New antistaphlycoccal agents: Hopes and limitations

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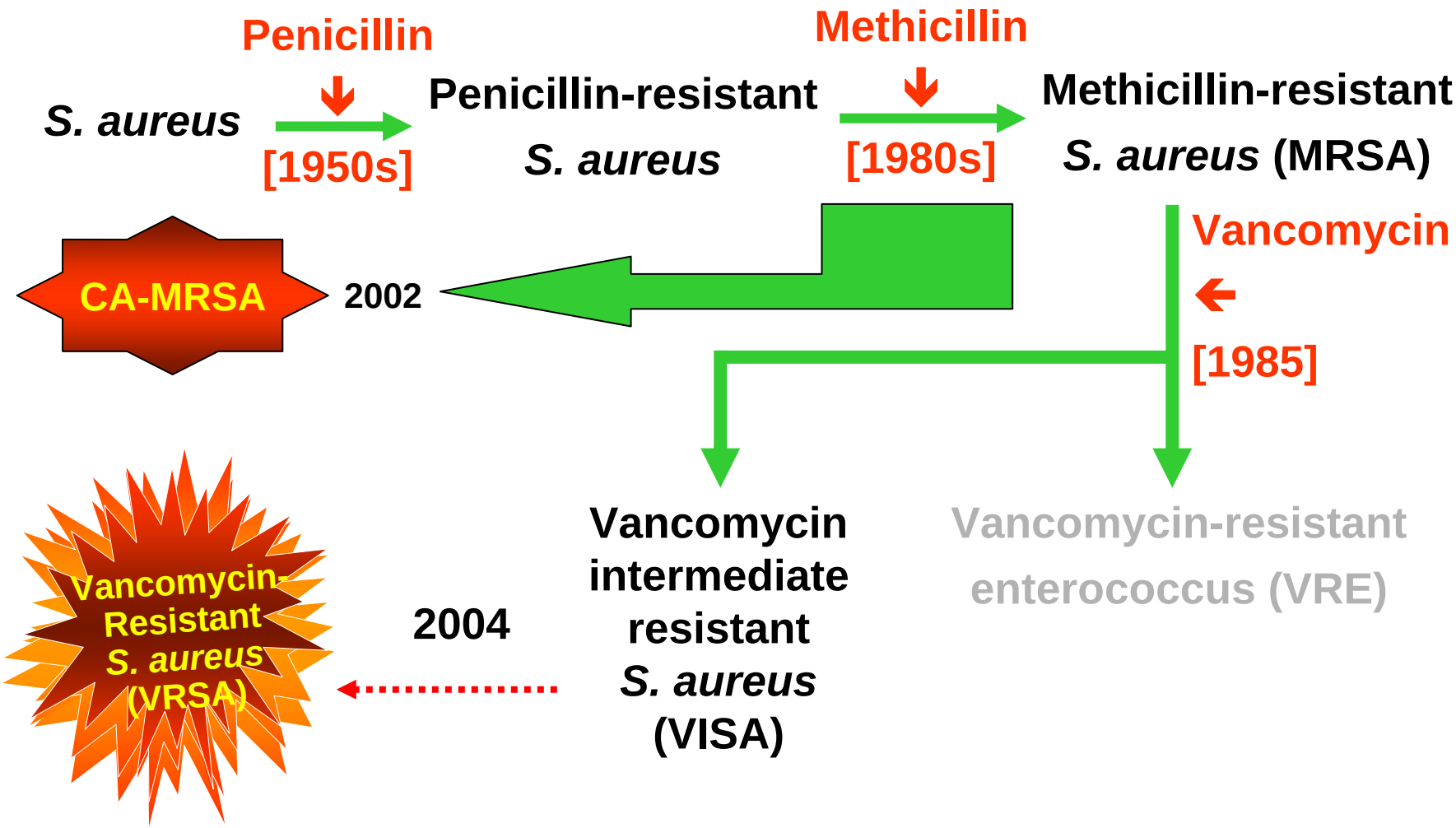
Why do we need <u>new</u> antistaphylococcal agents ?

- rising resistance … reaching the limits of what we can give to patients …
- intrinsic PK/PD limitations of conventional glycopeptides towards *S. aureus* is severe infections
- intracellular development of *S. aureus*… causing recurrence, relapses, and perhaps also resistance …

The (sad) story of the *S. aureus*



Intrinsic limitations of glycopeptides …

- only slowly bactericidal …
- require higher dosages than originally thought to be effective … (AUC/MIC ≥ 400 …)*

  ➔ the classical dose of 2 x 15 mg/kg per day gives an AUC of 520, which will cover organisms up to a MIC of 1-2 mg/L only
- most often require the co-administration of another antibiotic because of too narrow spectrum
- yet, may cause severe surinfections …

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* Moise-Broder et al. Clin Pharmacokinet. 2004;43(13):925-42

Intracellular infection and recurrence/relapses

In vivo importance assumed based on in vitro data

J Bone Joint Surg Br. 2003 Aug;85(6):918-21.

Intracellular Staphylococcus aureus. A mechanism for the indolence of osteomyelitis.

Ellington JK, Harris M, Webb L, Smith B, Smith T, Tan K, Hudson M.

Clin Infect Dis. 2001 Jun 1;32(11):1643-7. Epub 2001 Apr 30.

Intracellular persistence of Staphylococcus aureus small-colony variants within keratinocytes: a cause for antibiotic treatment failure in a patient with darier's disease.

von Eiff C, Becker K, Metze D, Lubritz G, Hockmann J, Schwarz T, Peters G.

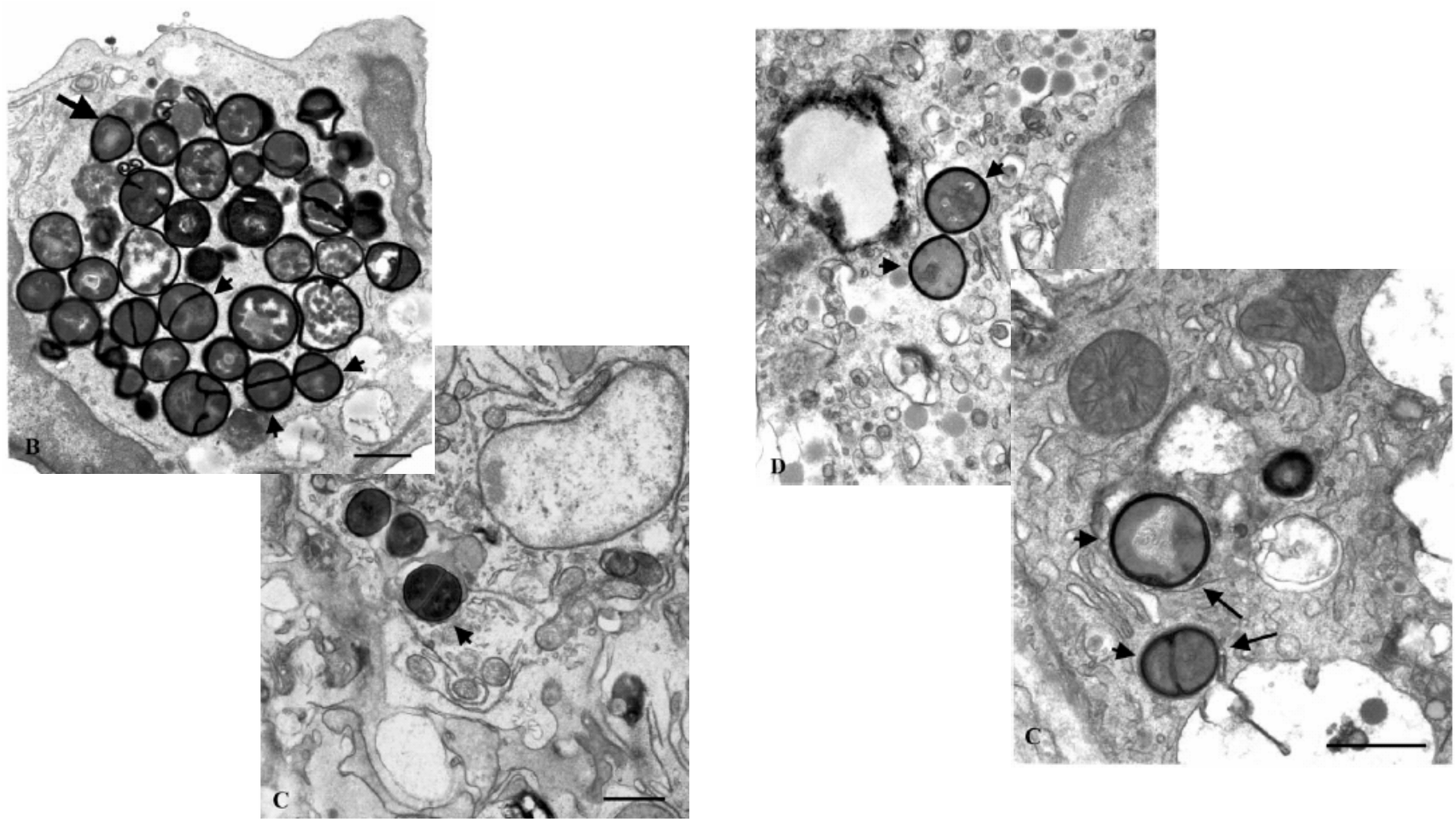
Infect Immun. 1986 Dec;54(3):833-6.

Phagocytosis of Staphylococcus aureus by cultured bovine aortic endothelial cells: model for postadherence events in endovascular infections.

Hamill RJ, Vann JM, Proctor RA.

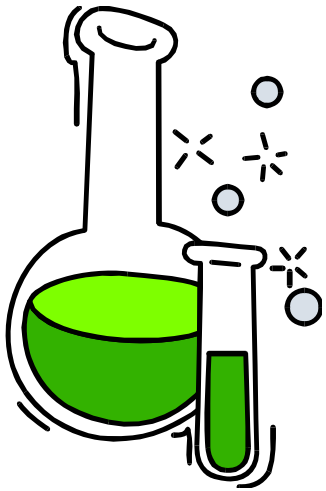
Intracellular infection and recurrence/relapses

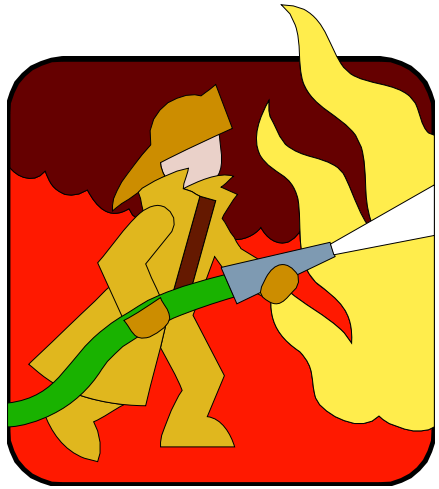
Phagocytic and non phagocytic cells in mastitis



Brouillette *et al.,* Microb. Pathog. *(*2003) 35:159-68

A real pipeline ?





Yes...

