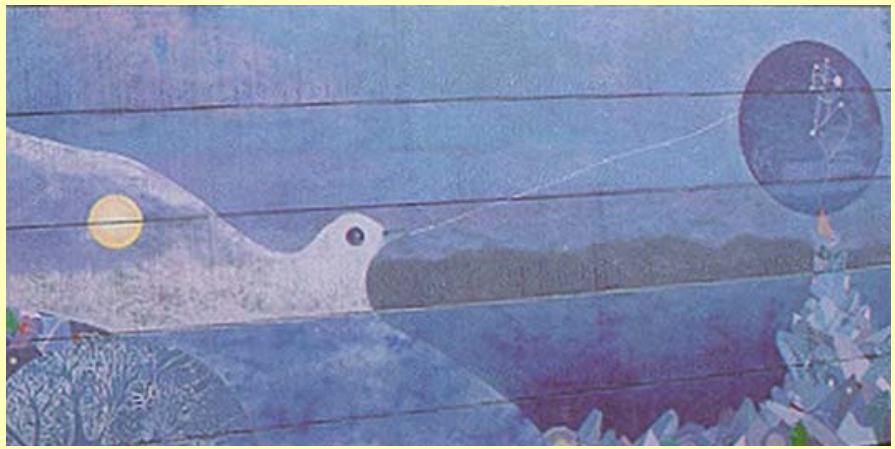
S. aureus: what do we need to know (and to do) in 2007 ?

The new antistaphylococcal drugs (tigecycline, daptomycin, telavancin, …):



is the future (really) shining ?

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Unité de Pharmacologie cellulaire et moléculaire
Université catholique de Louvain
Bruxelles, Belgium
http://www.facm.ucl.ac.be

do we need new drugs ?

gsk GlaxoSmithKline

Roche

ARPIDA

Vicuron Pharmaceuticals

Synercid I.V. quinupristin/dalfopristin

Avelox moxifloxacin

Once-A-Day CUBICIN (daptomycin for injection)

Theravance

Affinium Pharmaceuticals

Tygacil tigecycline IV Reducing treatment complexity

ZYVOX (linezolid)

MIGENIX

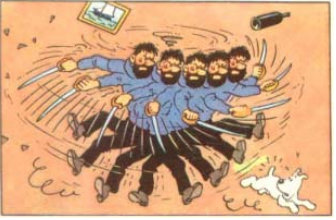
basilea PHARMACEUTICA

J&JPRD

Protez pharmaceuticals

Wyeth

Targanta Therapeutics



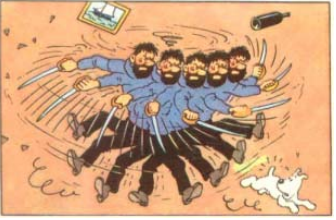
« old » antibiotics: still usable for CA-MRSA !

Community-acquired methicillin-resistant *Staphylococcus aureus* antibiotic susceptibilities in 45 samples

Antibacterial Agent	Samples, n (%)		
	Susceptible	Resistant	Intermediate
Vancomycin	45 (100)	—	—
Rifampin	41 (91.1)	4 (8.9)	—
TMP-SMX	45 (100)	—	—
Tetracycline	45 (100)	—	—
Ciprofloxacin	29 (64.4)	7 (15.6)	9 (20.0)
Linezolid	45 (100)	—	—
Clindamycin*	43 (95.6)	2 (4.4)	—
Erythromycin	9 (20)	36 (80)	—
Daptomycin†	45 (100)	—	—

TMP-SMX = trimethoprim-sulfamethoxazole.
*A total of 8 isolates (18.6%) demonstrated inducible resistance.
†According to the manufacturer, ≥16-mm zone is considered susceptible.

Rice, Am. J. Med. (2006) 119:S11-9



« old » antibiotics: still usable for CA-MRSA !

Suggested Doses of Antimicrobial Agents for the Treatment of CA-MRSA Infections in Adult Patients	
Antimicrobial Agent	**Oral Dose[a]**
Clindamycin	300–450 mg tid
Doxycycline, minocycline	100 mg bid
Gatifloxacin	400 mg qd
Levofloxacin	750 mg qd
Linezolid	600 mg bid
Moxifloxacin	400 mg qd
Trimethoprim/ sulfamethoxazole	320 mg bid (trimethoprim; equivalent to 2 double-strength tablets)
[a]Doses assume normal renal function.	

Sabol *et al*., Ann. Pharmacother. (2006) 40:1125-33

recent and novel agents for *S. aureus*

recently brought on the Belgian market	on the market; not yet in Belgium	(late) stage of clinical development	investigational
moxifloxacin	synercid	telavancin	CS-023/PZ-601
linezolid	daptomycin	oritavancin	MX-2401
	tigecycline	dalbavancin	API-1252
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

What will be your choice ?

recent and novel agents for *S. aureus*

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moxifloxacin	synercid	telavancin	CS-023/PZ-601
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	tigecycline	dalbavancin	API-1252
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

Let's try to find a way …

recent and novel agents for *S. aureus*

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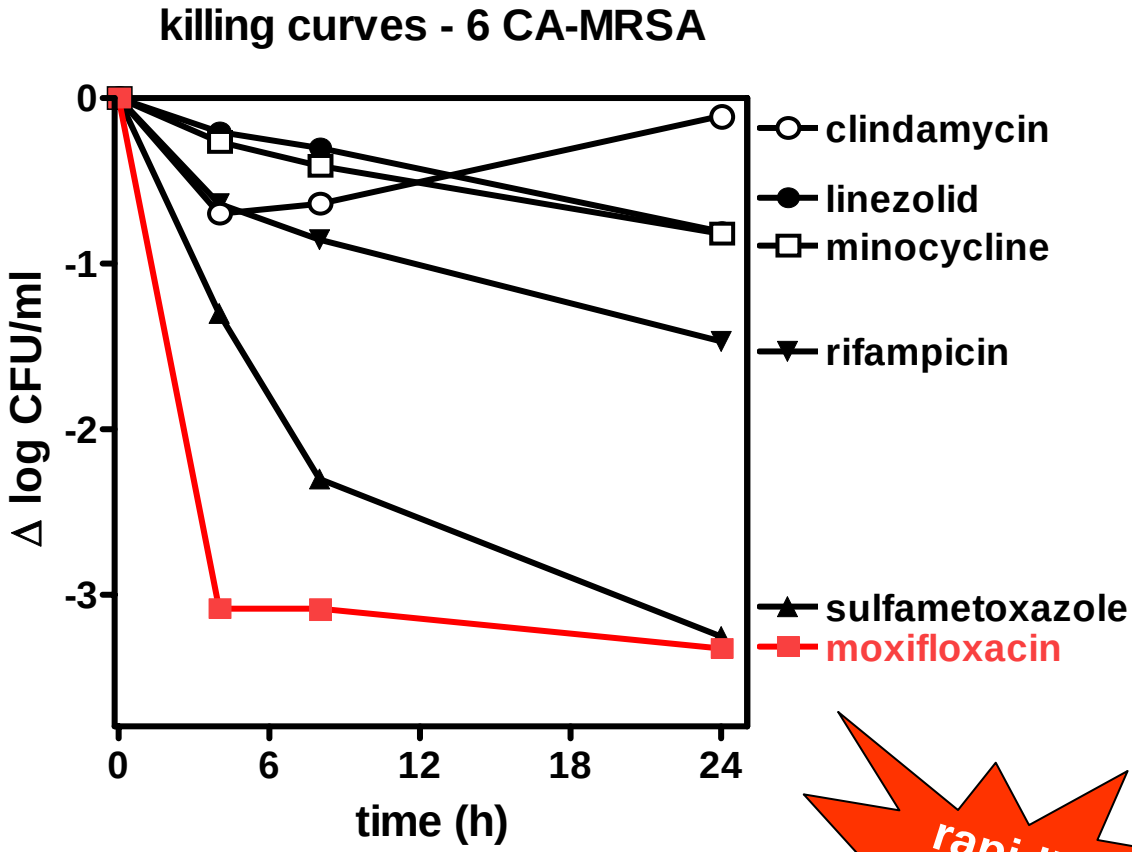
	tigecycline	dalbavancin	API-1252
		ceftobiprole	**DK-619**
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

