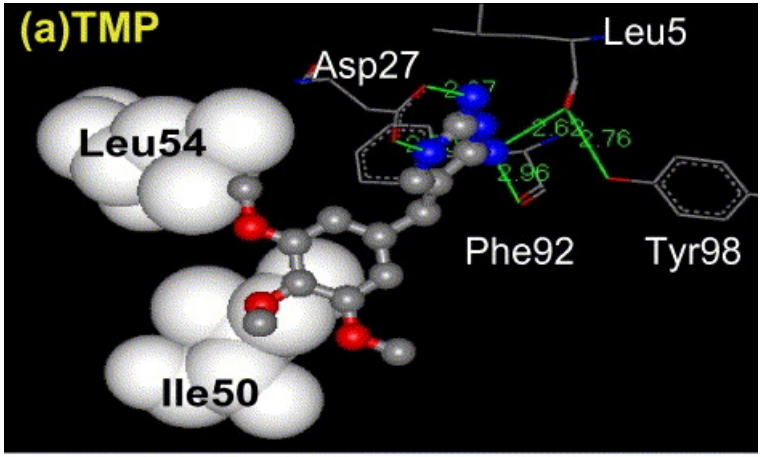
***Clostridium difficile* colitis**

Iclaprim,
a bactericidal diaminopyridine
that works without sulfamide combination

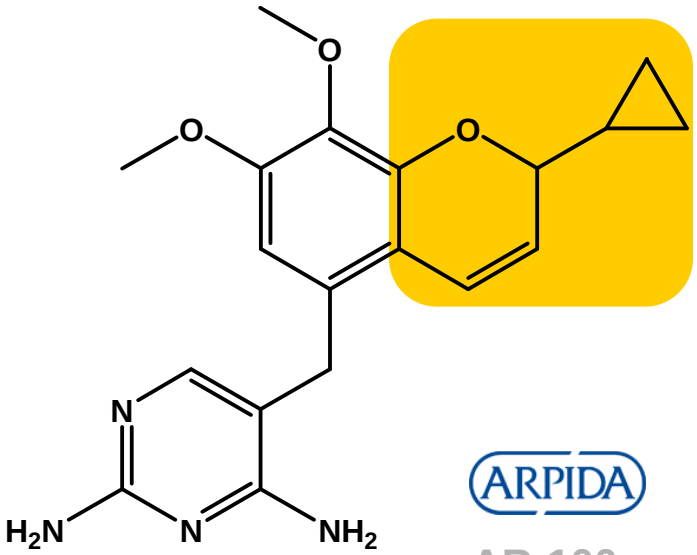
From trimethoprim to iclaprim

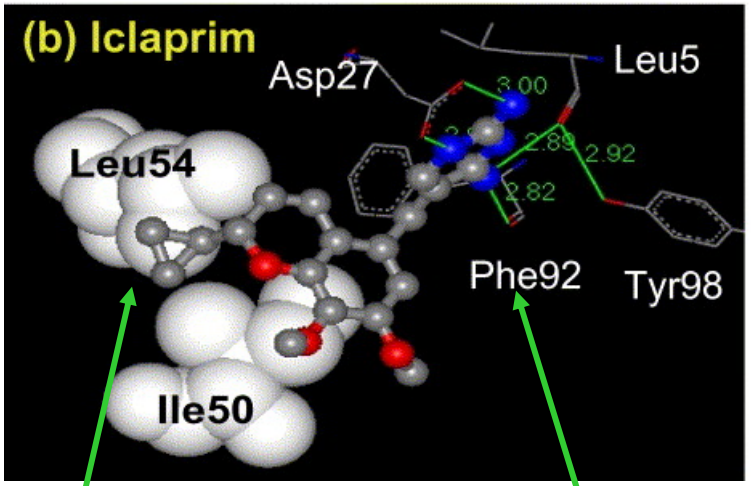


trimethoprim



iclaprim





additional interactions

stronger H bond, remains possible to mutated enzyme

ARPIDA

AR-100

Dale et al., J. Mol. Biol. (2007) 266:23–30

Iclaprim: pharmacokinetics

parameter	iclaprim (0.8 mg/kg)
Cmax (mg/L)	0.8
$T_{½}$ (h)	2.5
AUC (mg.h/L)	2.08

low !

