Orthopaedica Belgica 2013

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Antibiotics in bone and joint infections

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ISAP

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

LDRI LOUVAIN DRUG RESEARCH INSTITUTE

Antibiotics recommended in bone and joint infections

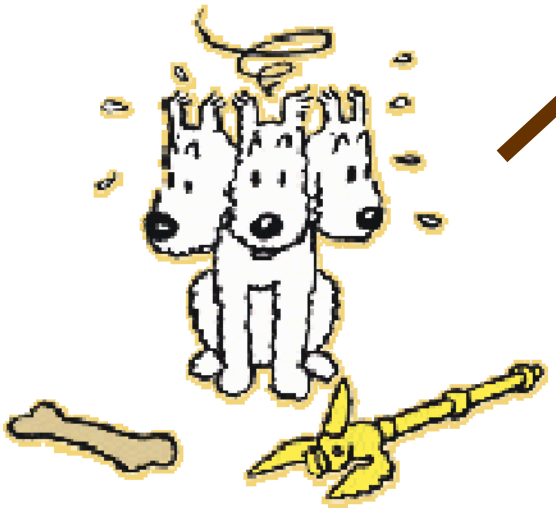
microorganisms	Preferred treatment	Alternative treatment
MSSA	nafcillin-cefazolin-ceftriaxone	vancomycin-daptomycin-linezolid
Enteroccoci; Pen-S	penicillin G-ampicillin	
MRSA	vancomycin	daptomycin-linezolid
Enteroccoci; Pen-R		
β-hemolytic streptococci	penicillin G-ceftriaxone	vancomycin
Propionibacterium		clindamycin-vancomycin
P. aeruginosa	cefepime-meropenem	ciprofloxacin-ceftazidime
Enterobacter spp	cefepime-ertapenem	ciprofloxacin
Enterobacteriacae	IV β-lactam-ciprofloxacin	

IDSA Guidelines; CID (2013) 56: e1-25

Pharmacologic criteria for antibiotic selection

PHARMACOKINETICS

PHARMACODYNAMICS



SPECIFIC FORMS OF INFECTION

SAFETY PROFILE

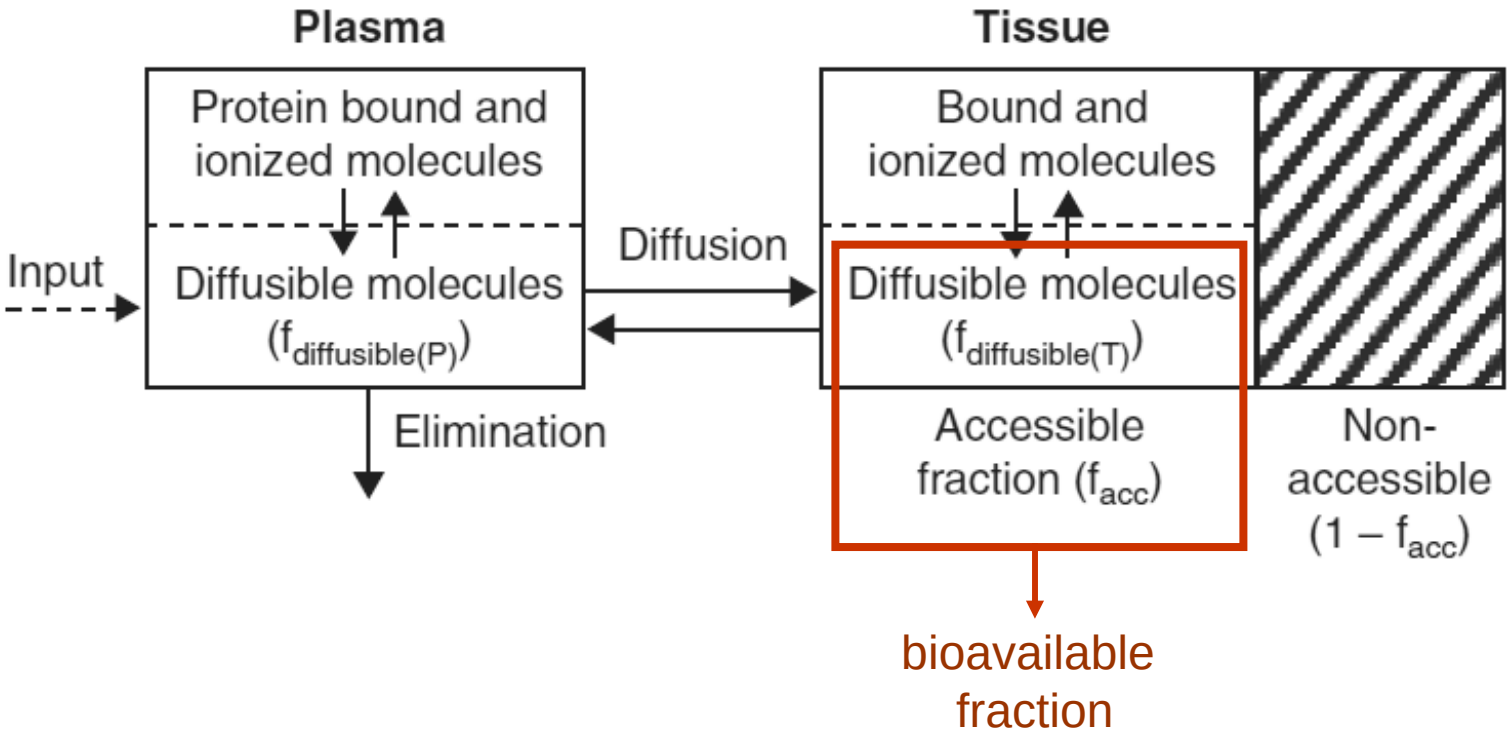
http://www.tintin.com/journal/journal/00757/C07%2058%20A.jpg