moxifloxacin and CA-MRSA



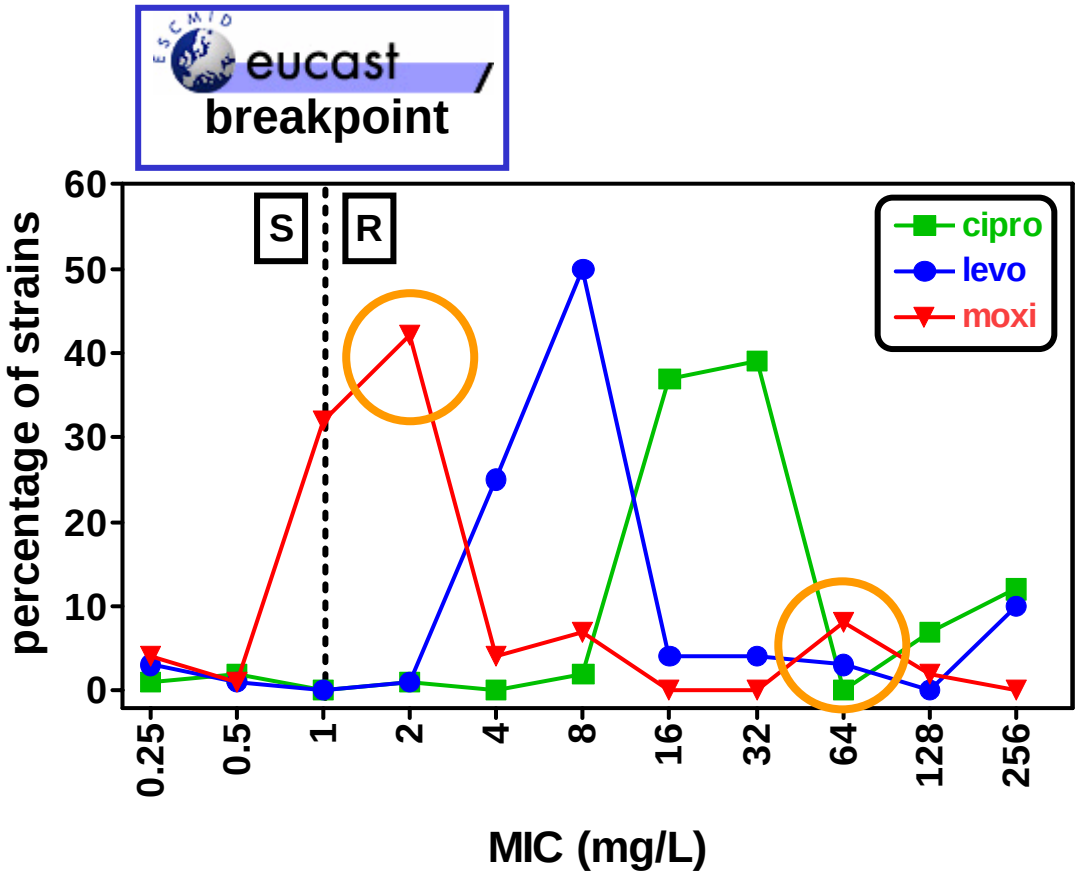
rapidly bactericidal

Kaka *et al.*, JAC (2006) 58:680-3

moxifloxacin: in vitro data

Distribution of MICs for 100 MRSA collected in 2002

Lowest MICs among currently available quinolones, but …

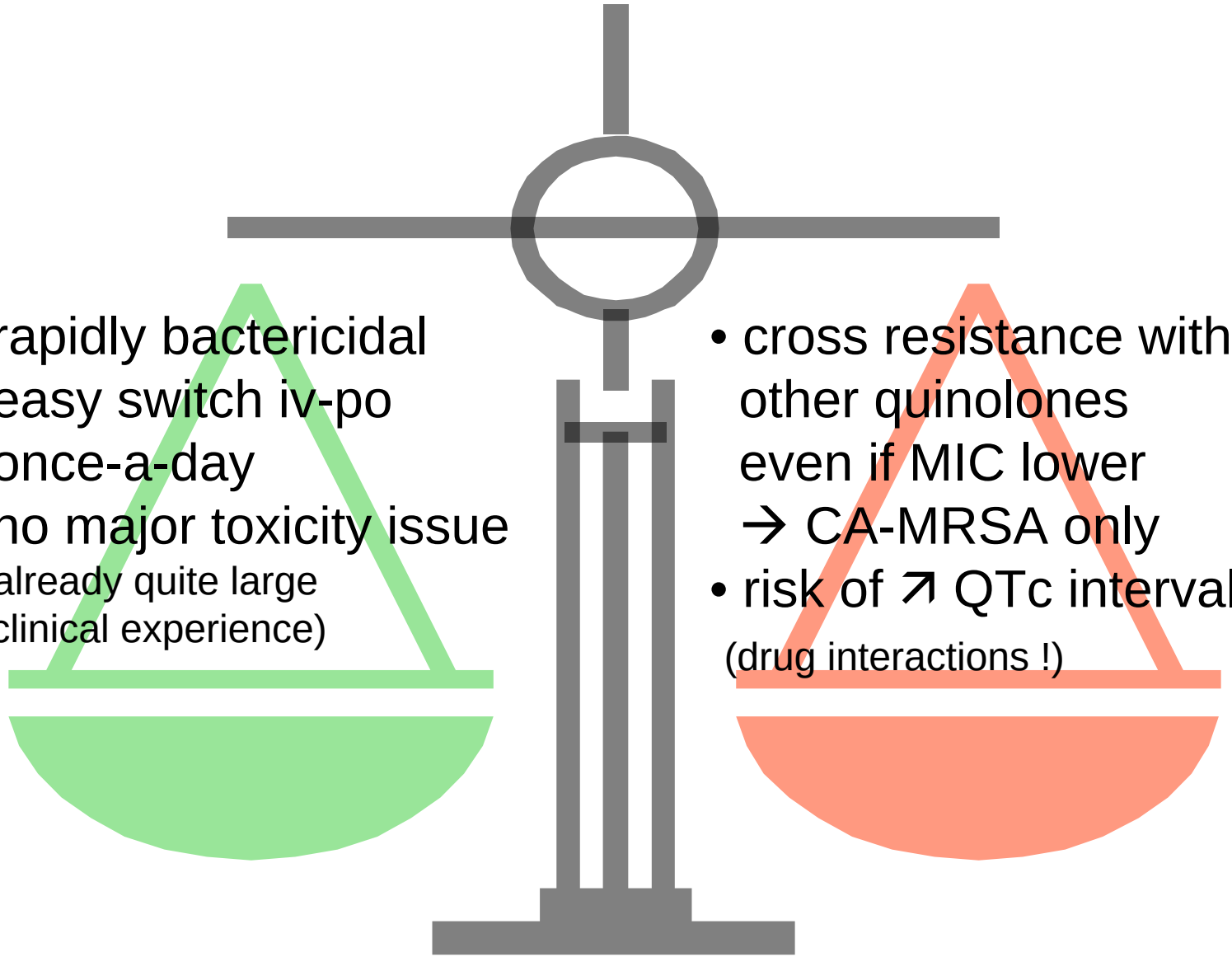


low level resistance

high level resistance

Noguchi *et al.,* Int. J. Antimicrob. Ag. (2005) 25:374-9

moxifloxacin: pros and cons



- rapidly bactericidal
- easy switch iv-po
- once-a-day
- no major toxicity issue
  (already quite large clinical experience)

- cross resistance with other quinolones even if MIC lower
  → CA-MRSA only
- risk of ↗ QTc interval
  (drug interactions !)

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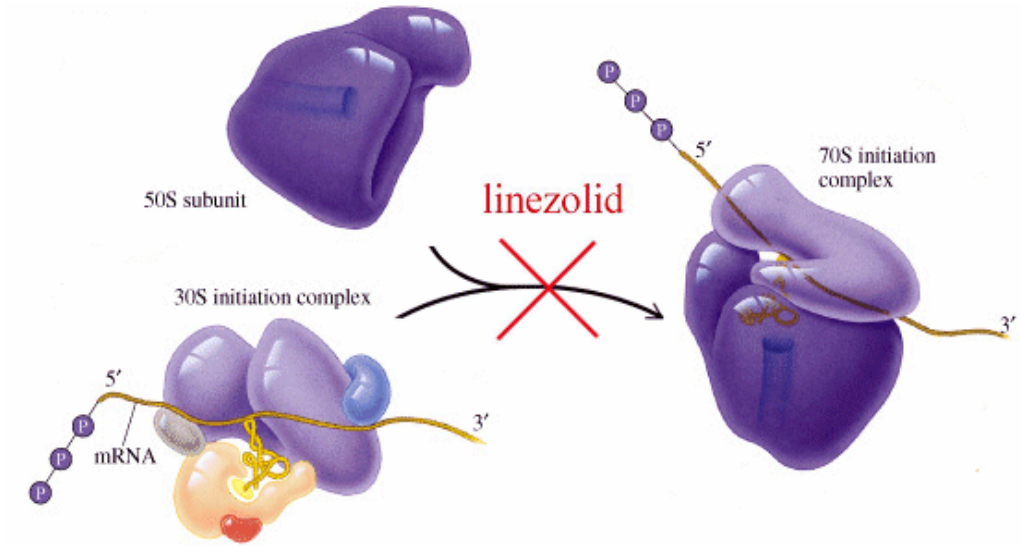
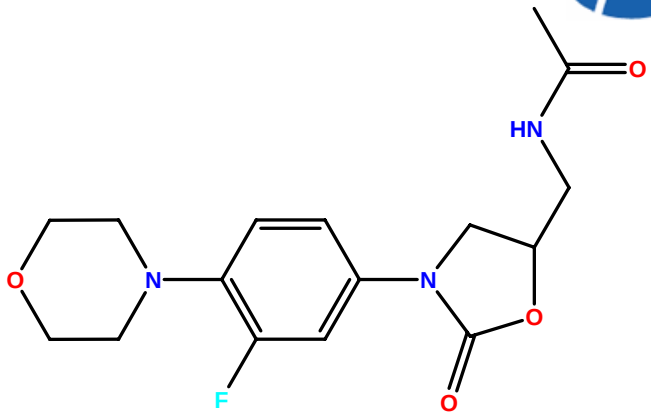
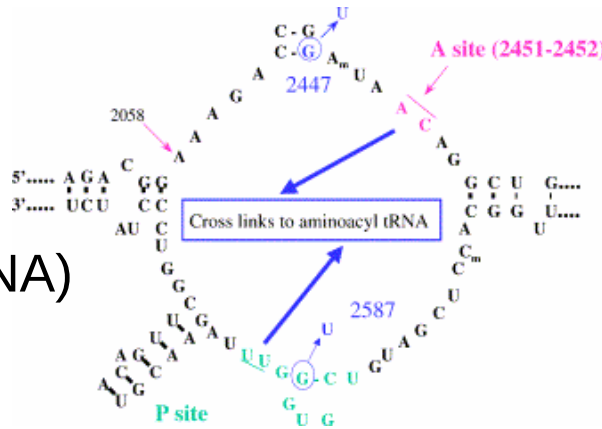
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

linezolid





- inhibits the formation of the initiation complex
- no cross resistance with other drugs acting on protein synthesis (MLS)
- resistance considered for long as improbable … but now well described (due to mutations in 23S rRNA)



linezolid: in vitro data

Distribution of MICs for 60 MRSA collected from diabetic foot

drug	range	MIC 50	MIC 90	eucast breakpoint
vancomycin	0.5-1	0.5	1	8
linezolid	2-8	4	4	4

We slowly reach the limit …

Goldstein *et al.,* AAC (2006) 50:2875-79

linezolid: in vitro data

Susceptibility of MRSA by site of isolation

Site	Patients (*n*, %)	Teicoplanin MIC (mg/L)			Linezolid MIC (mg/L)		
		MIC_{50}	MIC_{90}	range	MIC_{50}	MIC_{90}	range
Blood	22 (2.4%)	3	4	1.5–16	1.5	2	0.75–2
Catheter tip	20 (2.2%)	3	8	1.5–24	1.5	2	0.38–2
Nose/perineum	166 (18.1%)	3	8	1.5–32	1.5	2	0.38–3
Sputum/tracheal aspirate	48 (5.2%)	3	8	1.5–32	1.5	2	0.75–3
Wound	35 (3.8%)	4	8	0.25–24	1.5	2	0.75–4

eucast breakpoint

8 4

again we approach the limit …

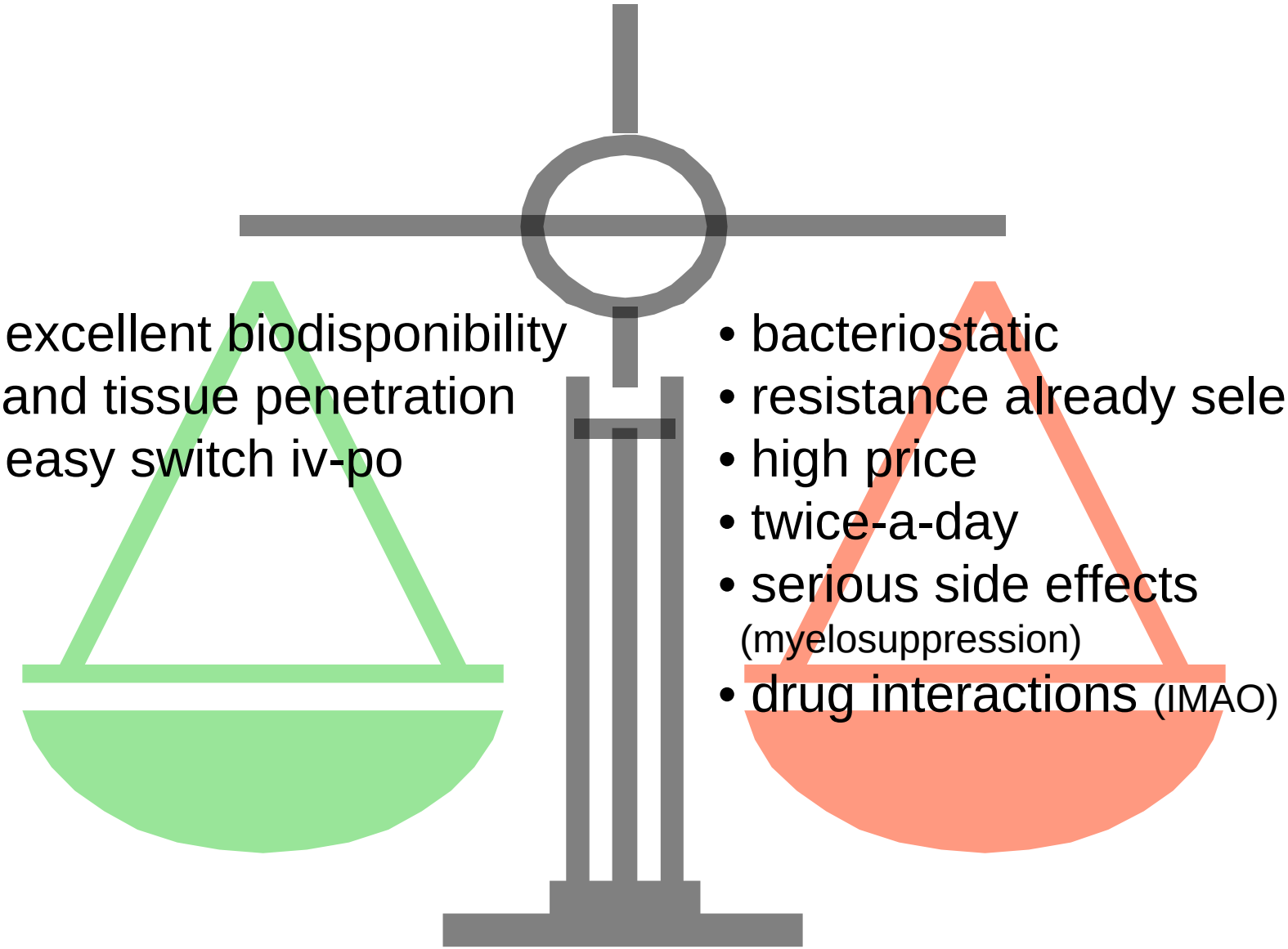
Wilson *et al.*, JAC (2006) 58:470-3

linezolid: clinical experience

indication	Linezolid 600 mg iv/po 2x/day	Vancomycin 1g iv 2x/day
cSSTI (1180)	99.2 %	88.5 %
Osteomyelitis (66)	84.8 %	--
MRSA bacteriaemia (53)	56 %	46 %
nosocomial pneumonia (1019) MRSA (160)	53 % 59 %	52.2 % 35.5 %