***In vitro* susceptibility of new agents against *Staphylococcus aureus*[a].**

Class	Agent	Development status	MIC_{90} (μg/mL)
β-Lactam	Ceftobiprole (BAL9141/ 5788, Ro 63-9141)	Clinical	0.5–1 M^S 2–4 M^R
β-Lactam	TAK-599	Preclinical	0.25 M^S 2 M^R
Quinolone	WCK-771	Clinical	0.015 Q^S 1 Q^R
Quinolone	WCK-919/1153	Pre-clinical	0.03 Q^S 2 Q^R
Quinolone	DX-619	Pre-clinical	0.06 M^S 1 M^R 0.5 Q^R
Oxazolidinone	Linezolid	Approved	4
Oxazolidinone	Ranbezolid (RBX 7644)	Pre-clinical	2
Ketolide	Telithromycin	Approved	0.12 E^S 0.25 $E^{R\text{-ind}}$ >128 $E^{R\text{-const}}$ 0.12 $E^{R\text{-msr}}$
Lincosamide	VIC-105555	Pre-clinical	0.5
Streptogramin	Quinupristin–dalfopristin	Approved	0.5
Glycopeptide	Teicoplanin	Approved	1–2
Glycopeptide	Oritavancin (LY333328)	Clinical	1–2
Glycopeptide	Dalbavancin (BI397)	Clinical	0.06–0.25
Lipopeptide	Daptomycin	Approved	0.5
Diaminopyrimidine	Iclaprim (AR-100)	Clinical	0.5
Glycylcycline	Tigecycline	Clinical	0.25–0.5
PDF-inhibitor	LBM415 (NVP PDF-713)	Pre-clinical	2–4

Appelbaum and Jacobs, Curr Opin Microbiol. (2005) 8:510-7.

The main classes…

Those already approved …

- tigecycline (the tetracyclines are back…)
- daptomycin (an old but really new drug…)
- moxifloxacin (quinolones do not give up…)

Those in late phase III …

- new quinolones …
- ceftobiprole (the first new anti-MRSA cephalosporins)
- the new lipoglycopeptides:
  - the real new one: telavancin,…
  - a not so novel but with unsual PK properties: dalbavancin

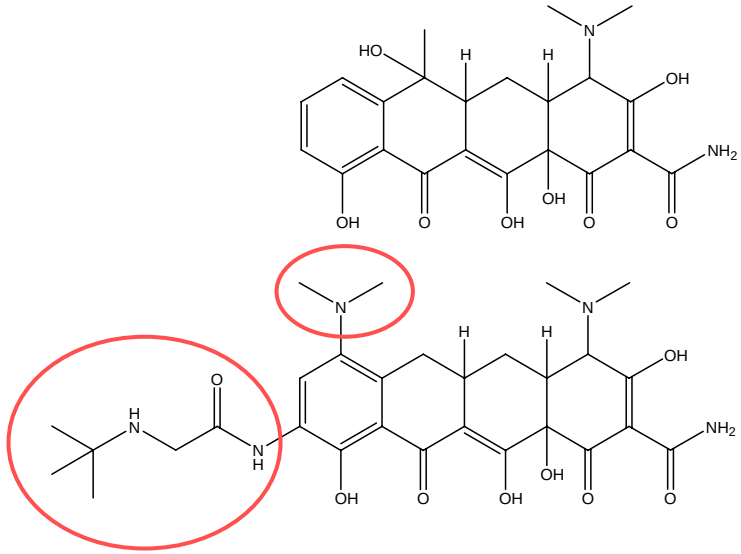
Those which will probably fail …

- new oxazolidinones …

And those which were approved and forgotten but may come back…

- SYNERCID ?
- arbekacin …

Tigecycline…

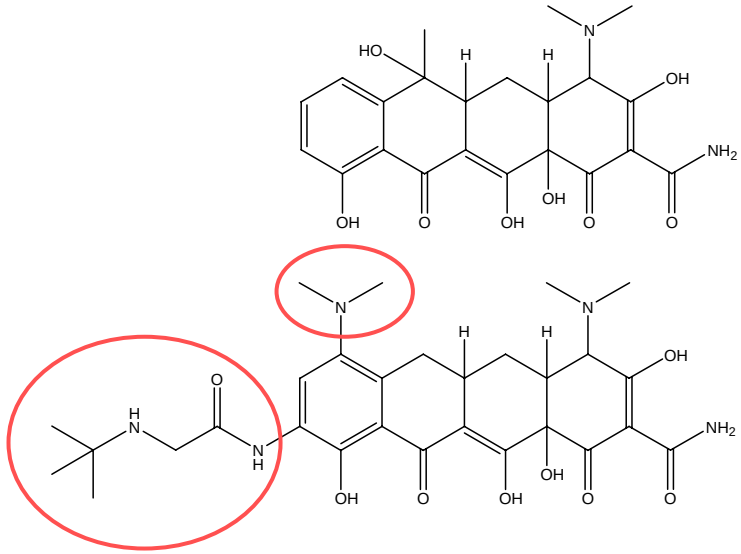


- truly made to resist efflux-mediated resistance in Gram(-) bacteria
- broad spectrum including MRSA (MIC < 2 mg/L) and VISA
- tet(M) [ribosomal protection] or tet(K) [efflux] have no discernible effect on MICs
  (AAC 2006 Feb;50(2):505-10).
- large tissue accumulation (Vd=7-9L/kg)
  - ➔ low C_{max} (1.5 mg/L; 70-80% protein-bound).

- approved by the FDA in June 2005 for
  - complicated skin infections, skin-structure infections;
  - intra-abdominal infections

    both at 100 mg IV (initial) followed by 50 mg/12h IV
  - bkpt for *S. aureus* (FDA): S ≤ 0.5 mg/L

Tigecycline in Europe…

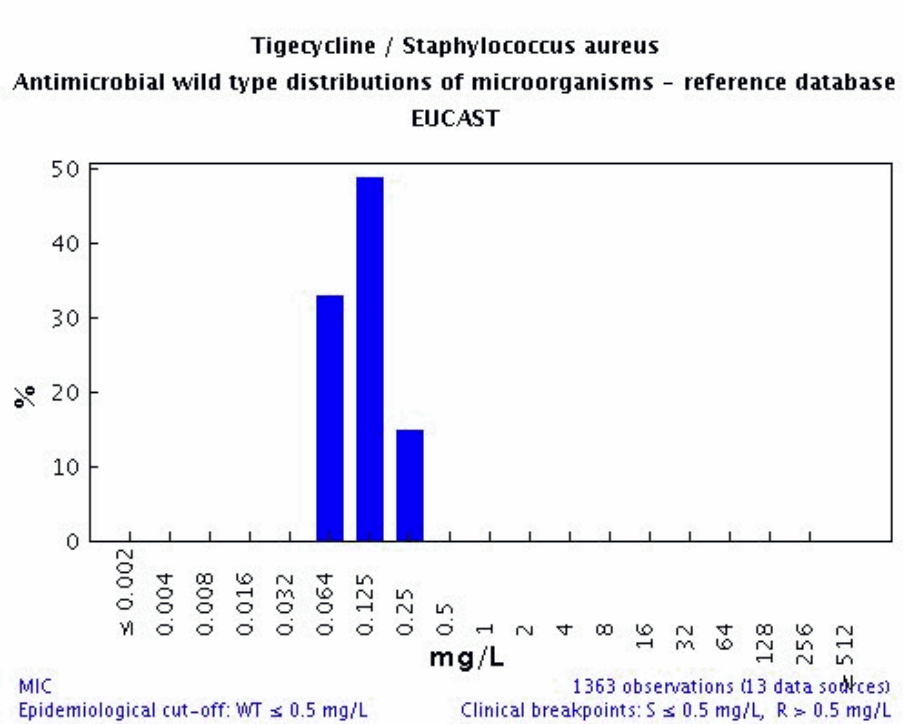


- **approval by the EMEA in April 2006 for**
  - Complicated skin and soft tissue infections
  - Complicated intra-abdominal infections

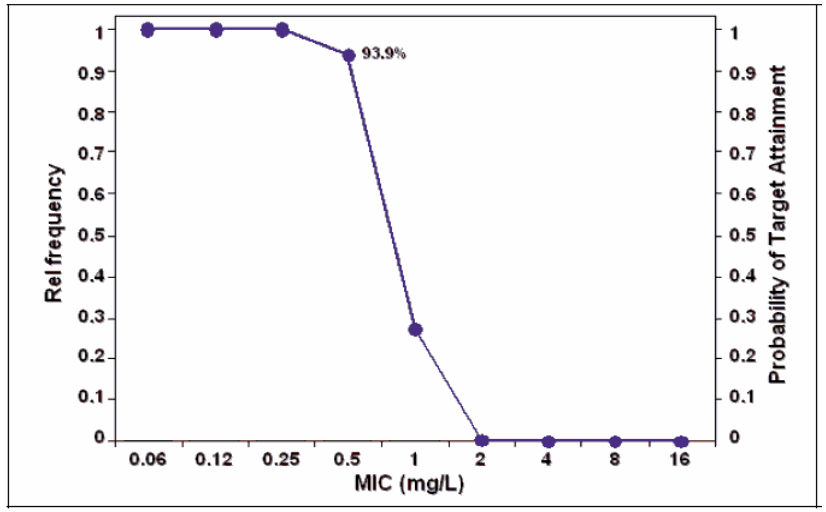
    both at 100 mg IV (initial) followed by 50 mg/12 h for 5 to 14 days.
  - bkpt for S. aureus (EUCAST): S ≤ 0.5 mg/L

    with the following comments:
    - Strains with MIC values above the breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.
    - The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

Tigecycline… why a breakpoint ≤ 0.5 mg/L ?