Pharmacokinetics

Herge

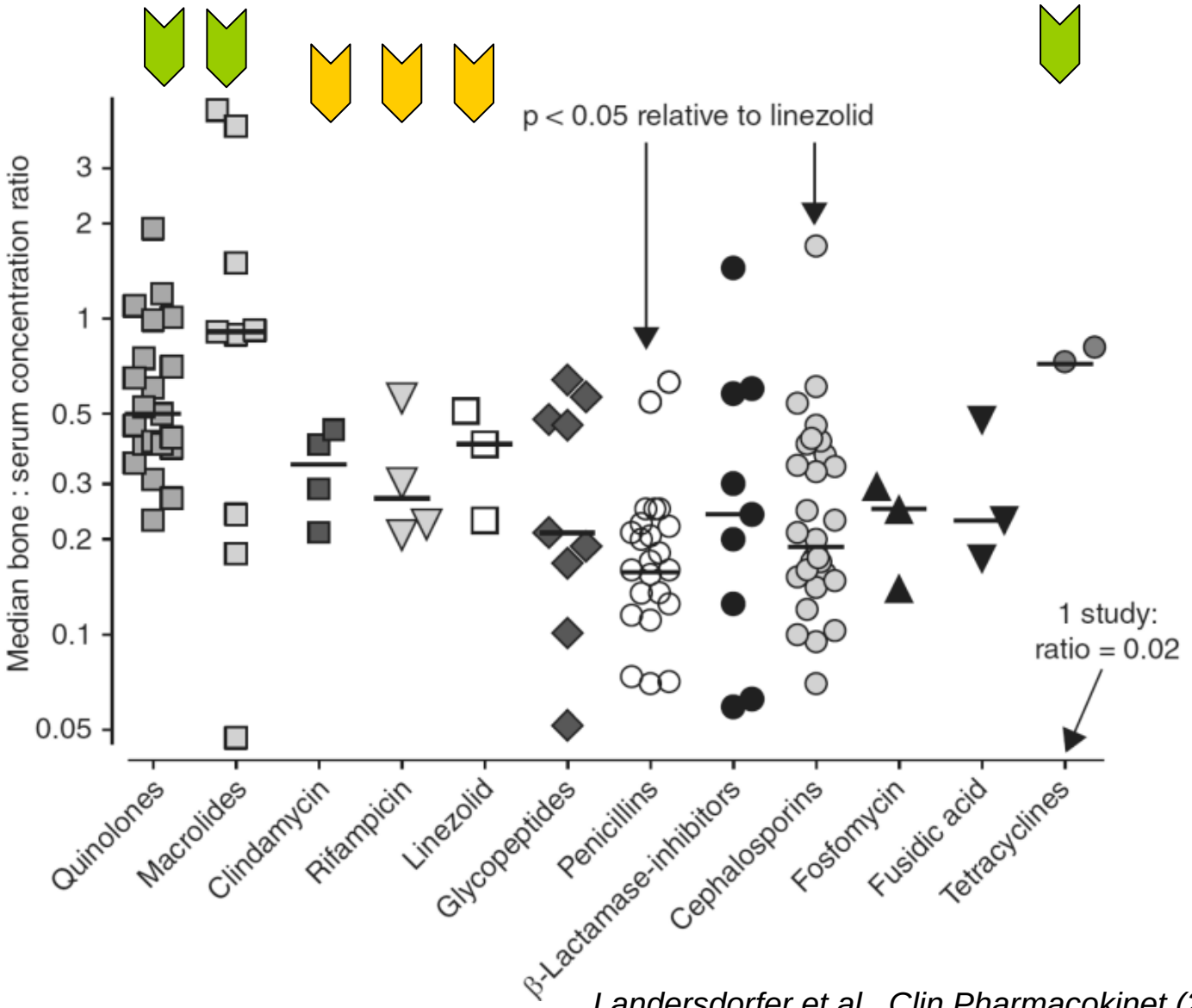
http://quotiriens.blog.lemonde.fr/files/2011/09/milou-sceptre.jpg