Weigelt *et al.,* AAC (2005) 49:2260-66; Senneville *et al.,* Clin Ther. (2006) 28:1155-63;
Shorr *et al.,* JAC (2005) 56:923-929; Wunderink *et al.,* Chest (2003)124:1789-97

linezolid: pros and cons



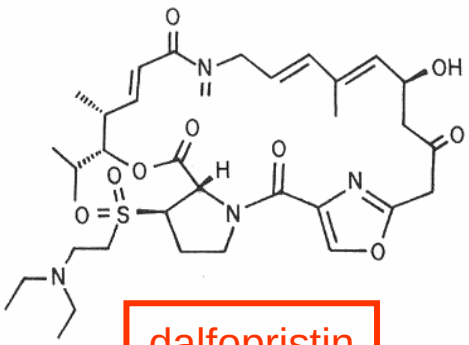
- excellent biodisponibility and tissue penetration
- easy switch iv-po

- bacteriostatic
- resistance already selected
- high price
- twice-a-day
- serious side effects (myelosuppression)
- drug interactions (IMAO)

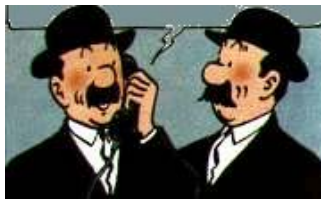
recent and novel agents for *S. aureus*

recently brought on the Belgian market	on the market; not yet in Belgium	(late) stage of clinical development	investigational
moxifloxacin	**synercid**	telavancin	CS-023/PZ-601
linezolid	daptomycin	oritavancin	MX-2401
	tigecycline	dalbavancin	API-1252
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