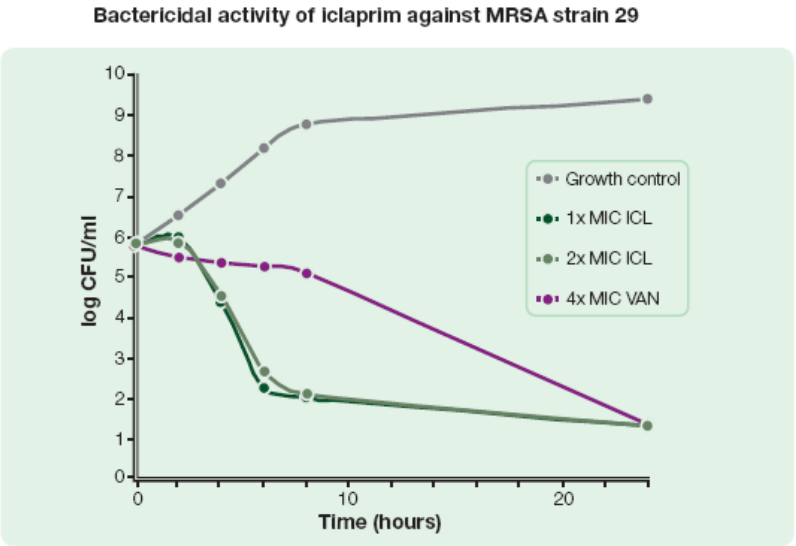
but needs to be considered in the light of MICs

parameter	iclaprim (1.6 mg/kg)
serum (mg/L)	0.6
ELF (mg/L)	12.6
Mϕ (mg/L)	24.5

Ullman et al., ECCMID (2008): P546
Andrews et al., JAC (2007) 60:677-70

Iclaprim: in vitro activity

strain	MIC_{90}	AUC/MIC
MSSA	0.06	35
MRSA	0.125	17
GAS	0.03	70
GBS	0.25	8



Weiss et al., ECCMID (2008): P588
ICAAC (2007) E904,907,911

Iclaprim: clinical experience

Phase 3 - Skin and skin structure infections

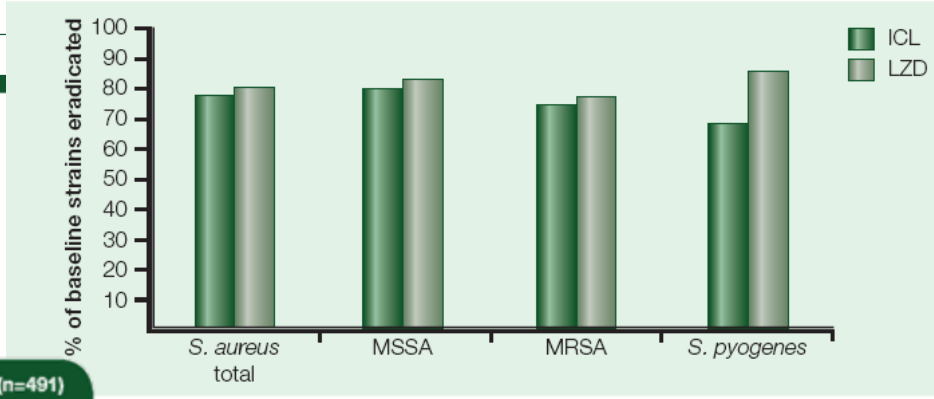
ICL 0.8 mg/kg q12 vs. LZD 600 mg q12h (10-14 days)

MIC_{50} and MIC_{90} of ICL and LZD against Gram-positive pathogens most frequently isolated at baseline.

Pathogen	# isolates	ICL		LZD	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Total *S. aureus*	584	0.12	0.25	2	2
MSSA	349	0.12	0.25	2	2
MRSA	235	0.12	0.12	2	2
S.pyogenes	112	0.015	0.12	1	1
β-haemolytic streptococci*	51	0.12	0.25	1	1

**S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis*

Eradication/presumed eradication (%) of baseline pathogens (MITT population).