Tissue penetration



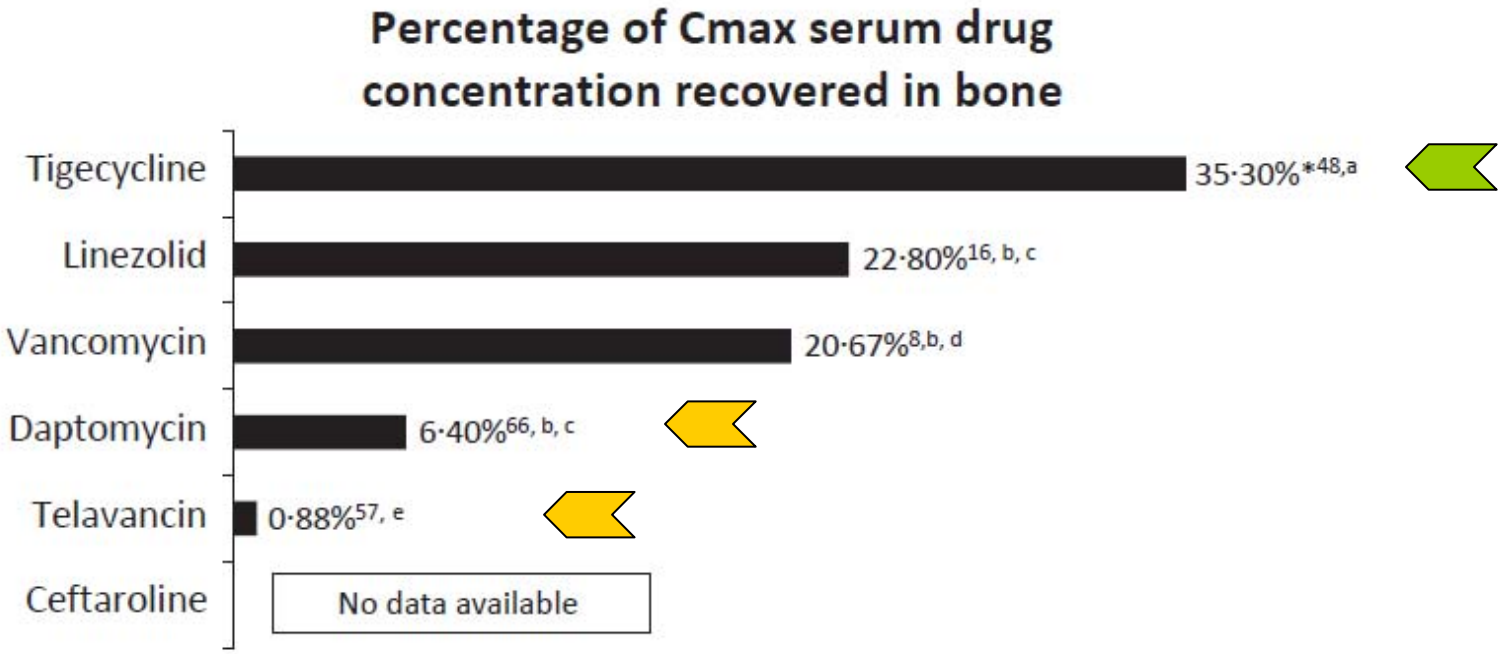
Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

Tissue penetration



Landersdorfer et al., Clin Pharmacokinet (2009) 48: 89-124

Tissue penetration
what about more recent molecules ?