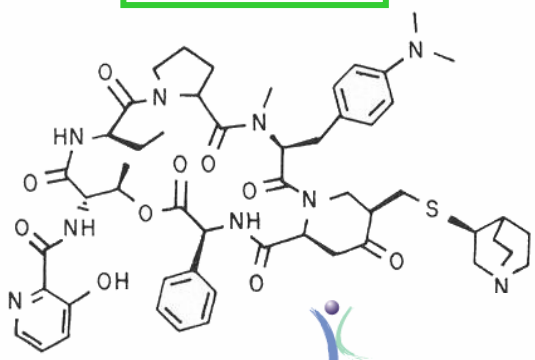
synercid



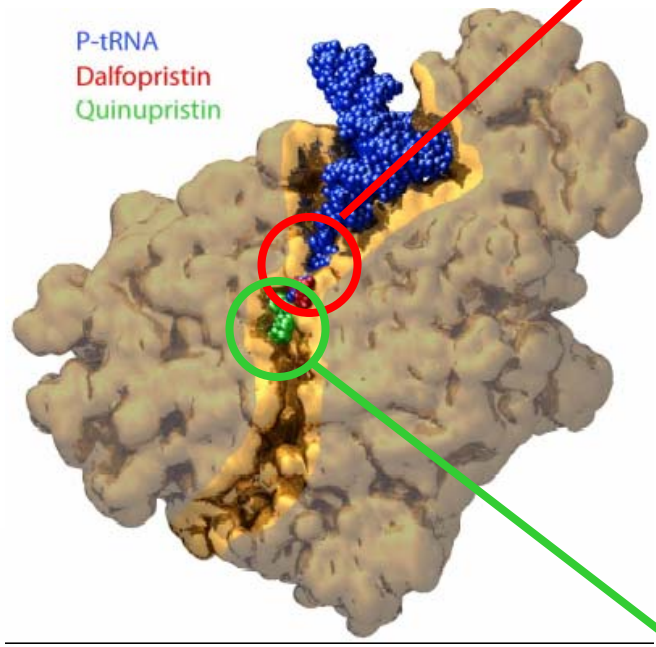
dalfopristin



quinupristin



King Pharmaceuticals



S_A blocks peptide bound formation

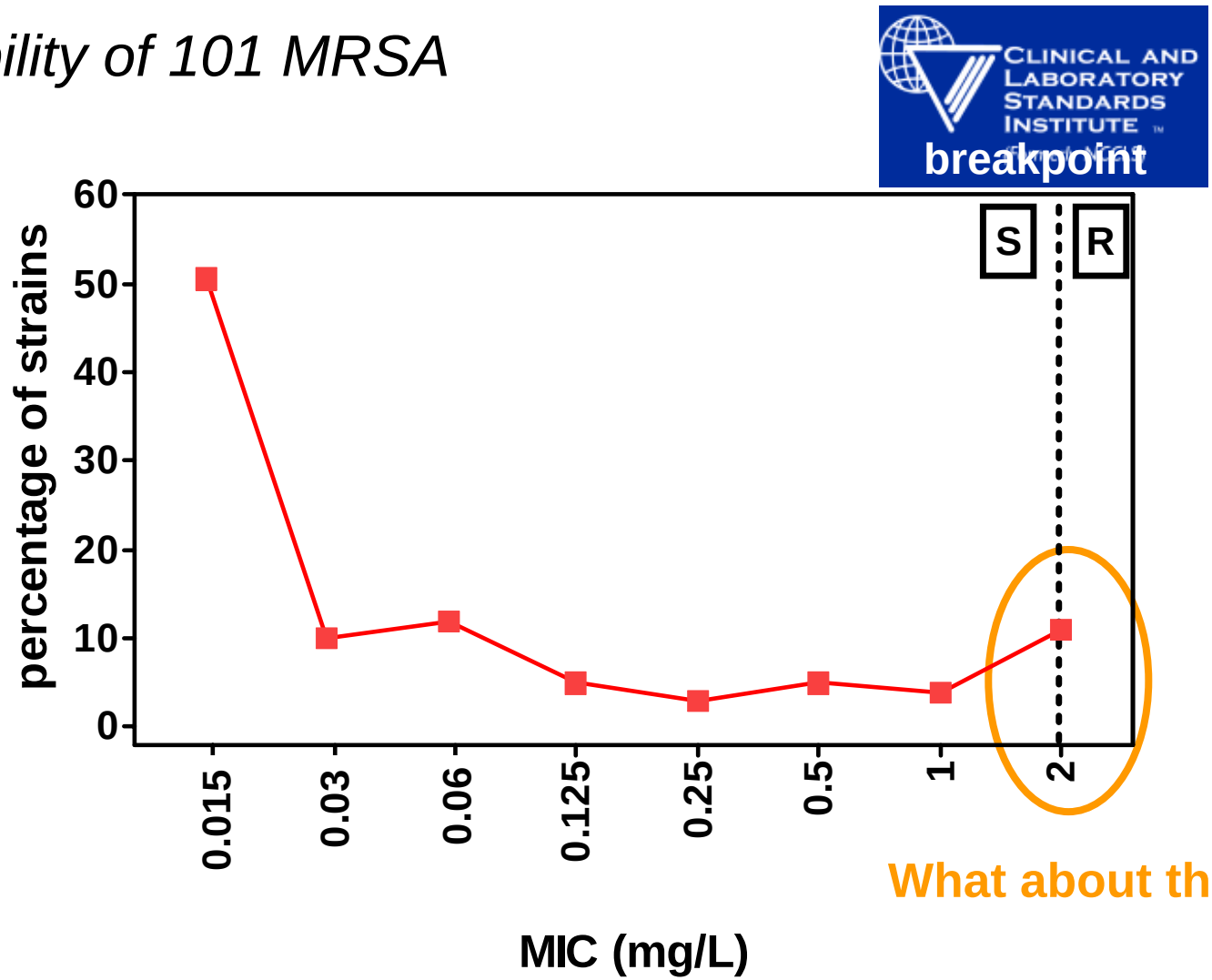
SYNERGY

S_B blocks the path of the nascent peptide

Harms *et al.*, BMB Biol (2004) 2:4

synercid: in vitro data

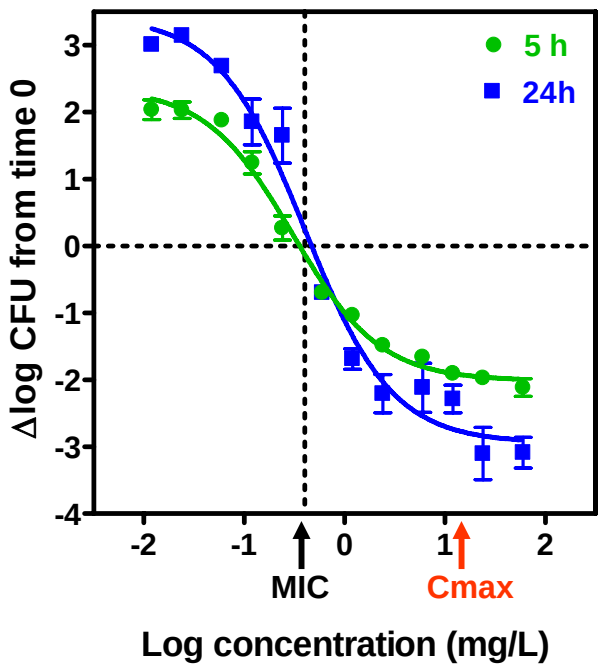
Susceptibility of 101 MRSA



Sambatakou *et al.*, JAC (1998) 51:349-55

synercid: in vitro data

In vitro models - MRSA

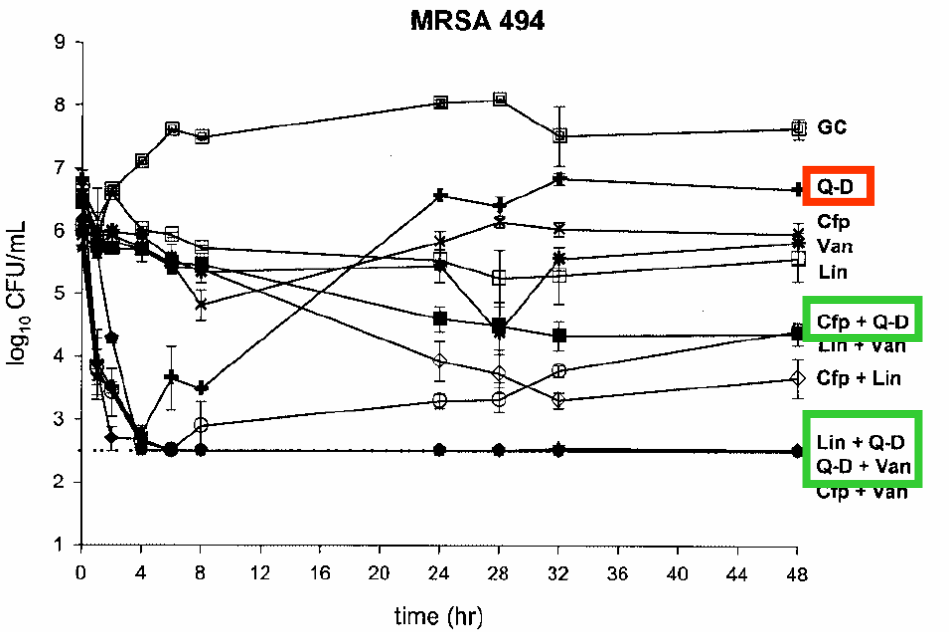


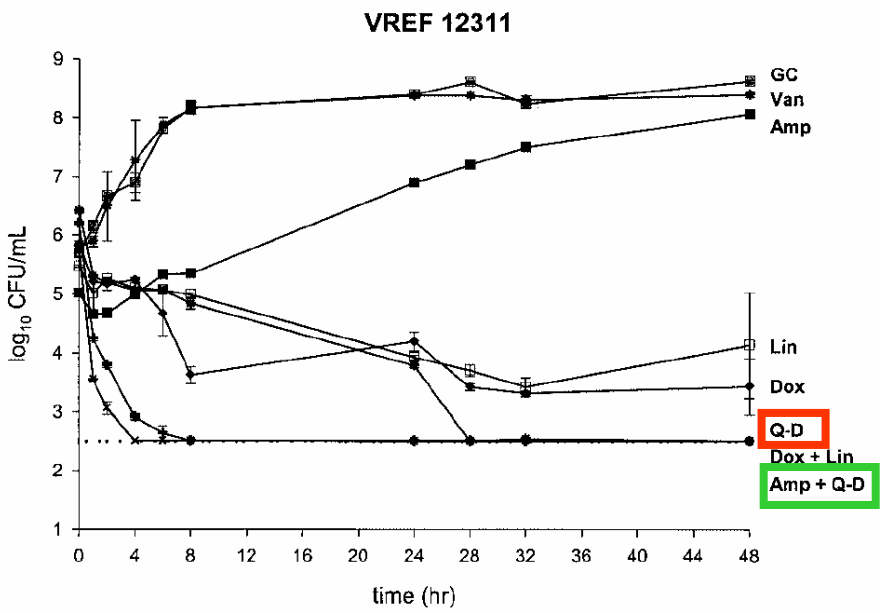
time- and concentration-dependent bactericidal effect

Baudoux *et al.*, ECCMID (2007)

synercid: in vitro data

In vitro pharmacodynamic models

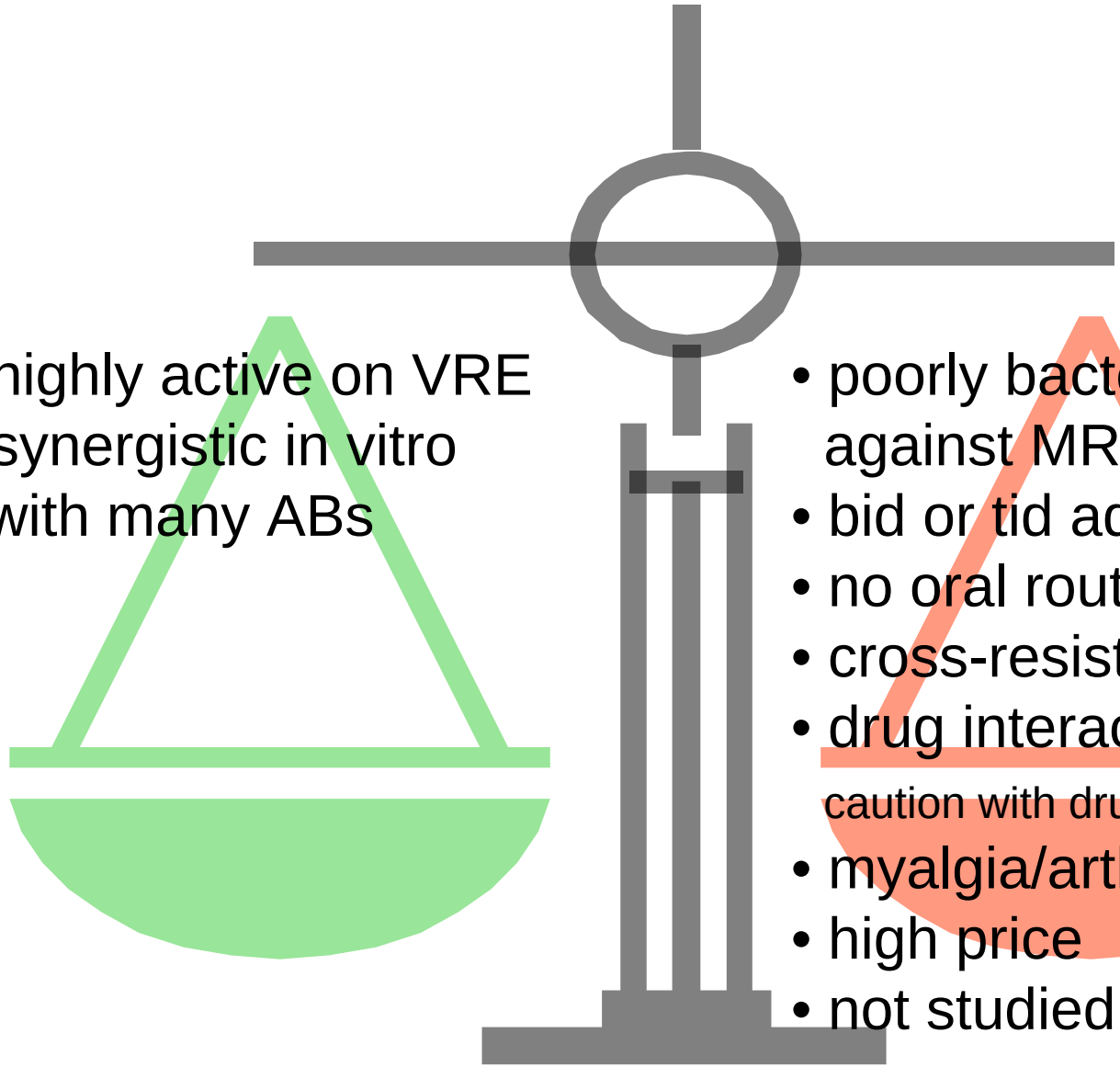




- **poorly active alone against MRSA; highly active on VRE**
- **combinations synergistic towards MRSA**

Allen *et al.*, AAC (2002) 46:2606-12

synercid : pros and cons



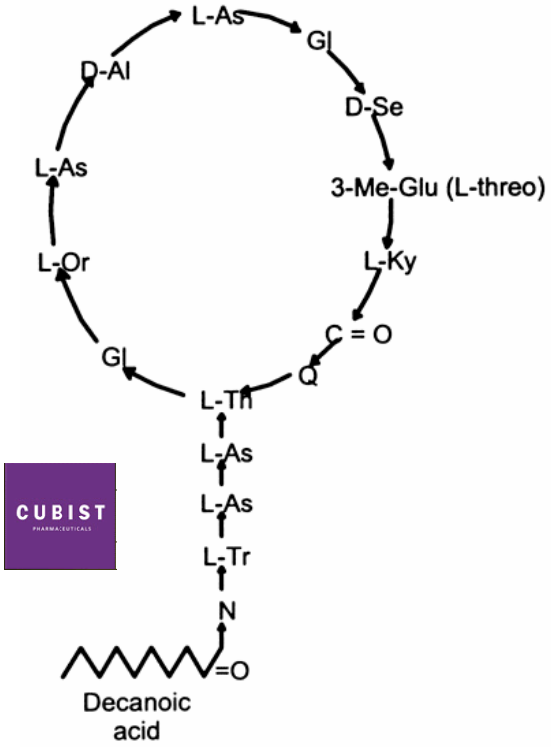
- highly active on VRE
- synergistic in vitro with many ABs

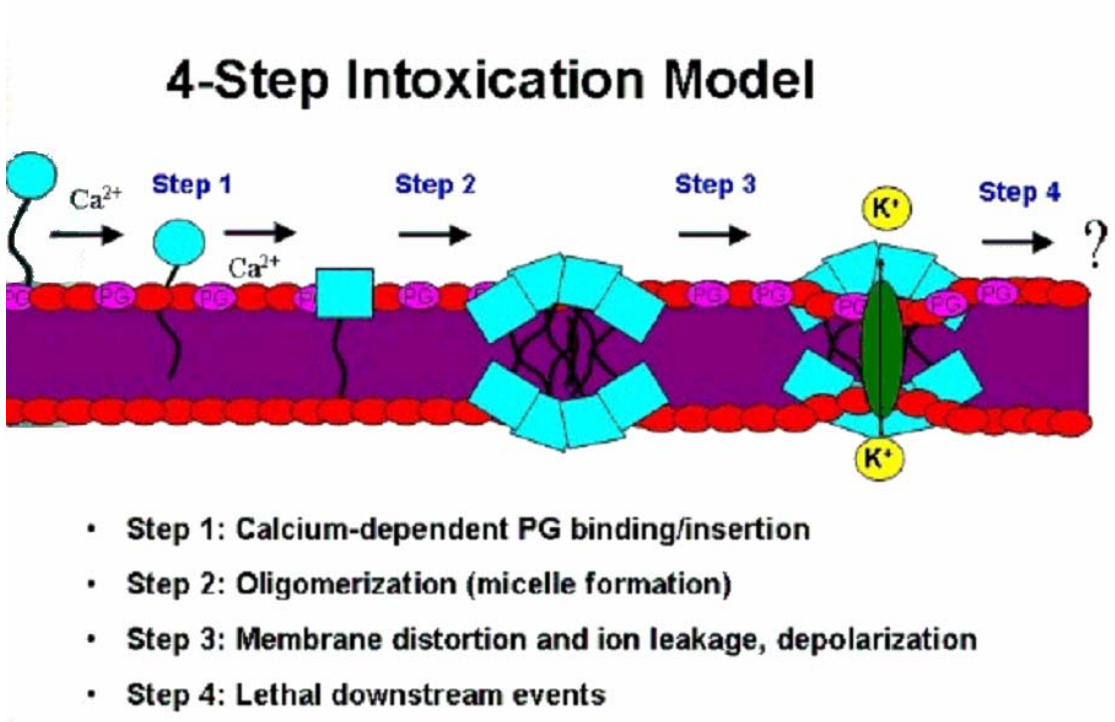
- poorly bactericidal against MRSA
- bid or tid administration
- no oral route
- cross-resistance with ML
- drug interactions (CYP450 3A4)
  caution with drugs prolonging QTc
- myalgia/arthralgia frequent
- high price
- not studied in children

recent and novel agents for *S. aureus*

recently brought on the Belgian market	on the market; not yet in Belgium	(late) stage of clinical development	investigational
moxifloxacin	synercid	telavancin	CS-023/PZ-601
linezolid	**daptomycin**	oritavancin	**MX-2401**
	tigecycline	dalbavancin	API-1252
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

daptomycin





- very bactericidal towards Gram (+) organisms through membrane destabilization
- spare mammalian cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes)