Distributions of MIC as submitted to EUCAST

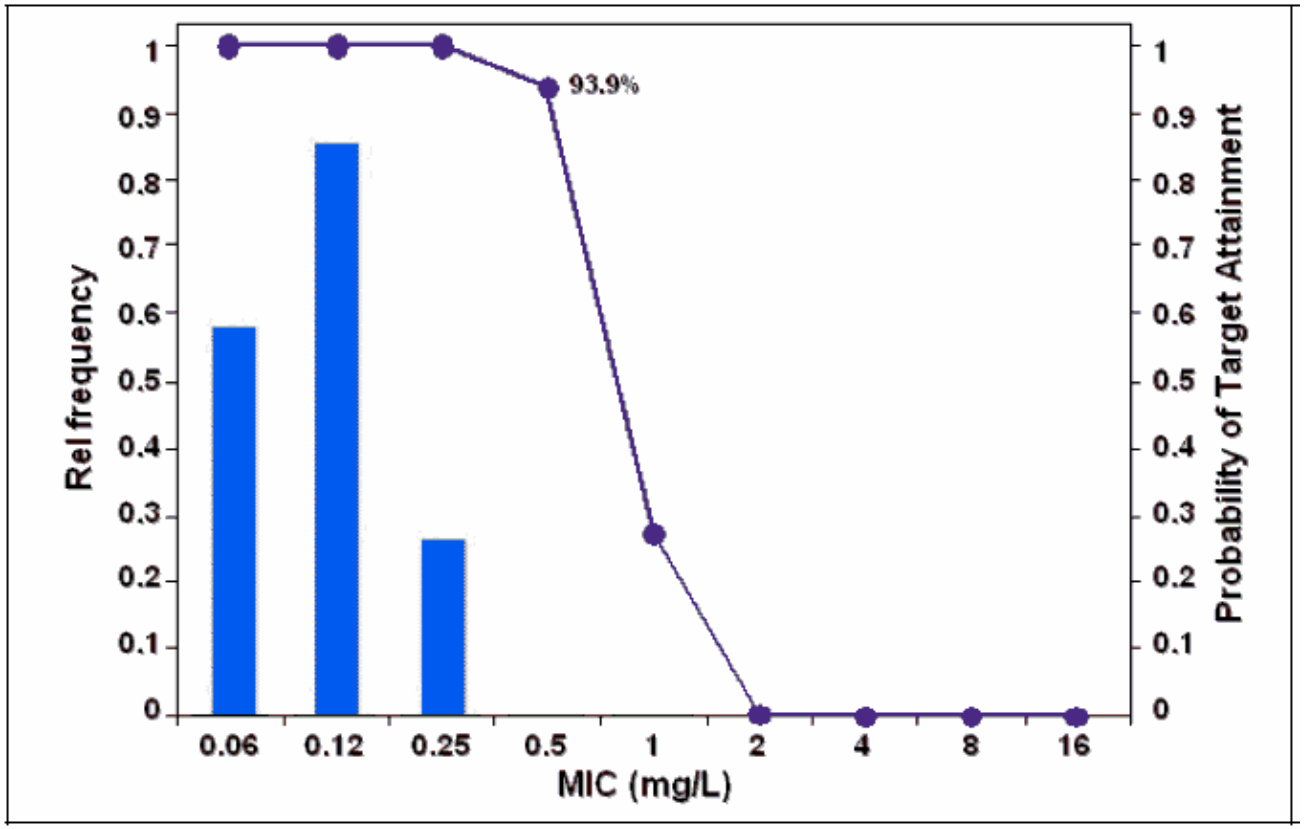


Probability of target attainment of an suitable AUC/MIC ratio (≥ 7) for the recommended dosage

http://217.70.33.99/Eucast2/SearchController/regShow.jsp?Id=7563

Wyeth: data on file

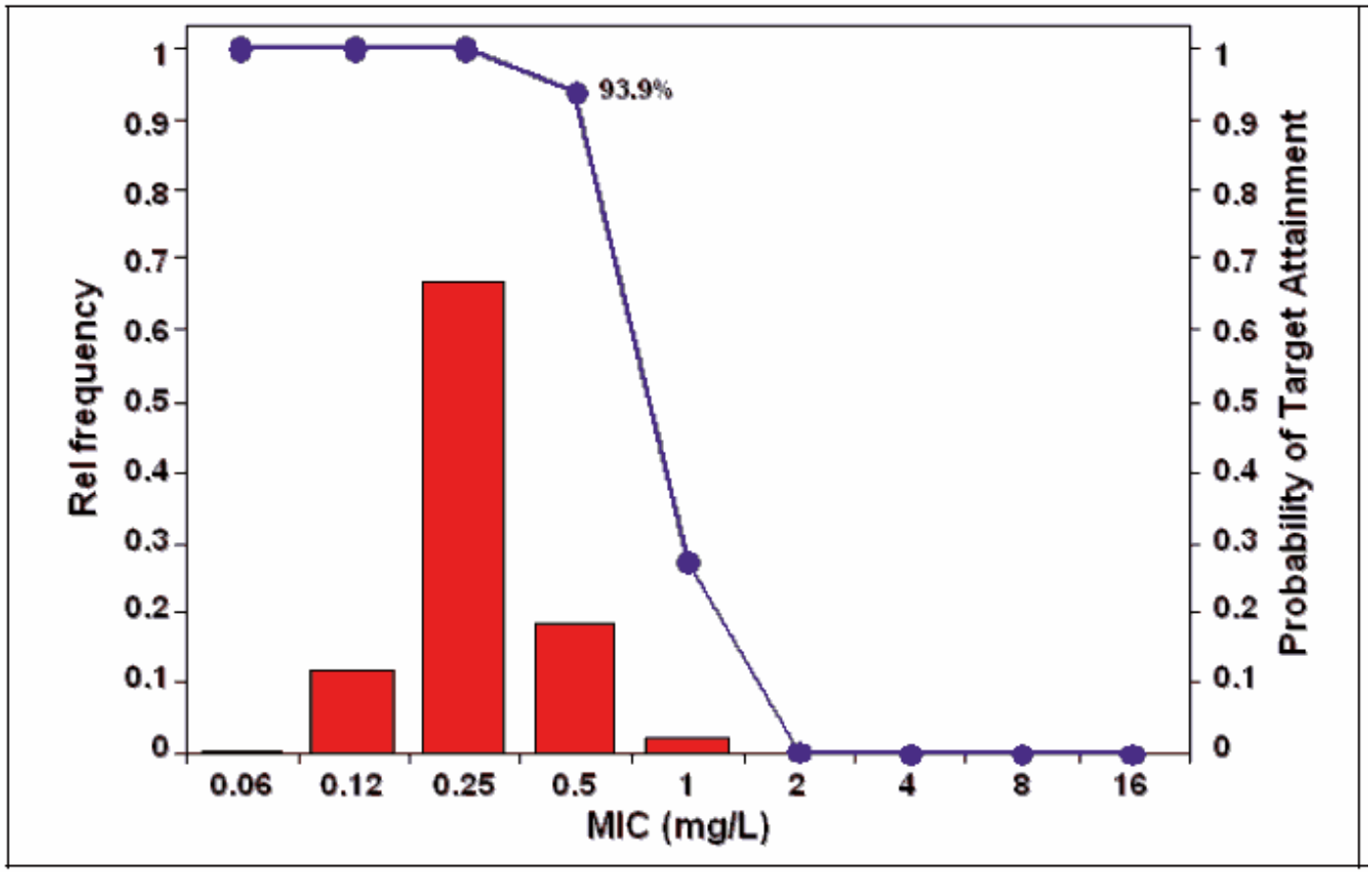
Tigecycline… why a breakpoint ≤ 0.5 mg/L ?



Putting all together ….

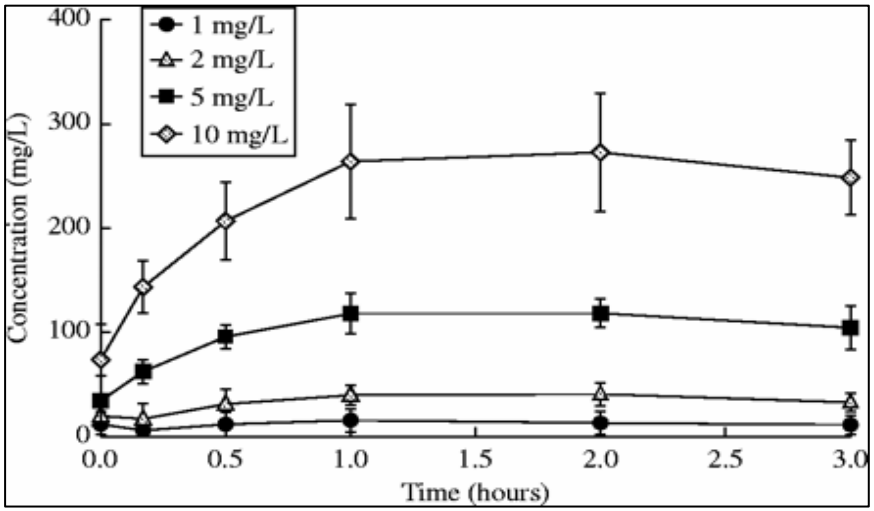
➔ you will be effective as long as the MIC remain ≤ 0.5 mg/L

Tigecycline… why a breakpoint ≤ 0.5 mg/L ?



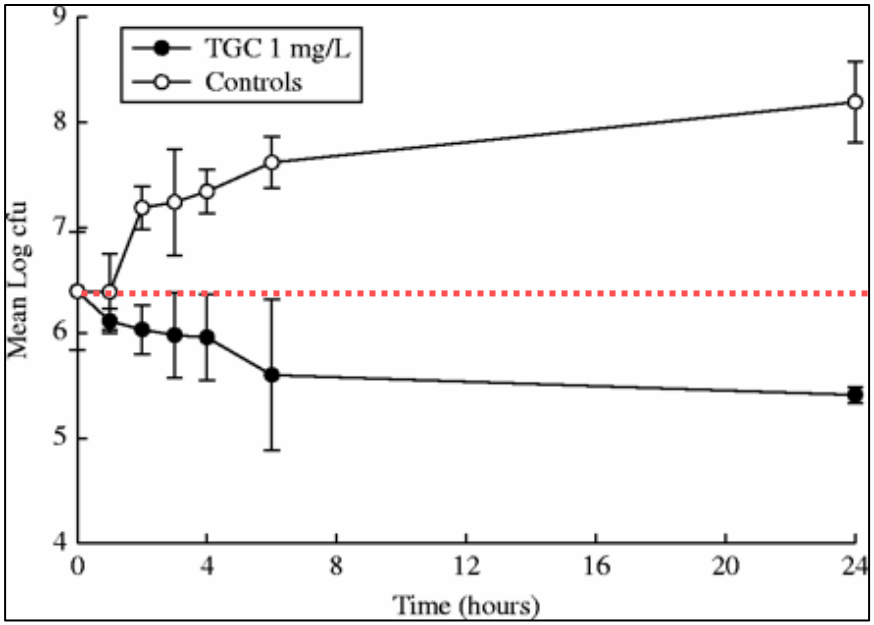
Probability of target attainment of an suitable AUC/MIC ratio (≥ 7) for the recommended dosage

Tigecycline and intracellular *S. aureus*…

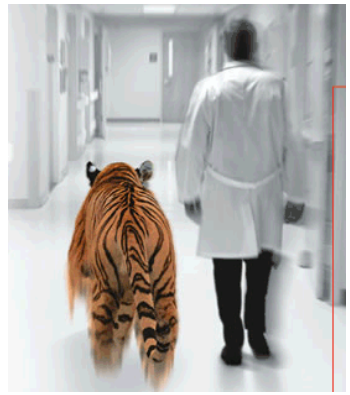


accumulation in PMN:
about 20-30 fold

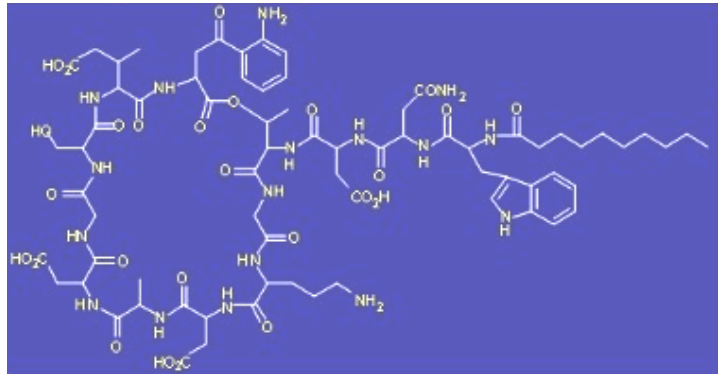
Ong et al. J Antimicrob Chemother. 2005 Sep;56(3):498-501.