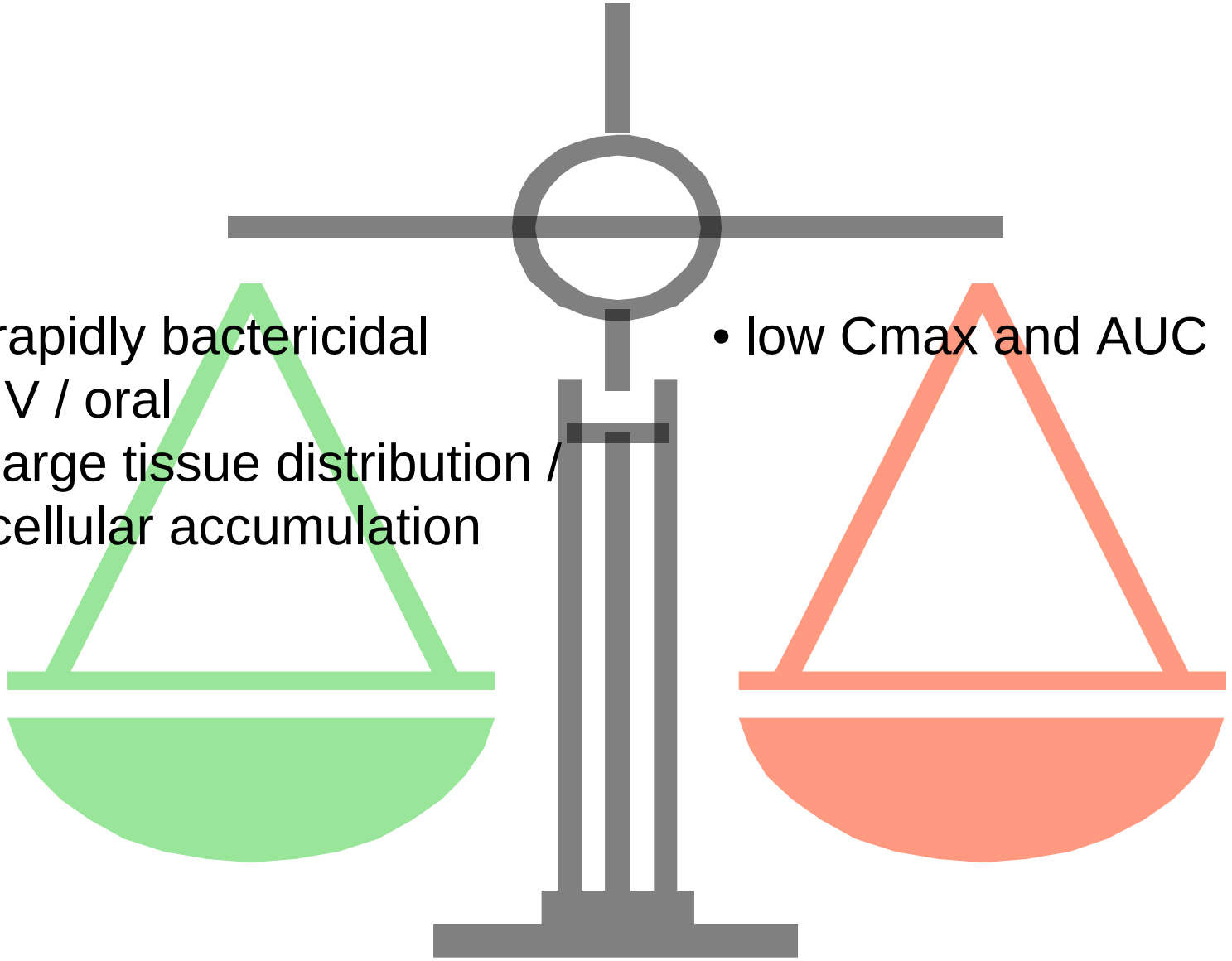


Safety and tolerability profile Adverse events (AEs) in the ITT population.

	ICL (n=500)	LZD (n=491)
	Total number of patients (%)	
Total AEs	245 (49.0)	249 (50.7)
Total AEs possibly/probably related to study drug	113 (22.6)	137 (27.9)
AEs possibly/probably related to study drug (by preferred term in at least 1% of patients) by system organ class:		
Gastrointestinal disorders	37 (7.4)	51 (10.4)
General disorders and administration site conditions	21 (4.2)	19 (3.9)
Investigations	42 (8.4)	48 (9.8)
Nervous system disorders	24 (4.8)	32 (6.5)
Skin and subcutaneous tissue disorders	21 (4.2)	22 (4.5)

Hadvari et al., ICAAC (2008) L1512

Iclaprim : pros and cons



- rapidly bactericidal
- IV / oral
- large tissue distribution / cellular accumulation

- low Cmax and AUC

Iclaprim: current status

IV form, cSSTI: Phase III completed

- NDA submitted to the FDA; to be discussed end of November
- MAA submitted to the EMEA

Currently running phase II studies

- oral form (bioavailability 40 %)
- HAP/VAP

Other molecule in the pipeline : AR-709

highly potent on MDR pneumococci

ICAAC 2006 F1 1959

Table. 4: Binding affinities of AR-709 and TMP

DHFR Enzyme	Ka ($x10^7$ M^{-1})	
	AR-709	TMP
Binary complex with NADPH		
S. pneumoniae ATCC 49619 wild-type, TMP^S	>684	6.41
S. pneumoniae I100L TMP^R	92	0.364
S. aureus NCTC 8325 wild-type, TMP^S	109	0.317
S. aureus F98Y TMP^R	2.5	0.093

Conclusion: what is the best choice ?

Ceftobiprole ?
Yes, but MIC already close to probable breakpoint ?

Oritavancin ?
Yes, but will it remain enough active on VISA ?

Tigecycline ?
Yes, but spectrum vs indication ?

Iclaprim?
Yes, but what will be the breakpoint ?

The way is probably still long to the ideal molecule…