- fast track registration in the US because of activity against vancomycin-resistant enterococci (VRE)
- indications: cSSTI; Phase III trial on bacteriemia completed

daptomycin: in vitro data

Distribution of MICs for 60 MRSA collected from diabetic foot

drug	range	MIC 50	MIC 90	eucast breakpoint
vancomycin	0.5-1	0.5	1	8
daptomycin	0.25-1	0.5	0.5	1

wait and see …

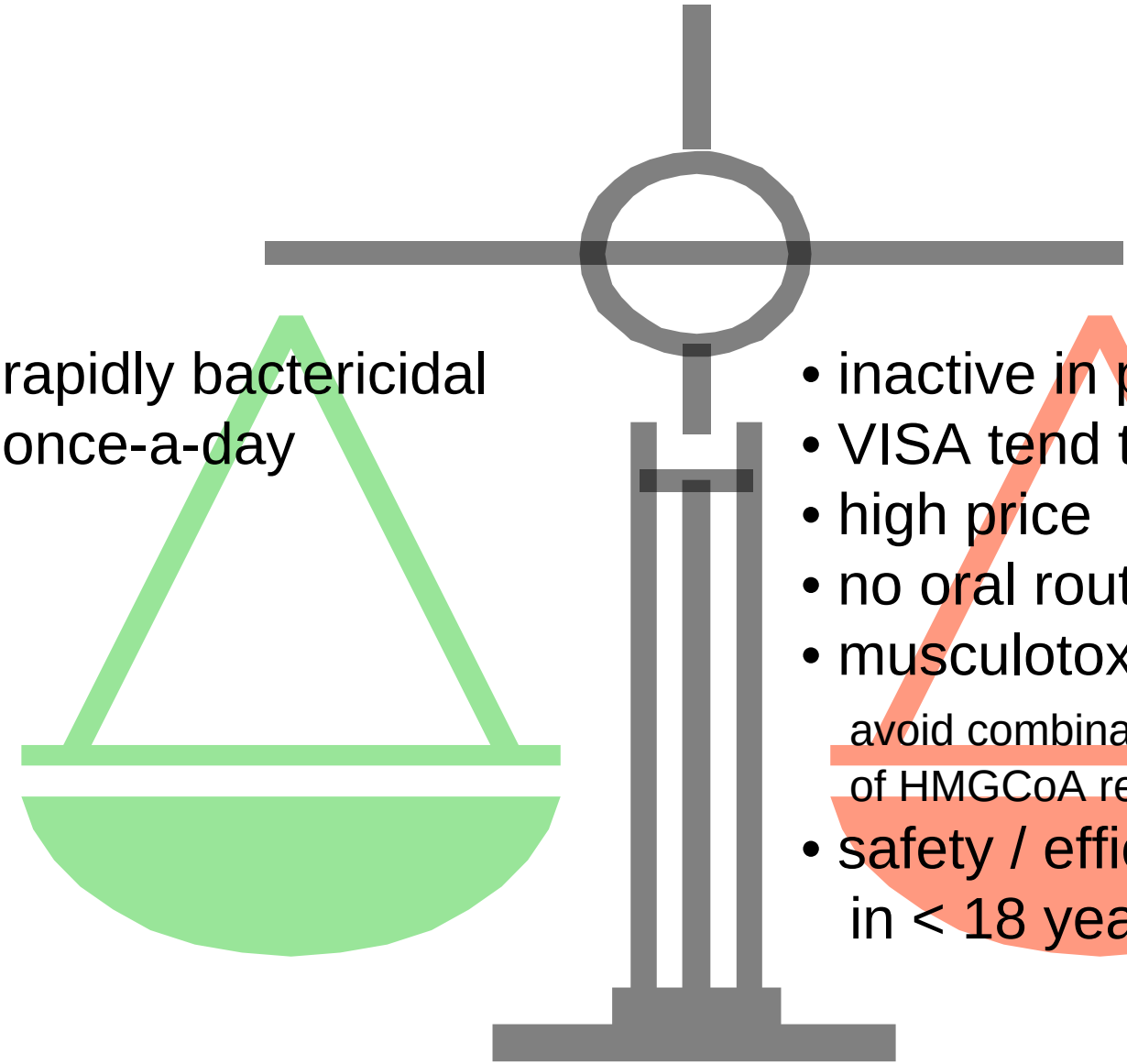
Goldstein *et al.,* AAC (2006) 50:2875-79

daptomycin: clinical experience

indication	Daptomycin iv 1x/day		Vancomycin or β-lactam
cSSTI (902) MRSA (28-36)	4 mg/kg	83.4 % 75 %	84.2 % 69.4 %
bloodstream (31) MRSA (11) VRE (11)	6 mg/kg	77 % 100 % 45 %	--

Arbeit *et al.,* CID (2004) 38:1673-81; Segreti *et al.,* Pharmacotherapy (2006) 26:347-352

daptomycin: pros and cons



- rapidly bactericidal
- once-a-day

- inactive in pneumonia
- VISA tend to have ↗ MICs
- high price
- no oral route
- musculotoxic in animals

  avoid combination with inhibitors of HMGCoA reductase
- safety / efficacy not studied in < 18 years

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linezolid	daptomycin	oritavancin	MX-2401
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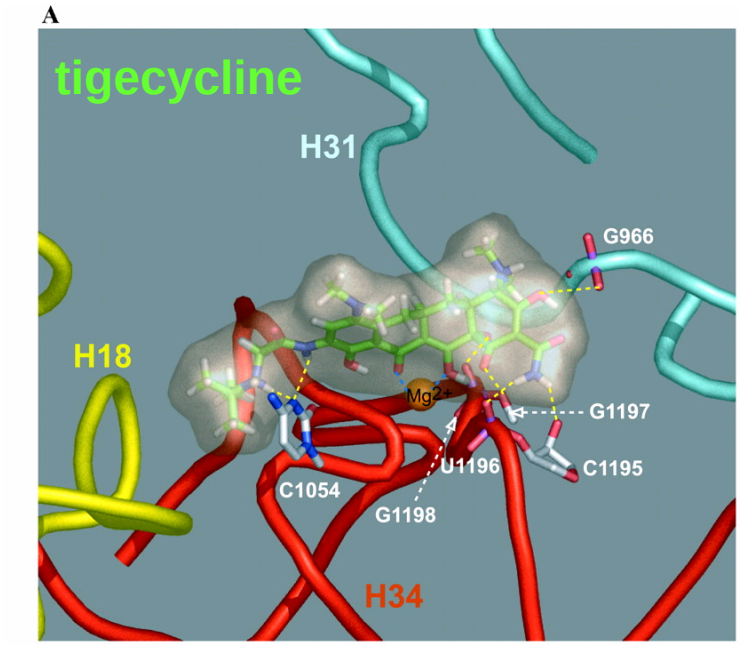
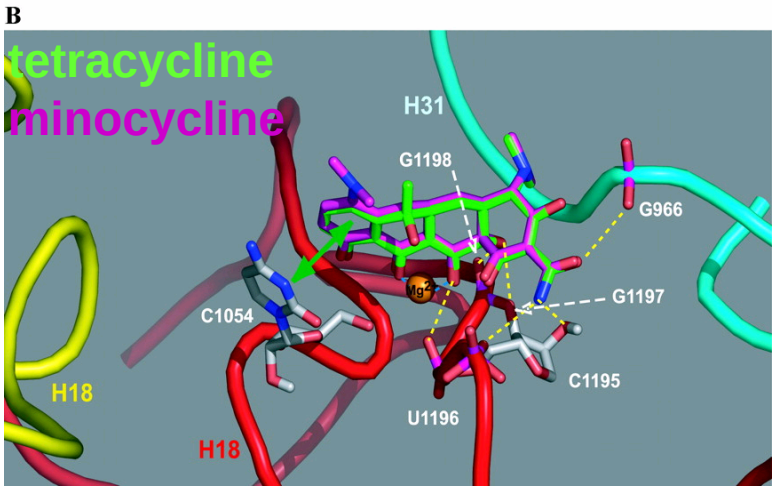
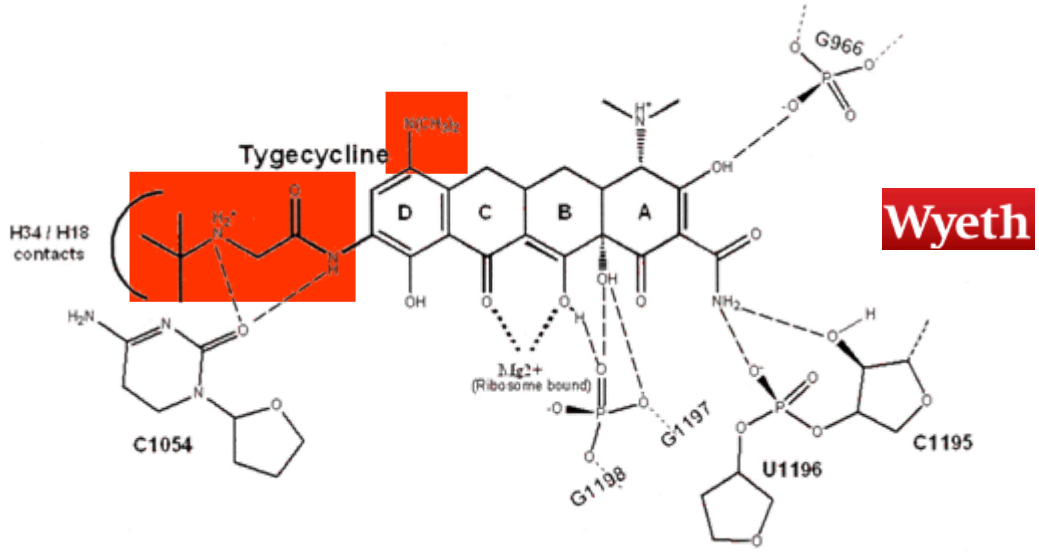
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

tigecycline







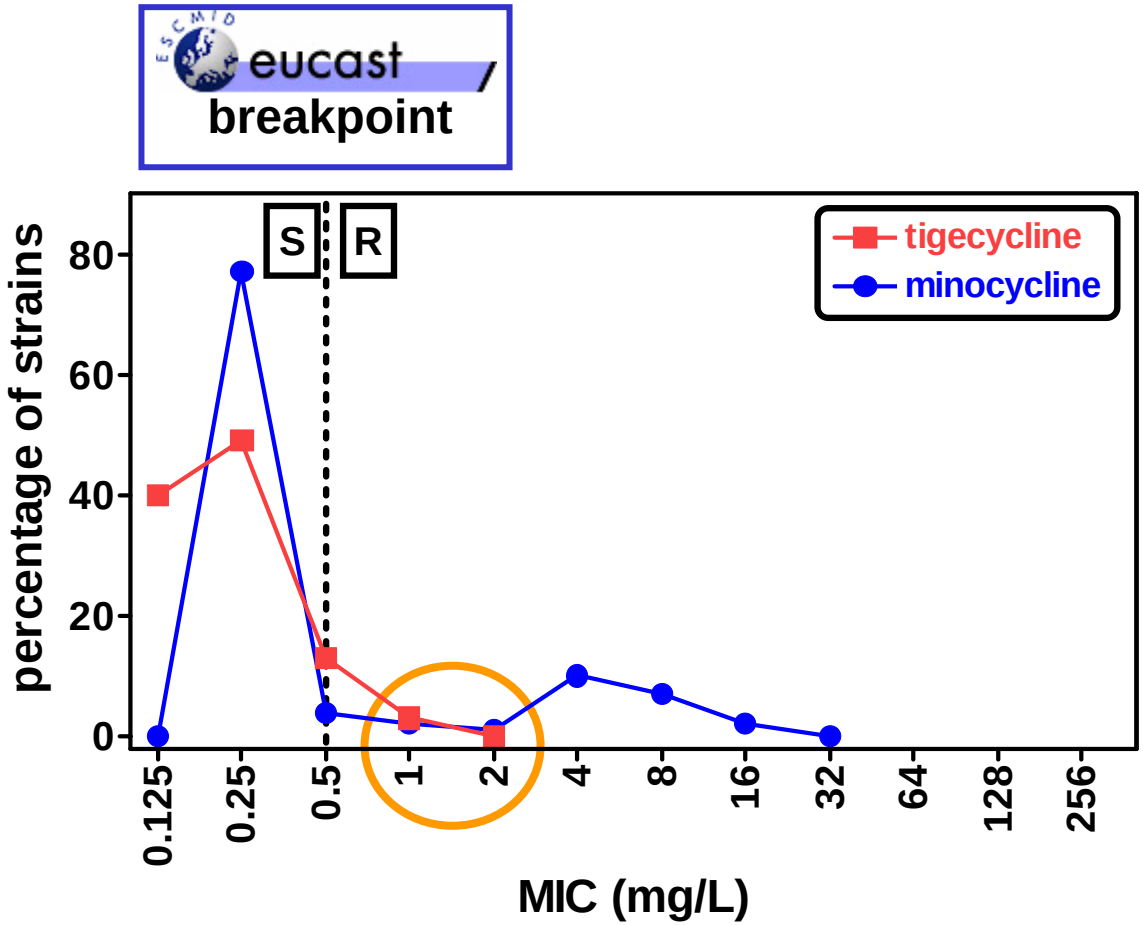
- same binding site as tetracyclines in ribosome 16S RNA; additional interaction site
- Unaffected by resistance due to
  - ribosomal protection
  - Tet efflux pumps
- Approved in USA in 2005 and in Europe in 2006
- wide spectrum, indicated for: cSSTI; intra-abdominal infections

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

tigecycline: in vitro data

Distribution of MICs for 128 MRSA from USA

active on minocycline-R population, but …



a few isolates above the breakpoint …

Low *et al.,* Int. J. Antimicrob. Ag. (2002) 20:220-2

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).