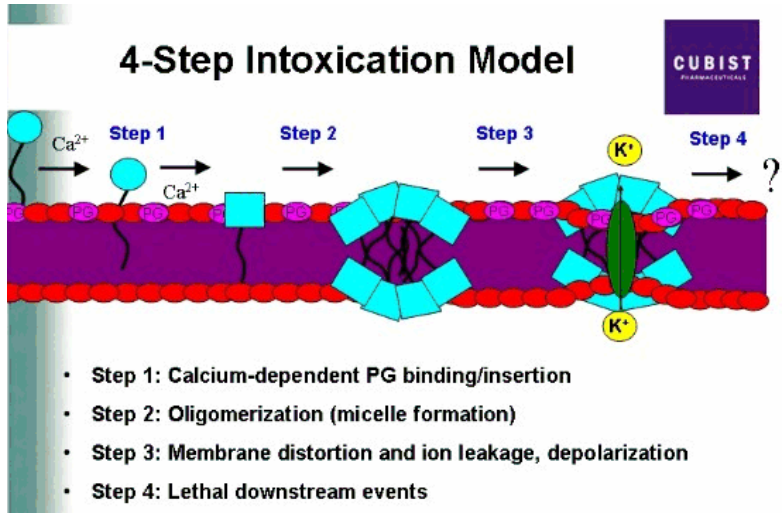
activity in PMN:
about 1 $\log_{10}$
at 1 mg/L
S. aureus ATCC 29213
(MIC = 0.25 mg/L)



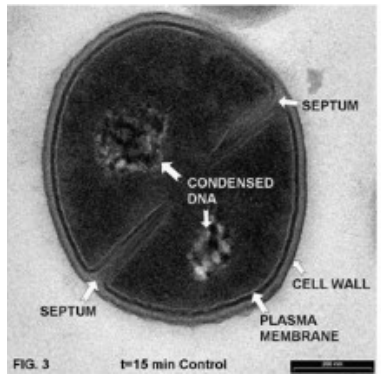
Daptomycin …

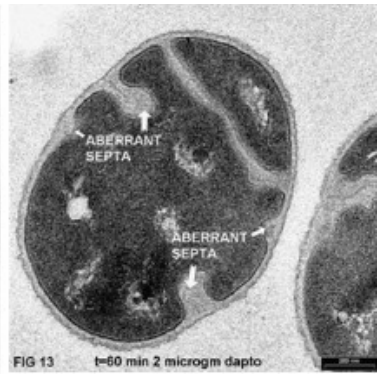


- very bactericidal towards Gram (+) organisms through membrane destabilization (no need of proteinaceous receptor!)
- BUT intrinsically inactive against Gram(-) due to LPS protection
- spare mammalian cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes



- got a fast track registration in the US because of activity against vancomycin-resistant enterococci (VRE)

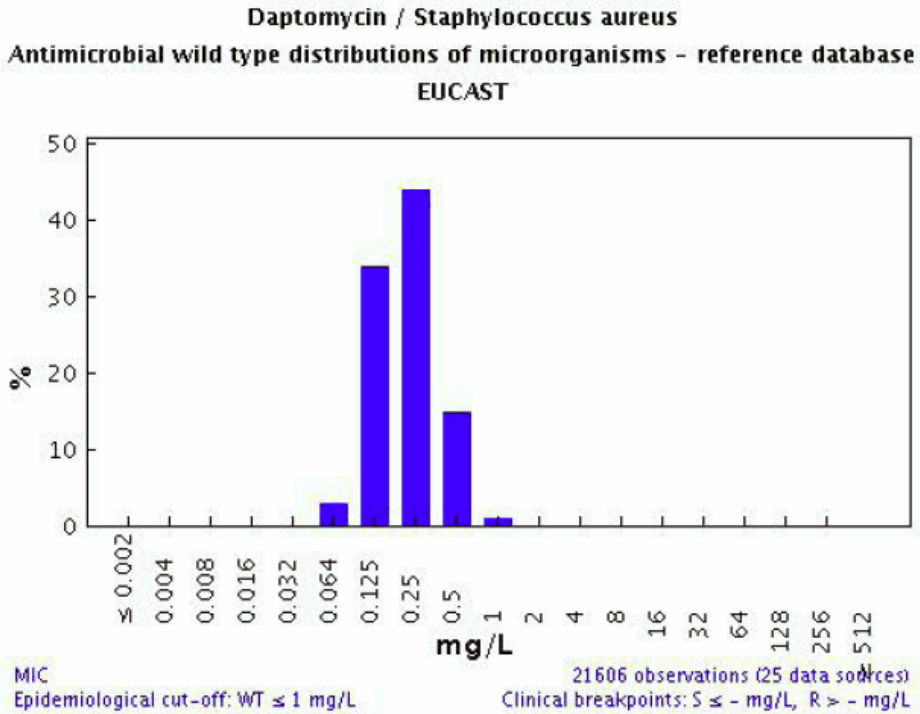


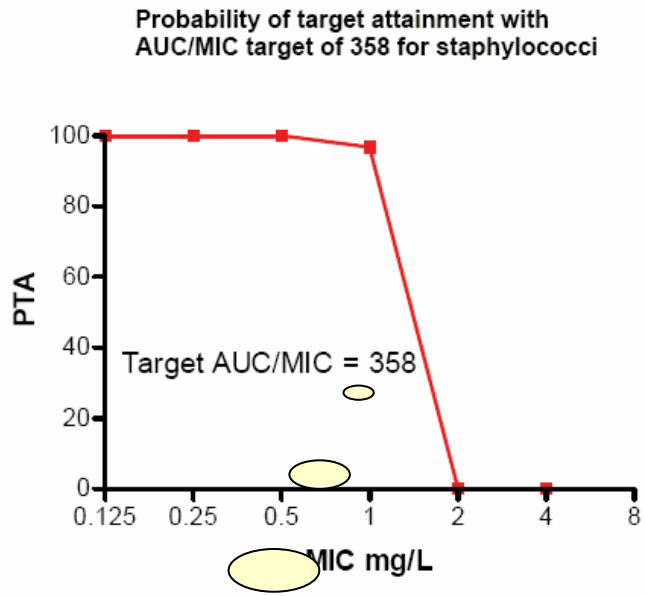


J. Silverman, 45thICAAC, 2005

Setting Daptomycin breakpoint …

Figure 1: Daptomycin MIC distribution and probability of target attainment for *S. aureus*





358 is the minimal value for efficacy based on animal and human data

Is there a place for daptomycin (in Europe) ?

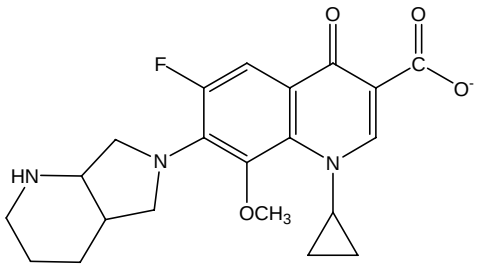
- breakpoint (as per EUCAST): 1 mg/L
- now registered in Europe for complicated skin and soft tissue infections
  (4 mg/kg administered once every 24 hours for 7-14 days)
- potential issues:
  - limited no. of clinical studies submitted in Europe so far (only equivalence to vancomycin !);
  - VISA strains tend to have MIC > 1 mg/L
  - safety (myopathy);
  - lack of Gram(-) coverage (no empiric treatment possible);
  - price (about 3-4 x vancomycin …)
- potential future: registration for bacteremia

May 26th, 2006 new FDA registration

***Staphylococcus aureus* bloodstream infections** (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see **CLINICAL STUDIES**). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis.

Moxifloxacin



Lowest MIC amongst currently available quinolones, but resistance does exist !

Distribution of fluoroquinolone MICs for 100 MRSA isolated in 2002

Drug	No. of strains with indicated MIC (mg/l)[a]										
	≤0.25	0.5	1	2	4	8	16	32	64	128	≥256
NFLX	0	0	1	0	0	1	1	15	42	21	19
ENX	0	0	0	3	0	1	0	1	12	73	11
CPFX	1	2	0	1	0	2	37	39	0	7	12
TFLX	4	0	1	32	27	18	2	0	17[b]	[c]	
FLRX	0	3	1	0	0	0	20	54	4	1	18
SPFX	4	0	1	17	24	37	6	2	0	4	6
LVFX	3	1	0	1	25	50	4	4	3	0	10
GFLX	4	0	7	43	29	5	3	0	3	4	3
MFLX	4	1	32	42	4	7	0	0	8	2	0

Abbreviation: NFLX, norfloxacin; ENX, enoxacin; CPFX, ciprofloxacin; TFLX, tosufloxacin; FLRX, fleroxacin; SPFX, sparfloxacin; LVFX, levofloxacin; GFLX, gatifloxacin; MFLX, moxifloxacin.

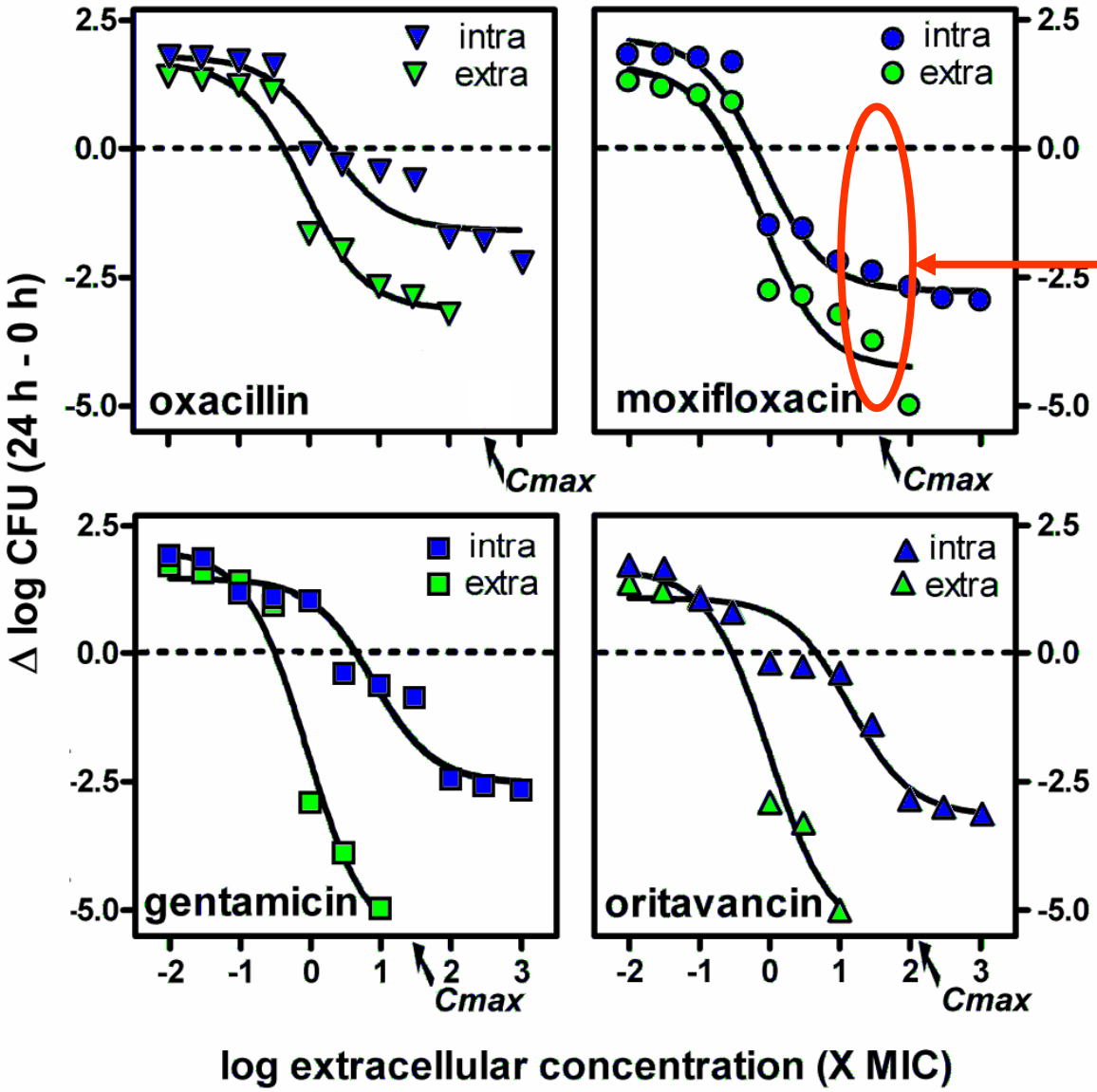
[a] The positions of breakpoints for resistance interpreted by the NCCLS are underlined. Breakpoints of MFLX and TFLX have not been established by the NCCLS.