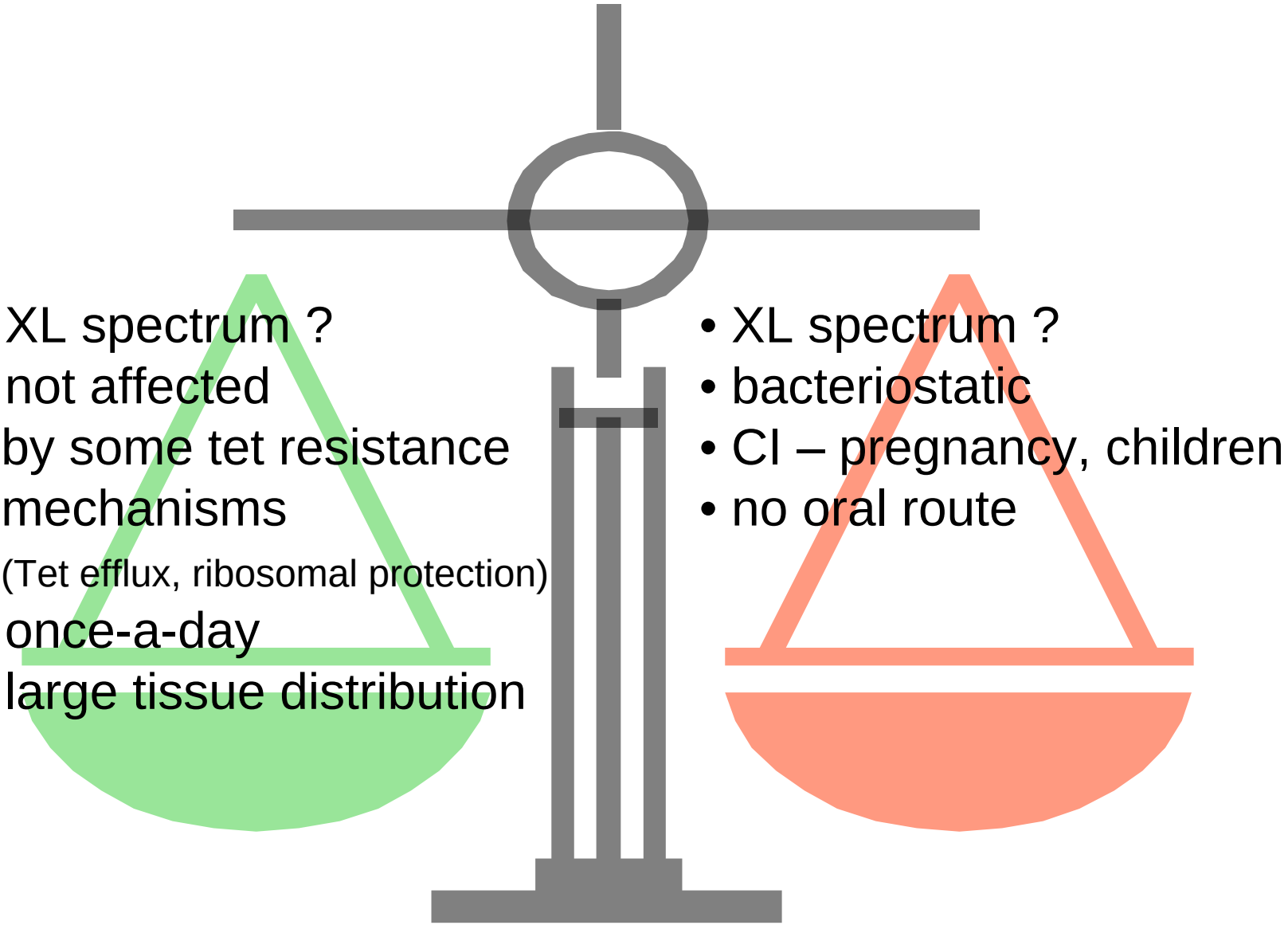
Isolate	Tigecycline		Vancomycin-aztreonam	
	No. of patients/total	Percentage of patients (95% CI)	No. of patients/total	Percentage of patients (95% CI)
Staphylococcus aureus				
Methicillin resistant	25/32	78.1 (60.0–90.7)	25/33	75.8 (57.7–88.9)
Methicillin susceptible	119/134	88.8 (82.2–93.6)	109/120	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 : pros and cons



- XL spectrum ?
- not affected
  by some tet resistance
  mechanisms
  (Tet efflux, ribosomal protection)
- once-a-day
- large tissue distribution

- XL spectrum ?
- bacteriostatic
- CI – pregnancy, children
- no oral route

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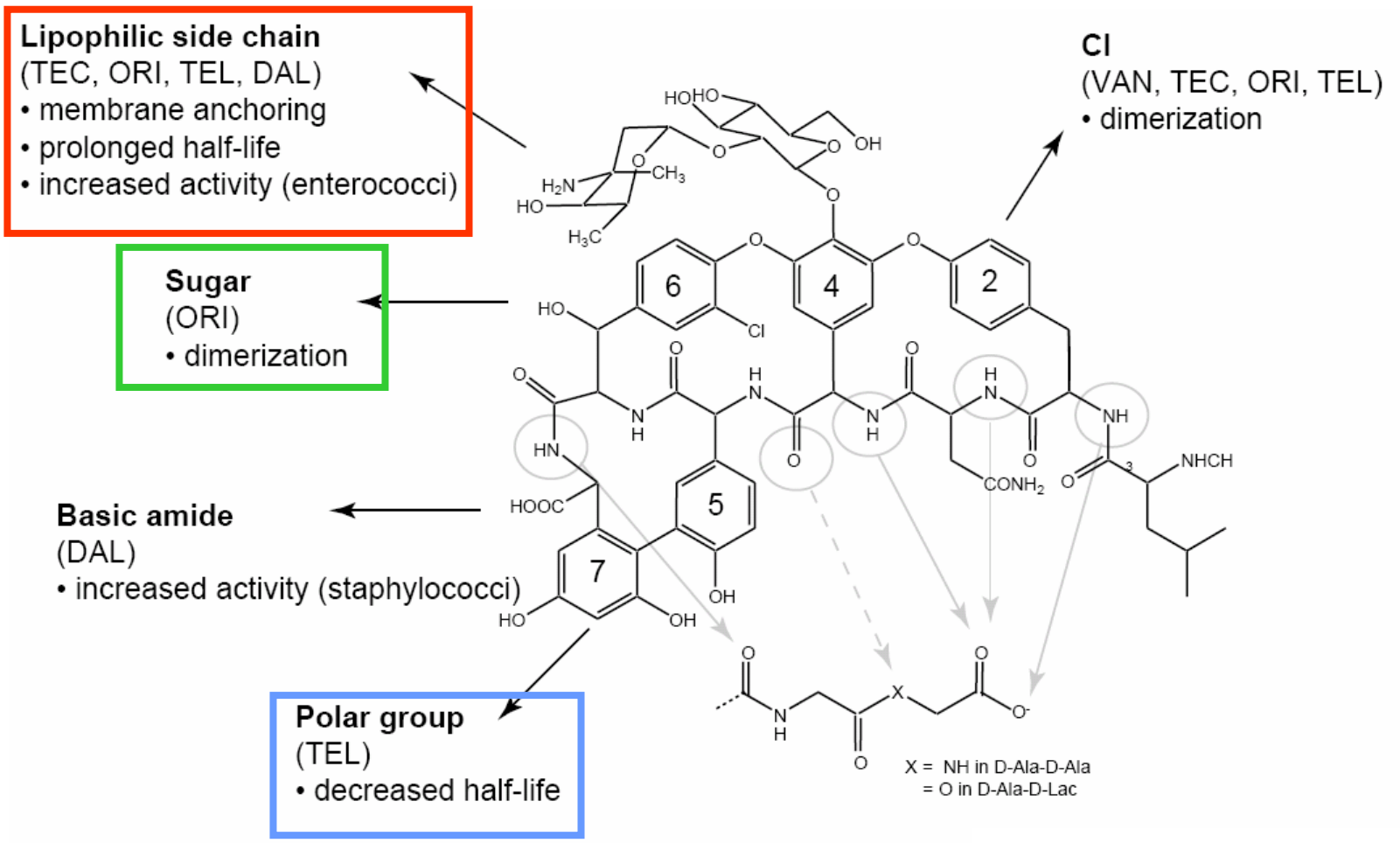
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

new glycopeptides: structure-activity relationship



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

new glycopeptides: in vitro data

Distribution of MICs for MRSA

drug	range		eucast breakpoint
	(a) *n = 23*	(b) *n=30*	
telavancin		0.125-1	
oritavancin	0.125-4		
vancomycin	0.5-4	1-2	4
dalbavancin	0.06-1		
teicoplanin	0.125-8	0.5-16	4

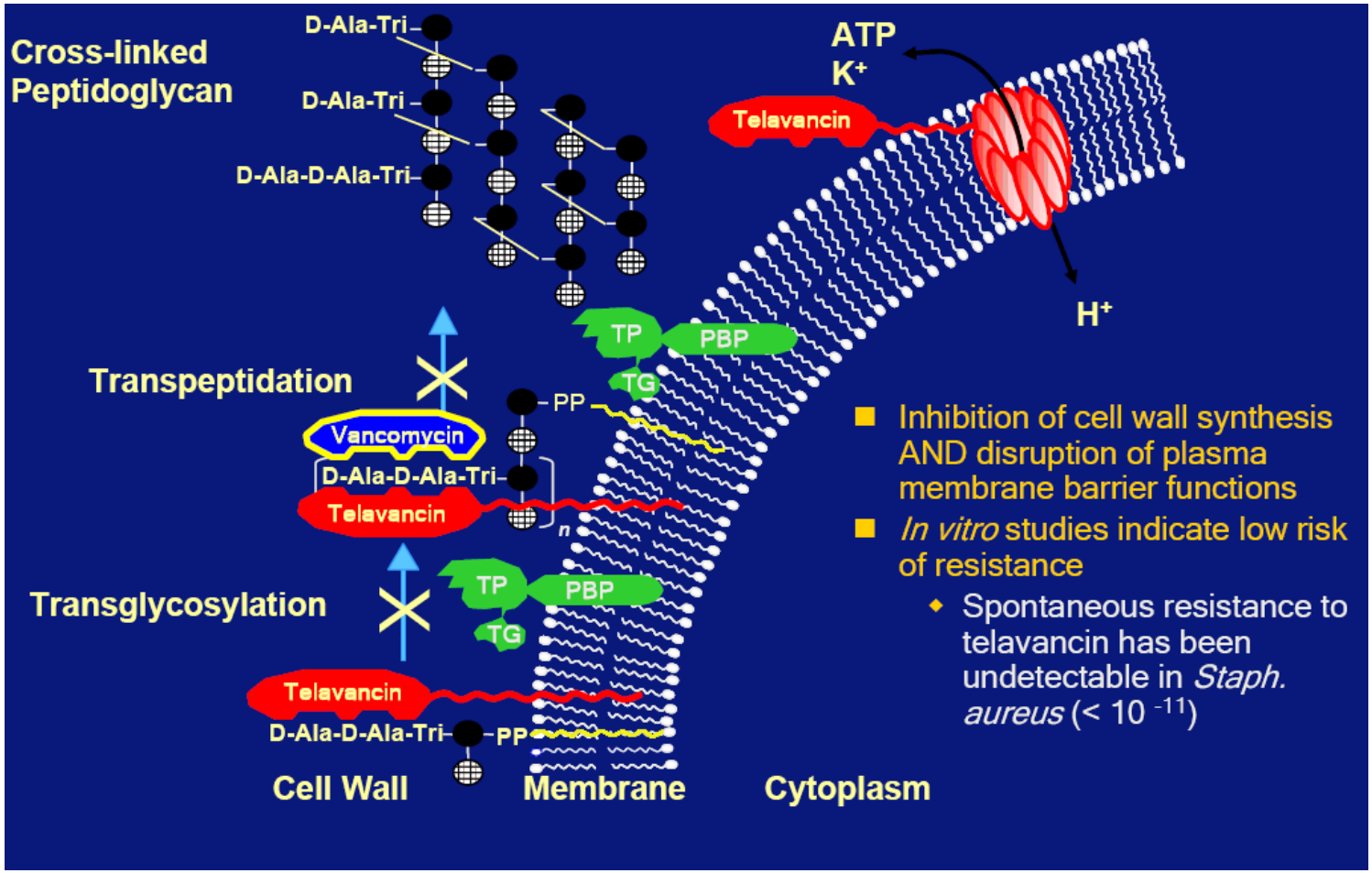
MICs of the same range as for vanco, but …

no breakpoint yet for new GP

(a) Candiani *et al.,* JAC (1999) 44:179-92; (b) King *et al.,* JAC (2004) 53:797-803

new glycopeptides: mode of action

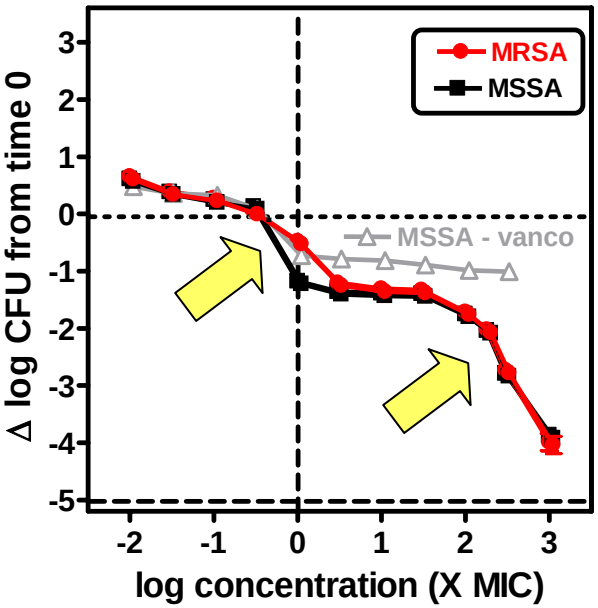
… rapid bactericidal effect, related to multiple modes of action

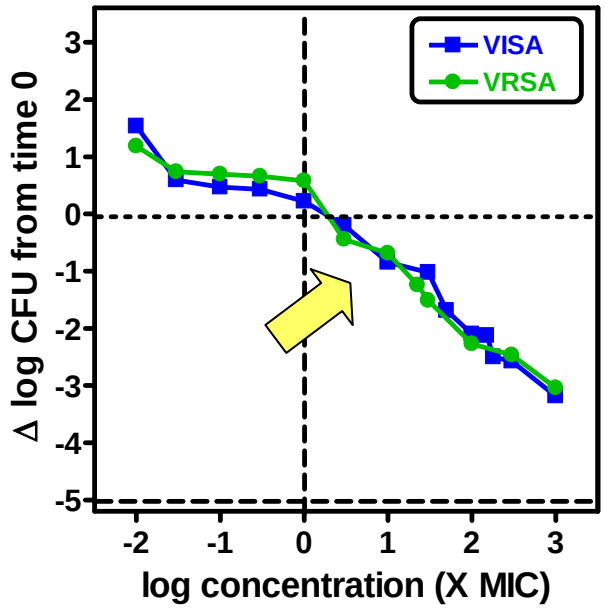


new glycopeptides: mode of action

… rapid bactericidal effect, related to multiple modes of action

Activity of telavancin after 3 h
towards S. aureus with different resistance phenotypes





Bimodal effect :
- inhibition of PG synthesis
- membrane permeabilization

Unimodal effect :
- ~~inhibition of PG synthesis~~
- membrane permeabilization

Barcia-Macay *et al*., JAC (2006) 58:1177-84

new glycopeptides: clinical experience

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

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

➔ 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

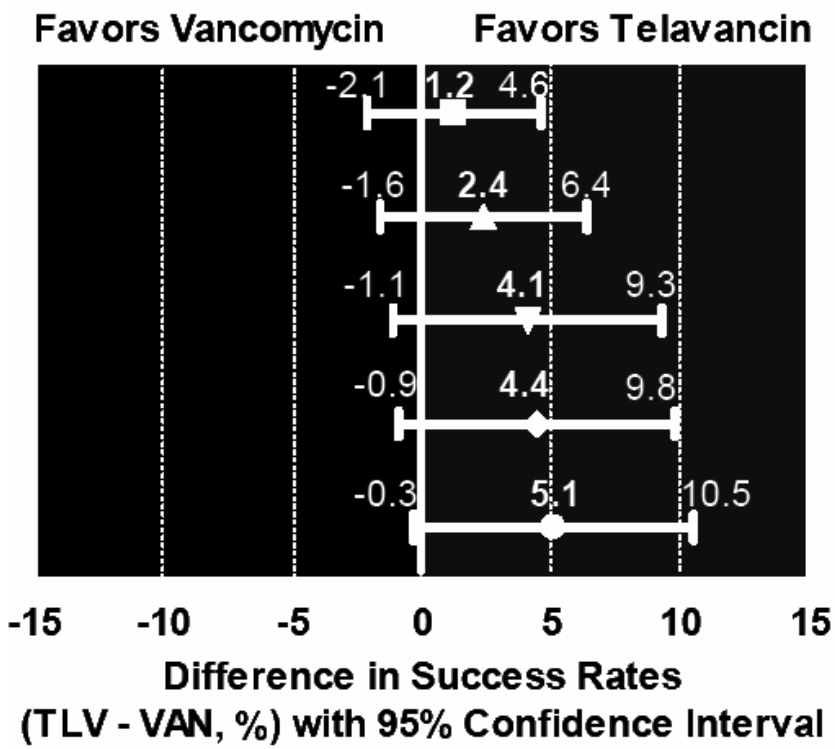
dalbavancin (1 g followed by 500 mg 1 week later)
- skin and skin structure infections (Phases II and III)
- catheter-related bloodstream infections (Phase II)

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

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

new glycopeptides: clinical experience

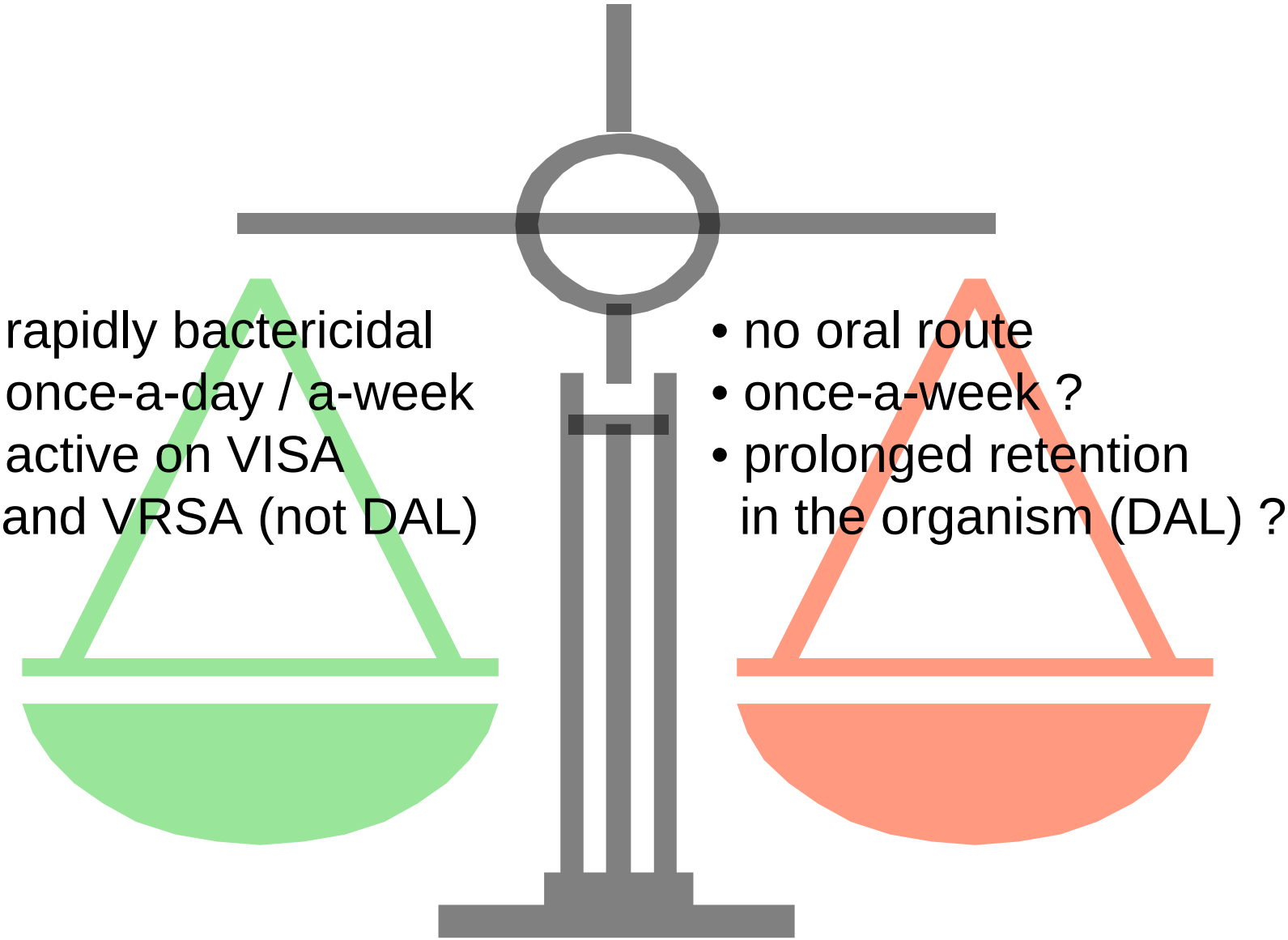
Phase 3 - Skin and skin structure infections



	TLV % Success (N)	VAN % Success (N)
Clinical Response in CE Patients	88.3 % (745)	87.1 % (744)
Overall Therapeutic Response in ME Patients	88.6 % (527)	86.2 % (536)
Clinical Response in MRSA	90.6 % (278)	86.4 % (301)
Microbiological Eradication in MRSA	89.9 % (278)	85.4 % (301)
Overall Therapeutic Response in MRSA	89.9 % (278)	84.7 % (301)

Kanafani, Exp. Rev. Anti-inf. Ther. (2006) 4:743-9; www.theravance.com

new glycopeptides : pros and cons



- rapidly bactericidal
- once-a-day / a-week
- active on VISA and VRSA (not DAL)