[b] MIC: ≥64 mg/l.

[c] Not determined.

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

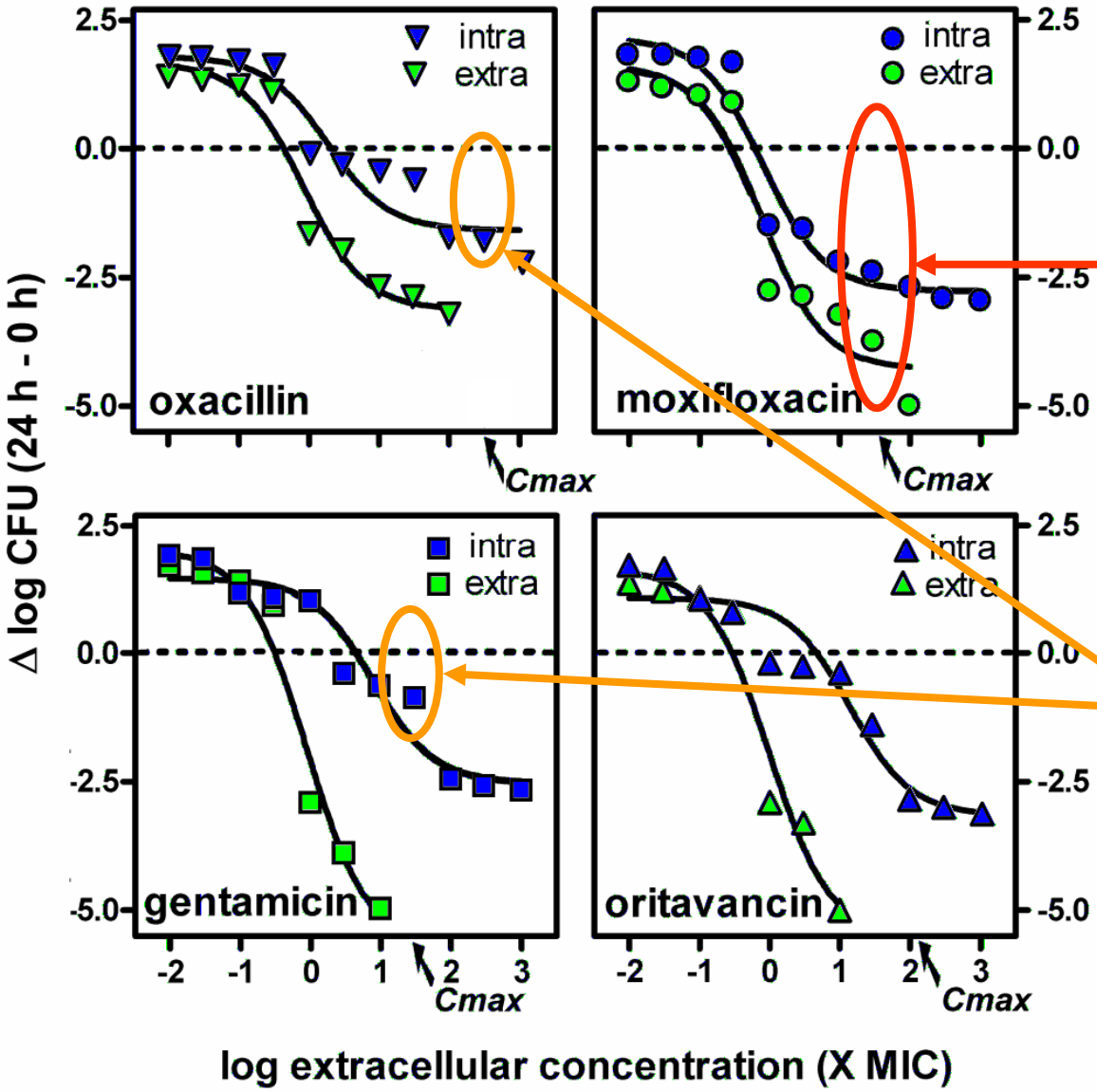
Moxifloxacin is very active against intracellular MSSA …



2.5 log decrease at C_{max} (4.5 mg/L)

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

Moxifloxacin is very active against intracellular MSSA …

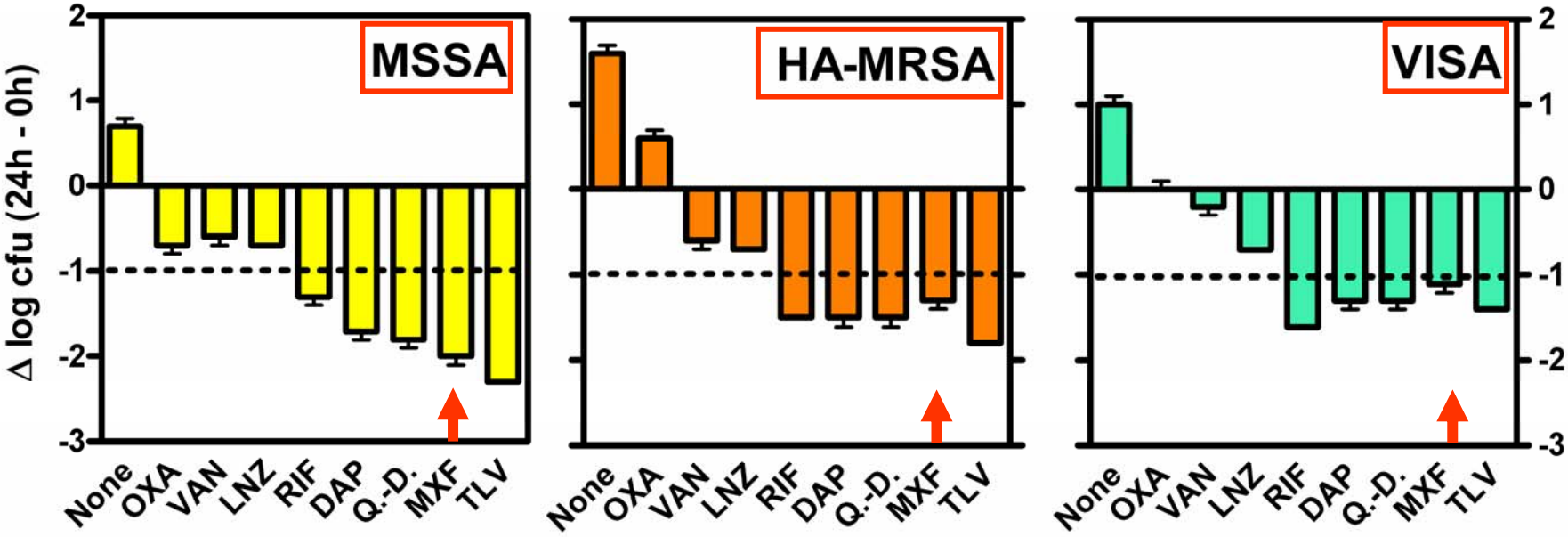


2.5 log decrease at C_{max} (4.5 mg/L)

which is much better than oxacillin or gentamicin

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

Moxifloxacin is also active against intracellular HA-MRSA and VISA …



Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

The main classes…

Those already approved …

- tigecycline
- daptomycin
- moxifloxacin

Those in late phase III …

- **new quinolones …**
- **ceftobiprole (or the new anti-MRSA cephalosporins)**
- **the new lipoglycopeptides: the real one (telavancin,…) and the not so novel (dalbavancin)**

Those which will probably fail …

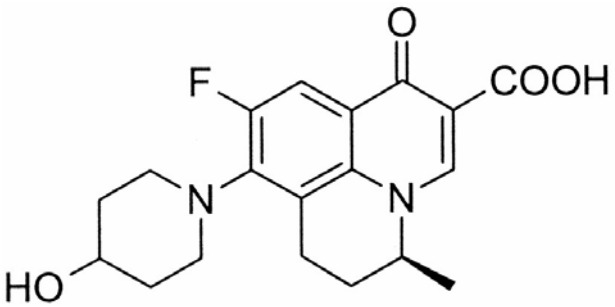
- new oxazolidinones …

And those which were approved and forgotten but may come back…

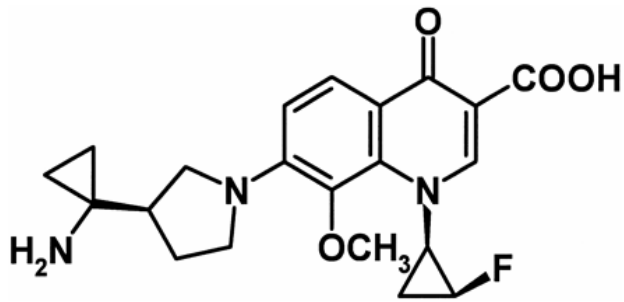
- SYNERCID ?
- arbekacin …

New quinolones : can we still do better ?

quinolone	Range of MIC of MRSA	MIC 50	MIC 90
Moxifloxacin	0.03-32	1-2	4-16
WCK 771	0.015-4	0.5	1
DX 619	0.008-2	0.125	1



WCK 771,
a new quinolone in clinical trials

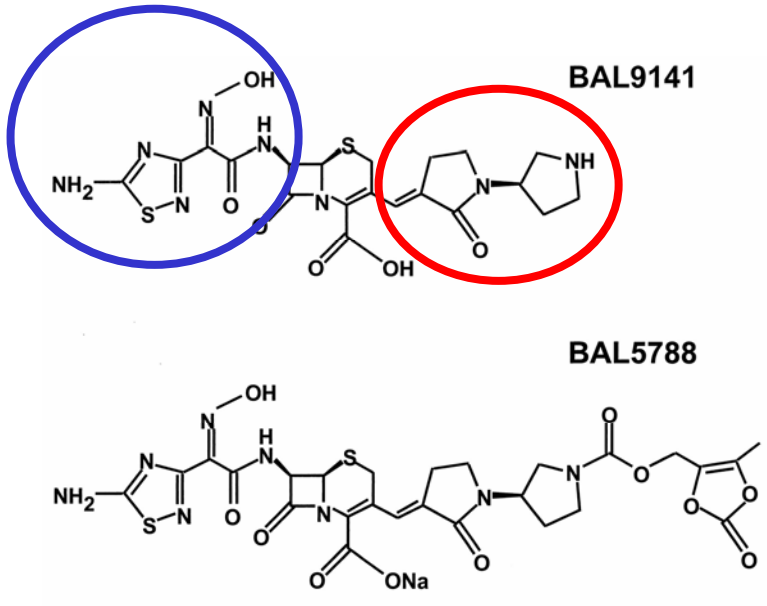


DK 619,
a new desquinolone in preclinical trials

Patel *et al.,* AAC (2004) 48:4754-4761Bogdanovich *et al.,* AAC. (2005) 49:3325-33.

Anti-MRSA cephalosporins (ceftobiprole)…

- Highly resistant to beta-lactamases
- High affinity for PBP2a



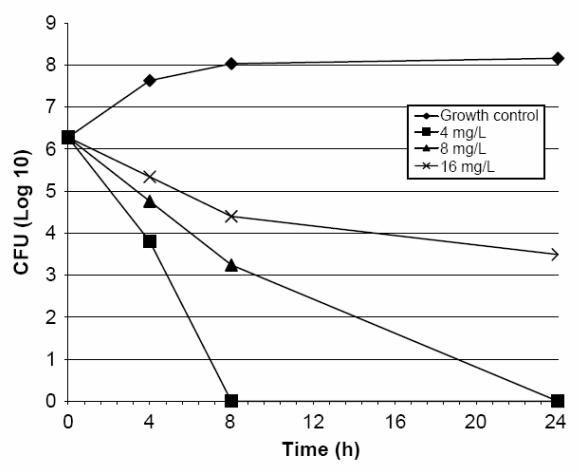
Ceftobiprole and its prodrug

- developed through Basilea Pharmaceutica Ltd. and Cilag AG International
- will be marketed by Ortho-McNeil Pharmaceutical, Inc. in the U.S. and by Janssen-Cilag in Europe, Japan and China.

Entenza *et al*., Antimicrob Agents Chemother. (2002) 46:171-7.

Anti-MRSA cephalosporins (ceftobiprole)…

- MIC range: 0.25-0.5 mg/L for MSSA
  0.25-2 mg/L for MRSA
  0.5-2 for SCV
- bactericidal
- synergistic with aminoglycosides



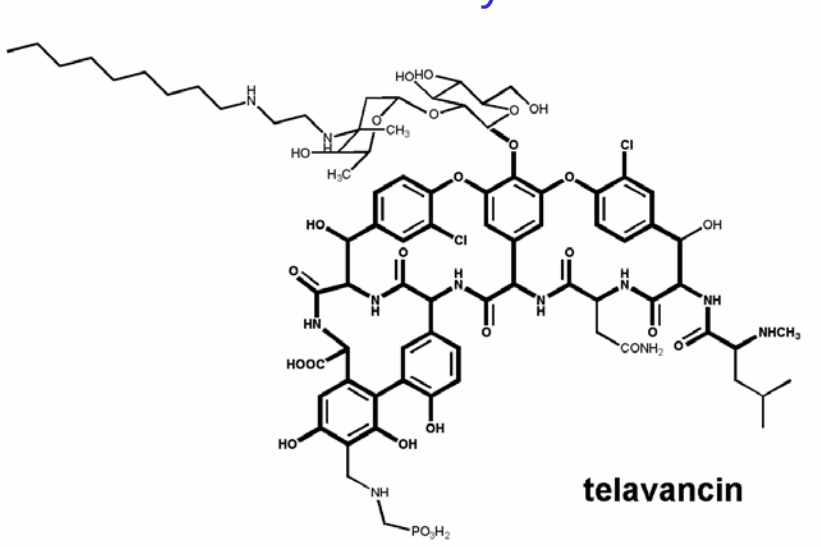
- FDA fast track designation for
  - the treatment of complicated skin and skin structure infections due to MRSA
  - a second indication in the treatment of hospital-acquired (nosocomial) pneumonia, including ventilator-associated pneumonia due to suspected or proven MRSA

- Excellent tissue penetration and powerful activity in models of
  - osteomyelitis
  - foreign-body infection
  - aortic valve endocarditis

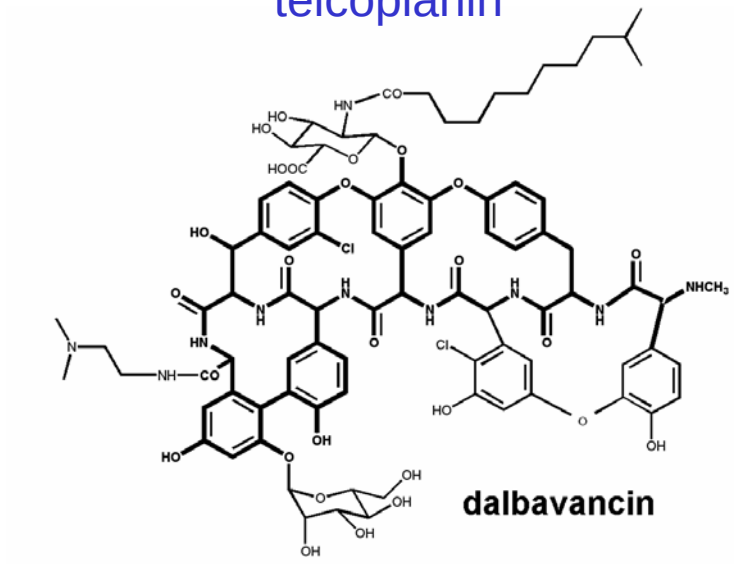
new glycopeptides (dalbavancin-telavancin)…

Hemi-synthetic derivatives derived from

vancomycin



teicoplanin

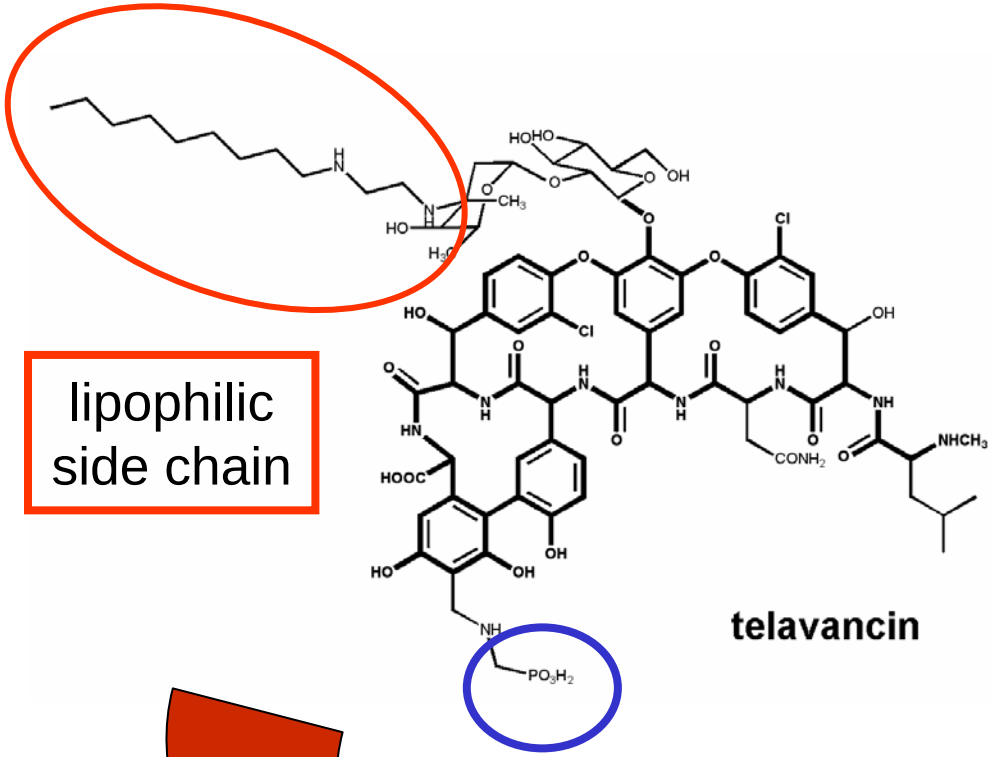


Phase III,
Theravance → Astellas

Marketed,
Vicuron → Pfizer

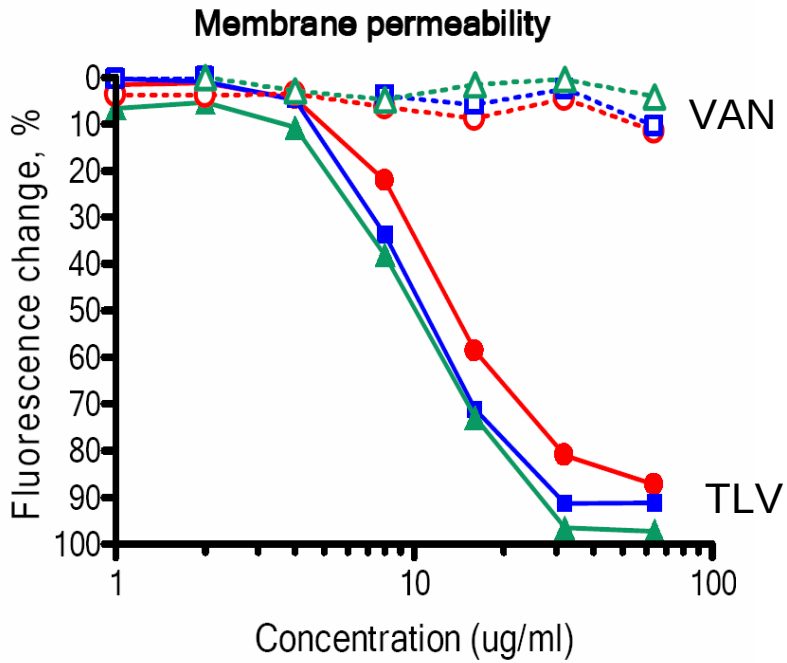
Van Bambeke: Current Opinion in Pharmacology (2004) 4:471-478 , 2005