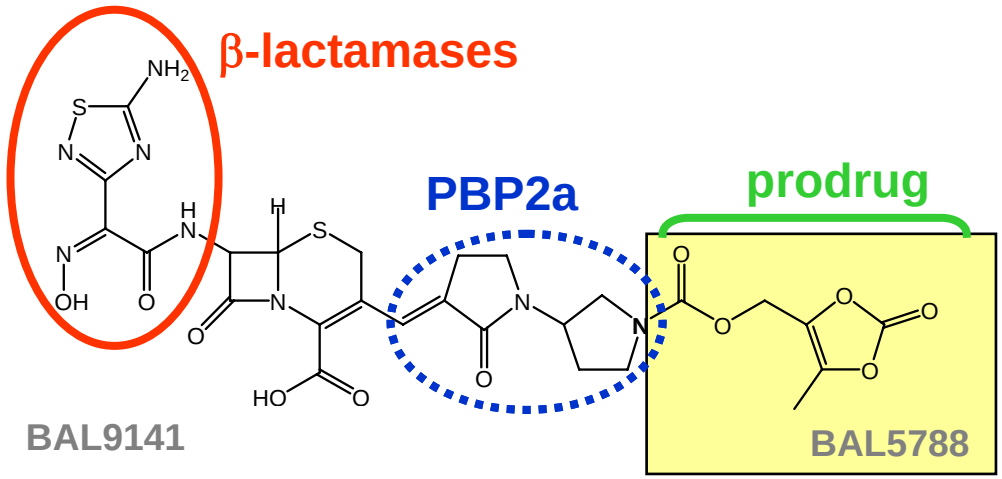
- no oral route
- once-a-week ?
- prolonged retention in the organism (DAL) ?

recent and novel agents for *S. aureus*

recently brought on the Belgian market	on the market; not yet in Belgium	(late) stage of clinical development	investigational
moxifloxacin	synercid	telavancin	CS-023/PZ-601
linezolid	daptomycin	oritavancin	MX-2401
	tigecycline	dalbavancin	API-1252
		ceftobiprole	DK-619
		iclaprim	new oxazolidinones
		retapamulin	new ketolides
		WCK-771	...

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



basilea PHARMACEUTICA J&JPRD

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

- Capable of binding to PBP2a of MRSA
- Fast track designation from FDA for cSSTI and nosocomial pneumonia

Hebeisen *et al.*, AAC (2001) 45:825-31

ceftobiprole in vitro data

Susceptibility of 1275 MRSA

drug	range	MIC 50	MIC 90	eucast breakpoint
vancomycin	0.5-2	1	1	8
ceftobiprole	0.12-4	1	1	4 *

so far, so good, but for how long ? …

* provisional breakpoint

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

Sahm *et al.,* ICAAC (2006) E0113

Ceftobiprole clinical experience

cSSSI – 784 patients

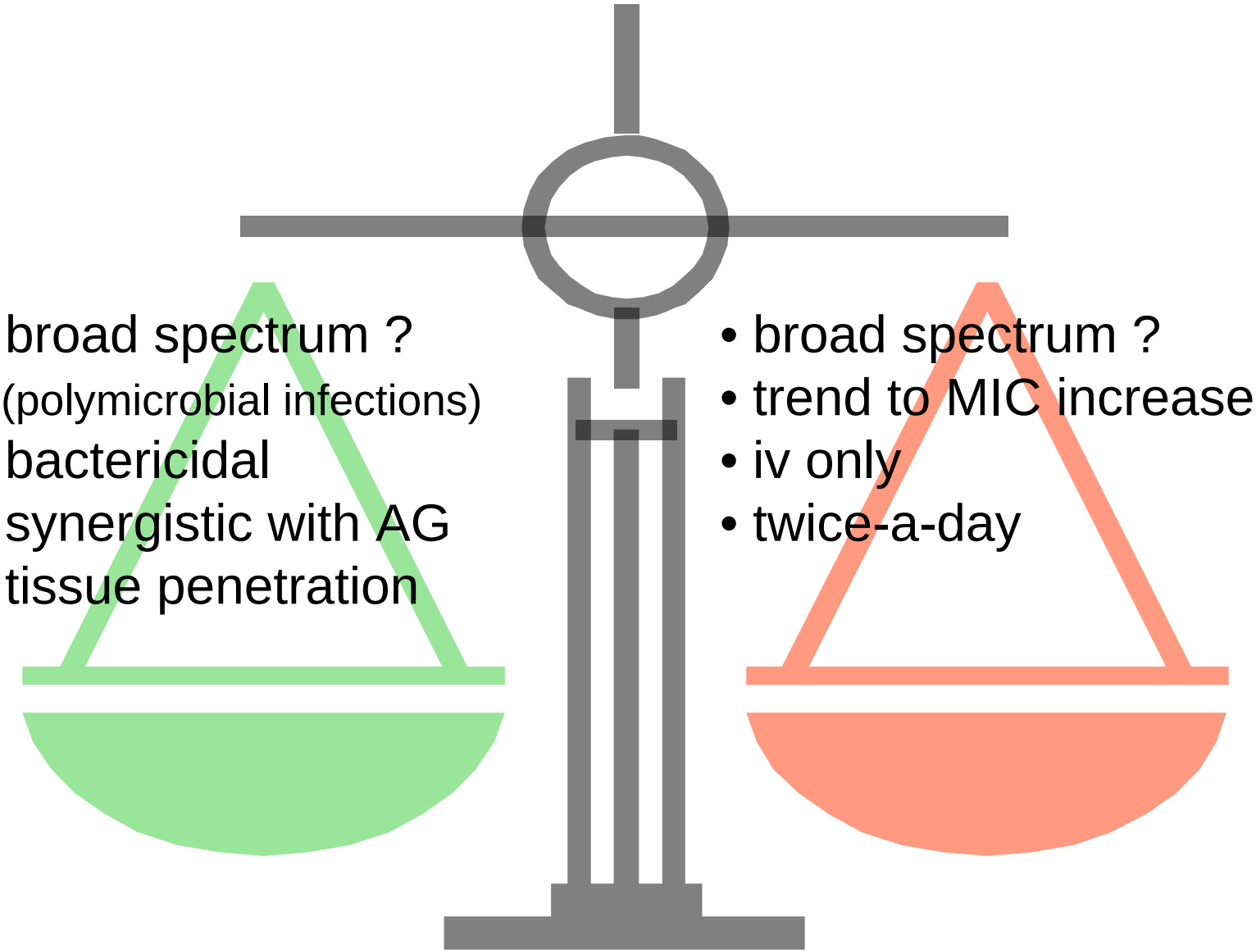
Table 6. Clinical cure rates (number [%]) in patients meeting criteria for a severe infection (CE population)

	Sepsis Syndrome		CRP >50 mg/ml		Deep Infection	
	Ceftobiprole	Vancomycin	Ceftobiprole	Vancomycin	Ceftobiprole	Vancomycin
All *S. aureus*	33/35 (94.3%)	29/31 (93.6%)	66/71 (93.0%)	69/75 (92.0%)	63/66 (95.5%)	50/55 (90.9%)
MRSA	8/9 (88.9%)	6/6 (100%)	20/23 (87.0%)	21/24 (87.5%)	19/21 (90.5%)	18/21 (90.5%)

CRP, C-reactive protein.

Noel *et al.,* ICAAC (2006) L1212

ceftobiprole: pros and cons



- broad spectrum ?
  (polymicrobial infections)
- bactericidal
- synergistic with AG
- tissue penetration

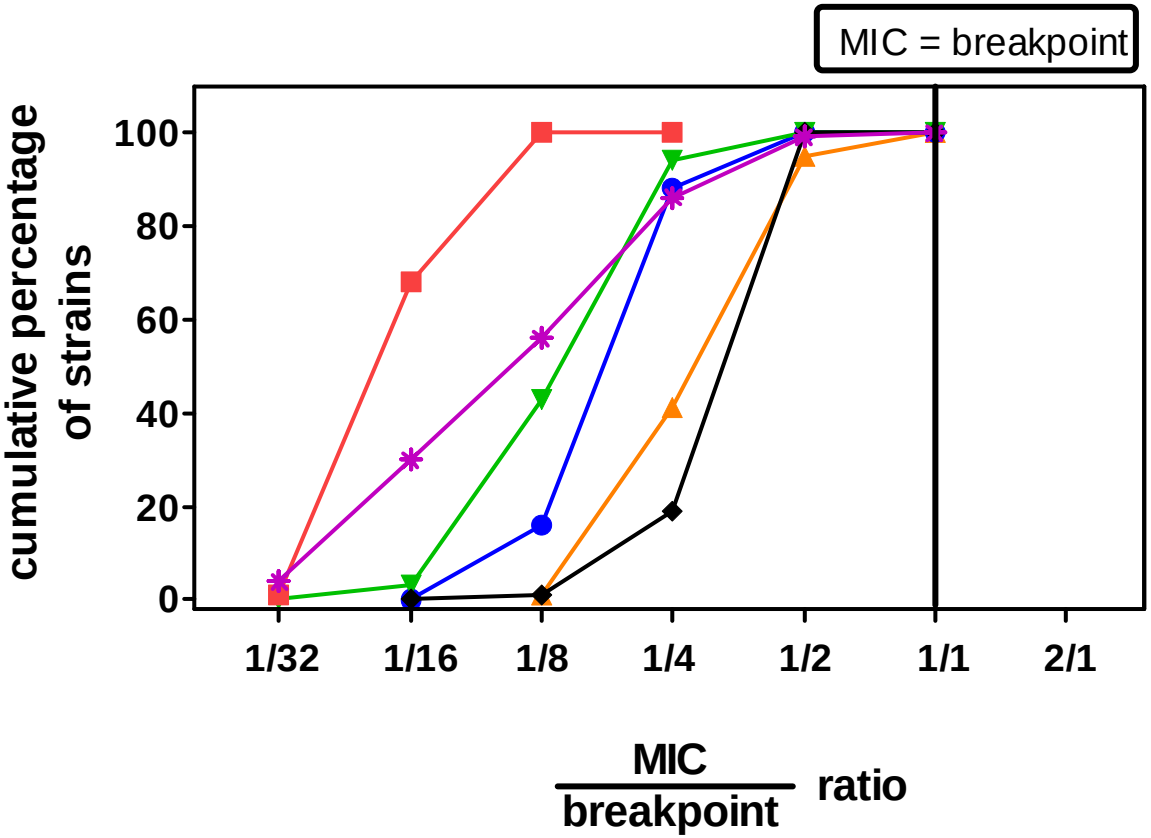
- broad spectrum ?
- trend to MIC increase
- iv only
- twice-a-day

a few additional criteria of choice …

what about Belgian isolates ?

Susceptibility of 511 MRSA from 112 hospitals

All isolates still below the breakpoint



eucast

CLINICAL AND LABORATORY STANDARDS INSTITUTE (Formerly NCCLS)

breakpoint

vancomycin	8
ceftobiprole	4
daptomycin	1
synercid	2
tigecycline	0.5
linezolid	4

but do we agree with all breakpoints ?

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

conclusion

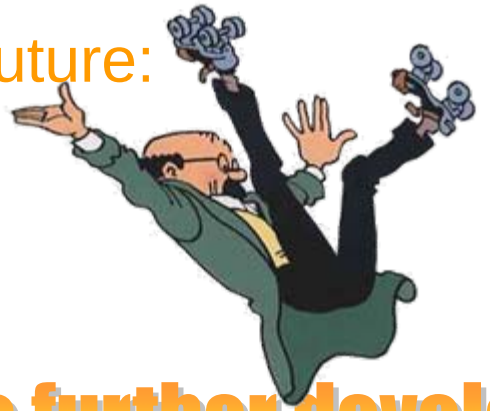
a lot of molecules in the pipeline

→ synercid: usefulness in Europe ?
→ daptomycin: bactericidal, but surfactant effect …
→ tigecycline: polymicrobial infections, but static …

really new still to come

→ new glycopeptides: bactericidal,
resistance probably difficult to select
→FabI inhibitors: totally new target, MICs very low

question for the future:



how to further develop them while restricting their use ?

Thank you for your attention

and happy birthday to Hergé…