Telavancin…



lipophilic side chain

polar group



this causes increase in bacterial membrane permeability

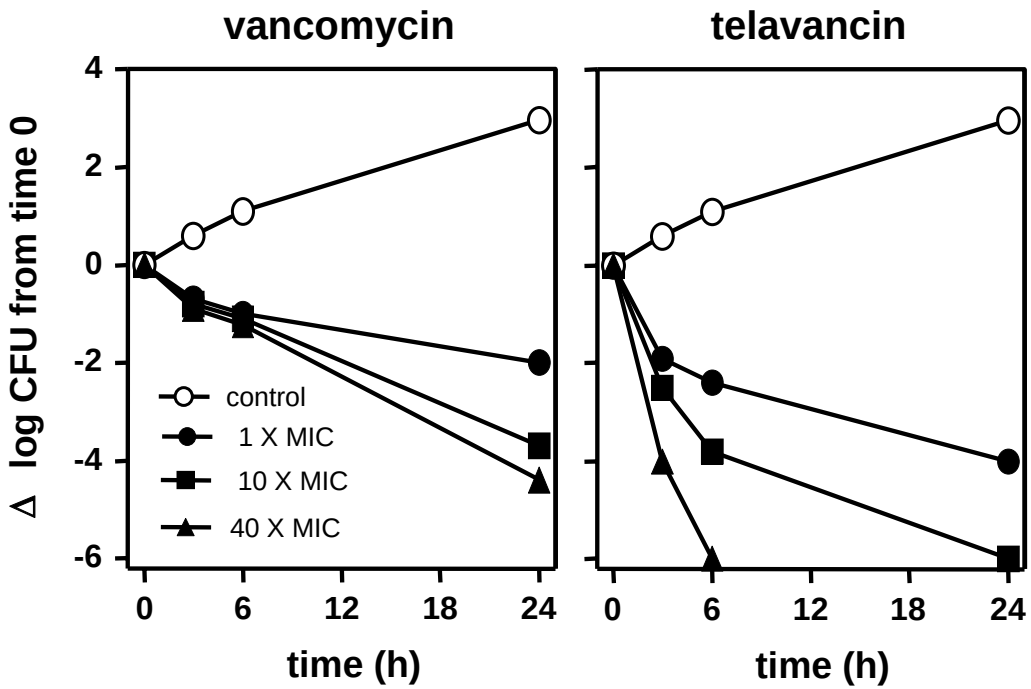
Higgins *et al*., Antimicrob Agents Chemother. (2005) 49:1127-34

Telavancin…

New pharmacodynamic profile due to new mode of action …

➔ strong <u>concentration-dependent</u> bactericidal effect

extracellular

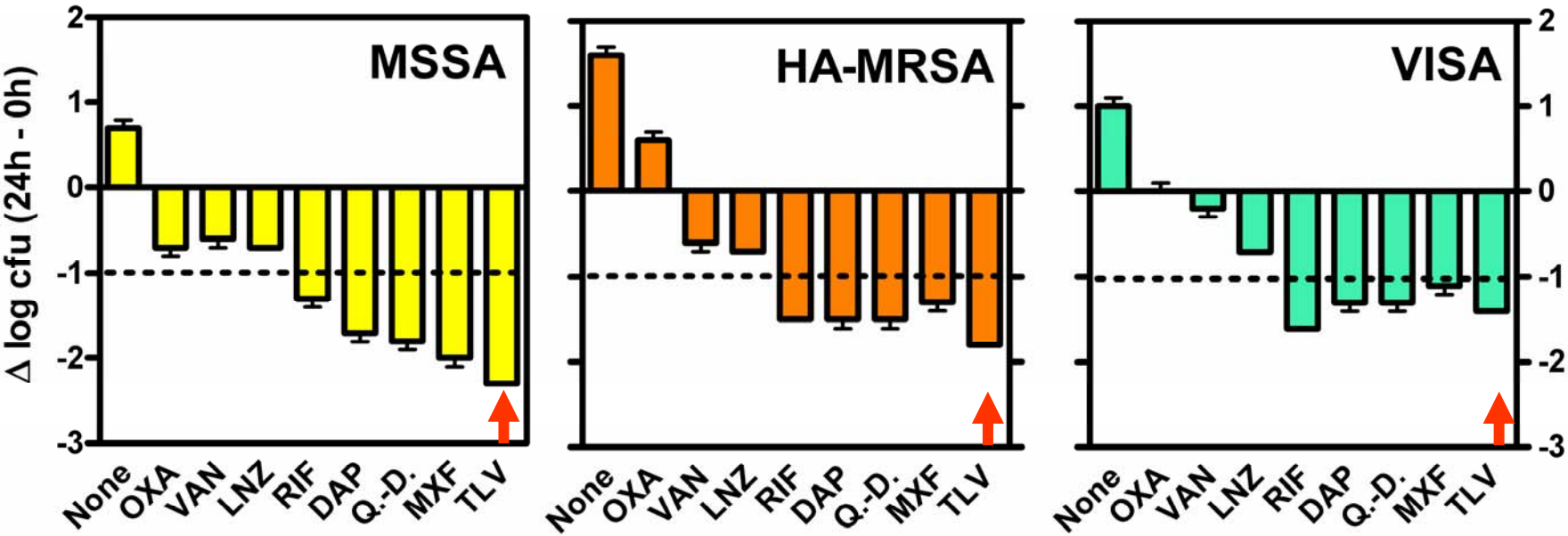


Barcia-Macay *et al.*, unpublished

Telavancin…

Cellular accumulation (and distribution in pahgolysosomes) …

➔ good intracellular activity



Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

Microbiology, pharmacokinetics and clinical indications under investigation for the new glycopeptides (dalbavancin-telavancin)…

	telavancin	dalbavancin
MIC MRSA VISA VRSA	< 0.06-2 2 2	0.06-1 2 **inactive**
Half-life	7 h → once-a-day	149 h → once-a-week !!
Tissular and cellular distribution	yes	yes
activity	skin & soft tissue HAP models of endocarditis	skin and soft tissue HAP catheter-related bloodstream infections

The main classes…

Those already approved …

- tigecycline (the tetracyclines are back…)
- daptomycin
- moxifloxacin

Those in late phase III …

- new quinolones …
- ceftobiprole (or the new anti-MRSA cephalosporins)
- the new lipoglycopeptides: the real one (telavancin,…) and the not so novel (dalbavancin)

Those which will probably fail …

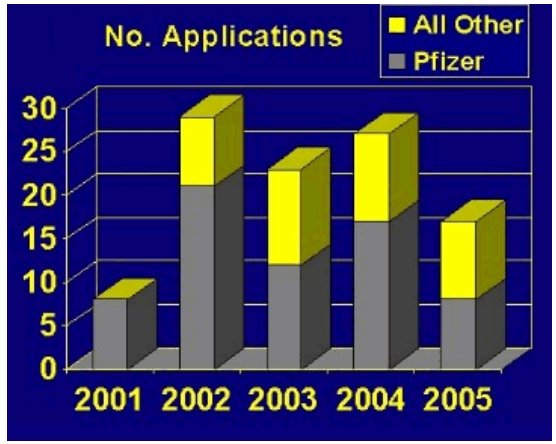
- **new oxazolidinones …**

And those which were approved and forgotten but may come back…

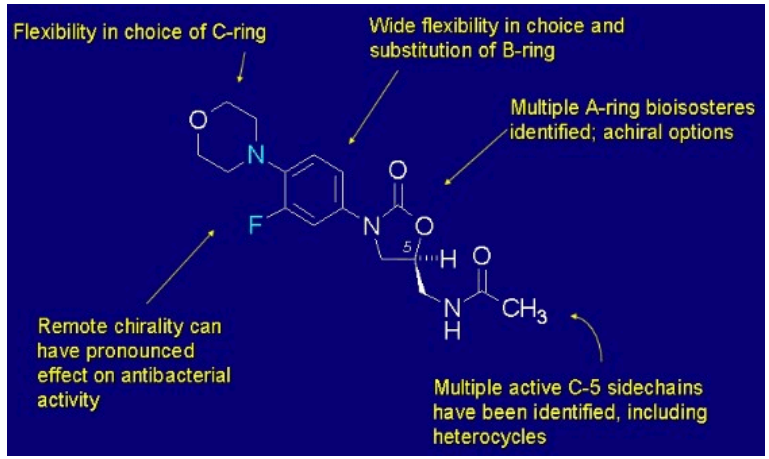
- SYNERCID ?
- arbekacin …

Oxazolidinones (linezolid…)…

- Linezolid:
  - resistance increases… and will continue because of increased use of LNZ against MRSA…
  - lower MIC desirable for PK/PD reasons…
  - neuropathy: limits therapy duration…
  - myelosuppression, MOA inhibition…



- Present patent situation for oxazolidinones: marked rise in 2002-2005
  (Pfizer, AstraZeneca/Syngenta, Bayer, DuPont, J&J, others…),
  BUT …
  - various analogues tested …
  - modest to fair improvements in MIC (0.12 mg/L for VIC104203)
  - only marginal safety improvements obtained
  - no clinical candidate so far …



ICAAC 2005

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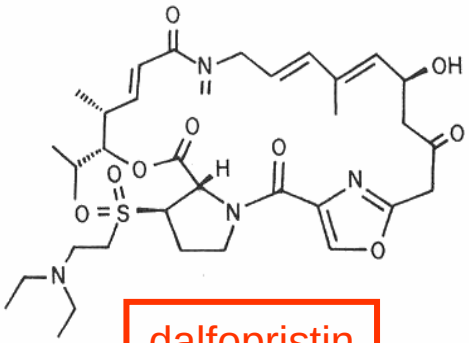
And those which were approved and forgotten but may come back…

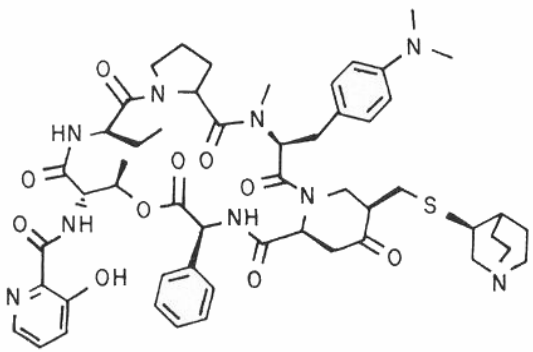
- **SYNERCID ?**
- **arbekacin …**

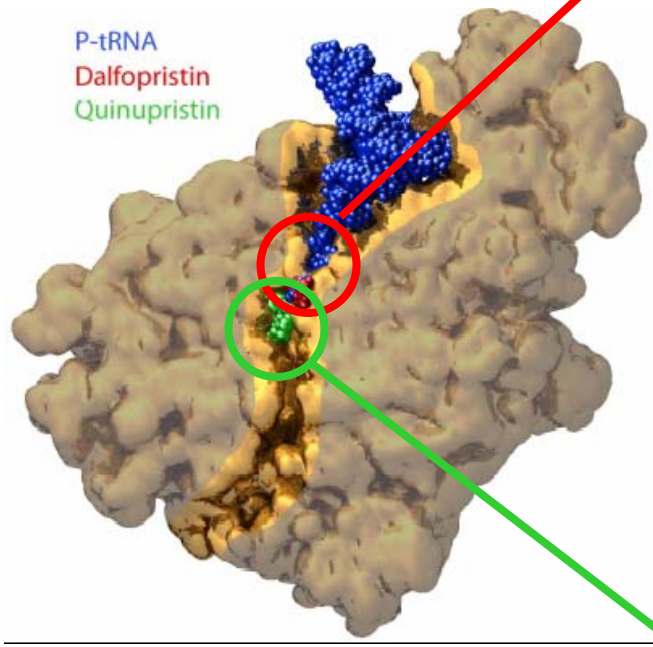
SYNERCID® = quinupristin + dalfopristin



dalfopristin

quinupristin





S_A blocks peptide bound formation

SYNERGY

S_B blocks the path of the nascent peptide

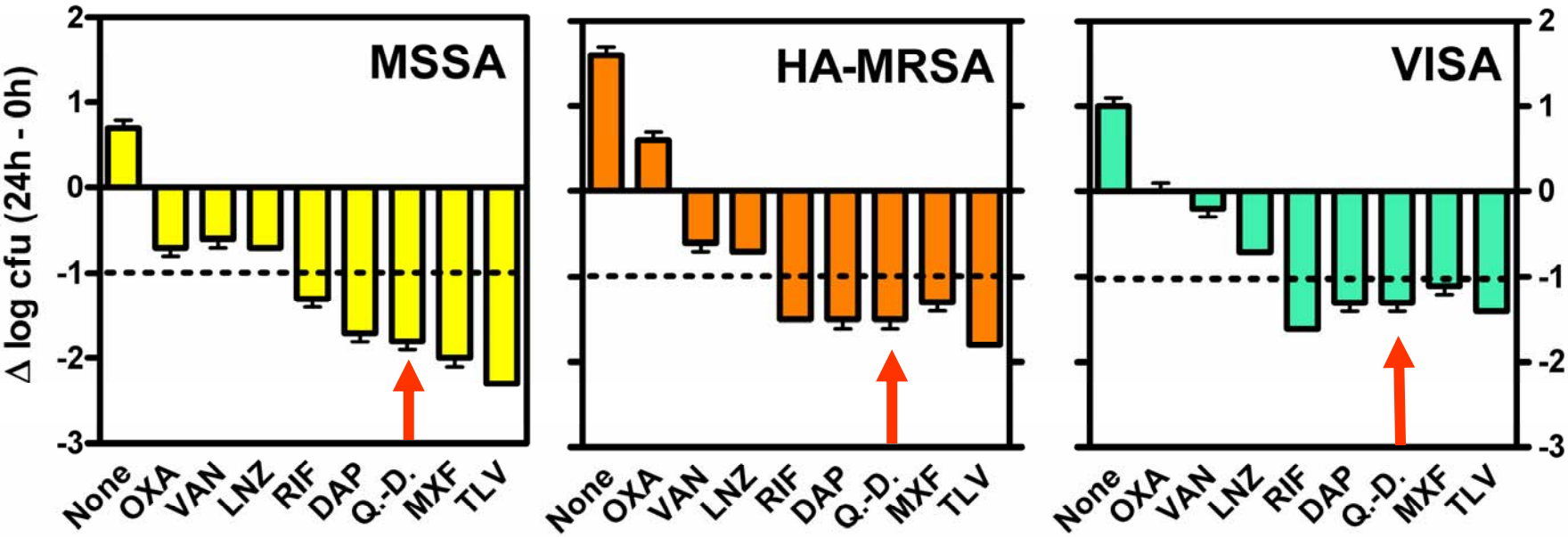
Harms *et al,* BMB Biol (2004) 2:4

SYNERCID®

- originally discovered and developed by Rhône-Poulenc (France)
- European (mutual recognition) and FDA approval in the late 90's for:
  - complicated skin and soft tissues infections by MSSA/strepto
  - bacteremia due to VR *E. faecium* (fast track at FDA)
  - efficacy also desmonstrated in nosocomial pneumonia (= vanco; lower success if MRSA in both groups)
- abandoned in early 2000's because of
  - side effects (rash; infusion-site inflammation; pain and edema; thrombophlebitis …) and inhibition of cytochrome P450 3A4
  - difficulties of production in large quantities
  - loss of interest after the merge of Rhône-Poulenc with Hoechst-Marion-Roussel to form AVENTIS…

- presently commercialized at a low scale by
  - Nordic Pharma in Europe
  - King Pharmaceuticals in the US

SYNERCID® does not behave too badly for intracellular *S. aureus*…

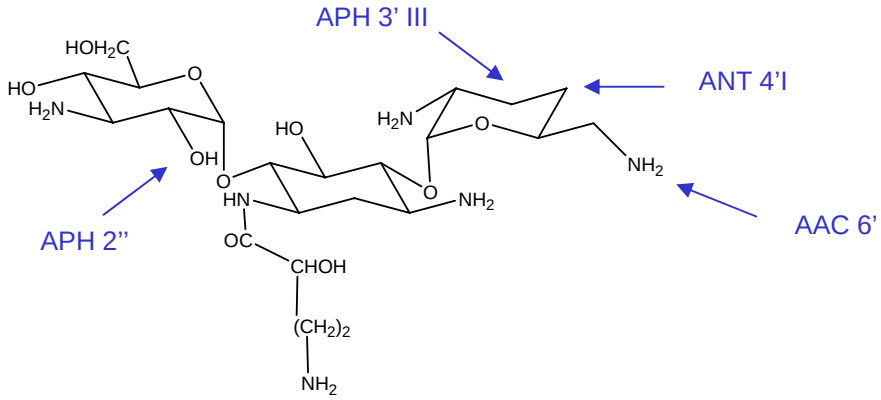


ISSSI 2006

Lemaire et al., ISSSI 2006 – Sept. 3-6, 2006

and why not an aminoglycoside ?

Arbekacin



remains active against most MRSA producing inactivating-enzymes (including bi-functionals)

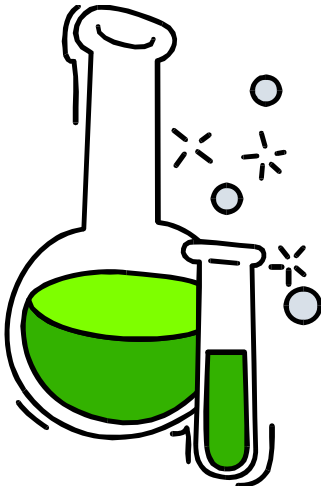
TABLE 3. AME and aminoglycoside resistance

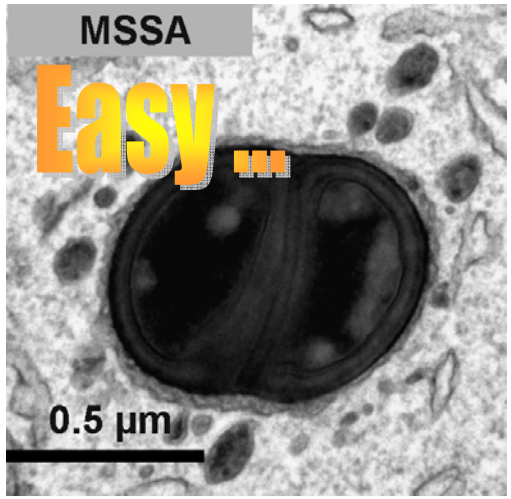
AME gene present			Total no. of strains	% of isolates resistant to[a]:					
aac(6')-aph(2")	*ant(4')-I*	*aph(3')-III*		Gm (8)	Tob (8)	Lvdm (256)	Sm (32)	Km (32)	Abk (8)
+	+	+	6	100	100	100	100	100	0
+	+	−	183	100	100	0	8.2	100	11.5
+	−	+	18	100	100	100	100	100	5.6
+	−	−	28	100	82.1	0	0	100	7.1
−	+	+	3	0	100	100	100	100	0
−	+	−	130	0	100	0	3.8	100	0
−	−	+	7	0	0	100	100	100	0
−	−	−	6	0	0	0	0	0	0
Total			381	61.7	95.3	8.9	14.2	98.4	6.3

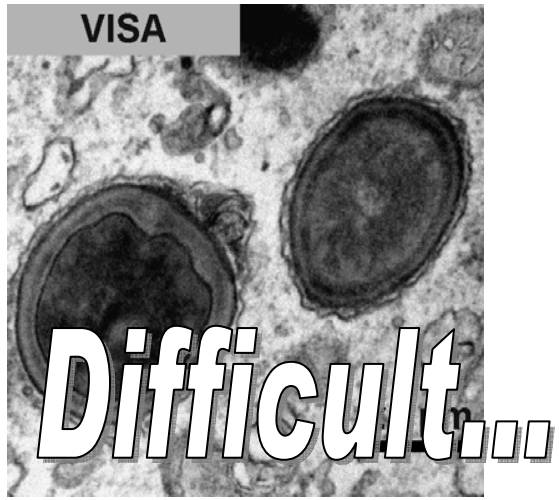
[a] Gm, gentamicin; Tob, tobramycin; Lvdm, lividomycin; Sm, streptomycin; Km, kanamycin; Abk, arbekacin; the cutoff MIC (in micrograms per milliliter) is given in parentheses.

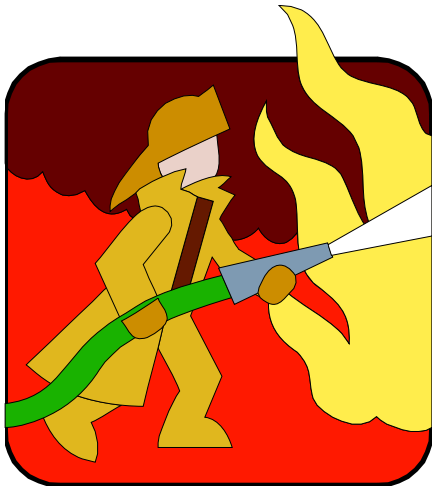
Ida *et al*., J. Clin.Microbiol., (2001) 39: 3115-3121

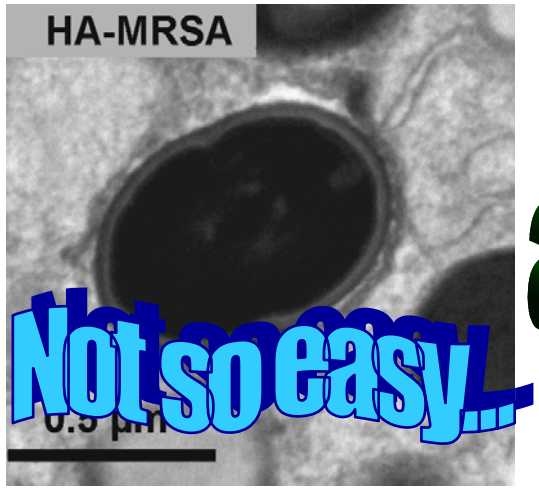
Will this be successful ?











Where can you find more information ?

- Gemmell *et al.* Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK.
  J Antimicrob Chemother. 2006 Apr;57(4):589-608.
- Appelbaum. The emergence of vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus.
  Clin Microbiol Infect. 2006 Mar;12 Suppl 1:16-23.
- Brown *et al.* Guidelines for the laboratory diagnosis and susceptibility testing of methicillin-resistant Staphylococcus aureus (MRSA).
  J Antimicrob Chemother. 2005 Dec;56(6):1000-18. Epub 2005 Nov 17. Review.
- Schmidt-Ioanas *et al.* New antibiotics for the treatment of severe staphylococcal infection in the critically ill patient.
  Curr Opin Crit Care. 2005 Oct;11(5):481-6.
- Appelbaum & Jacobs. Recently approved and investigational antibiotics for treatment of severe infections caused by Gram-positive bacteria.
  Curr Opin Microbiol. 2005 Oct;8(5):510-7. Review.
- Van Bambeke *et al.* Glycopeptide antibiotics: from conventional molecules to new derivatives. Drugs. 2004;64(9):913-36.

These slides will be available on http://www.facm.ucl.ac.be