Moenster et al., J Clin Pharm Ther. 2013; 38:89-96

Pharmacodynamics

J. Roba

www.fr.fnac.be

PK/PD:
more questions than answers

Do classical PD criteria apply in bone and joint infections ?

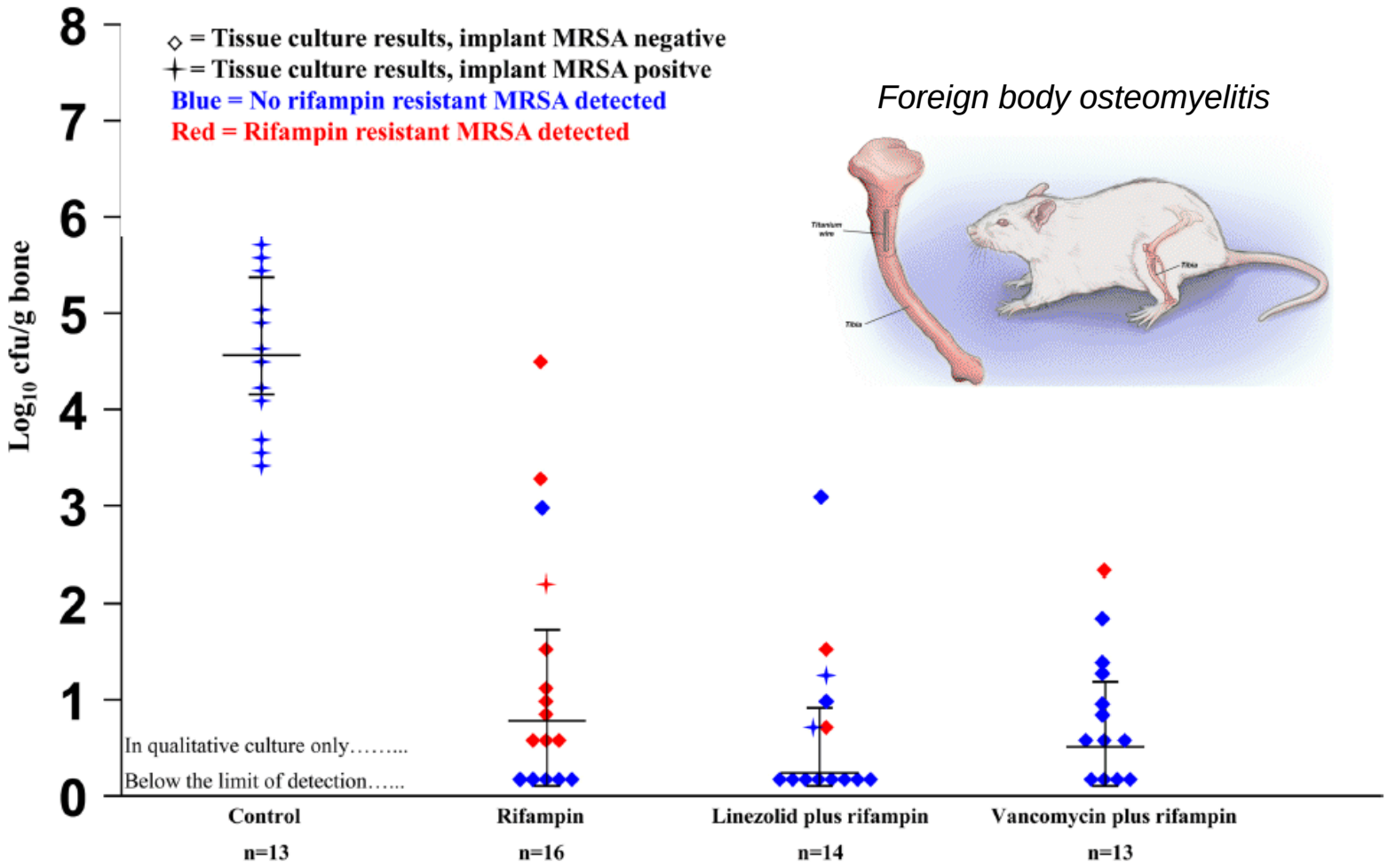
Bioavailable drug fraction ?

Cooperation with host defenses ?

Antibiotic expression of activity ?

Bacterial responsiveness ?

Antibiotic combinations



Foreign body osteomyelitis

combinations prevent emergence of resistance to rifampicin

Vergidis et al., AAC 2011; 55: 1182–6

Combinations with rifampicin

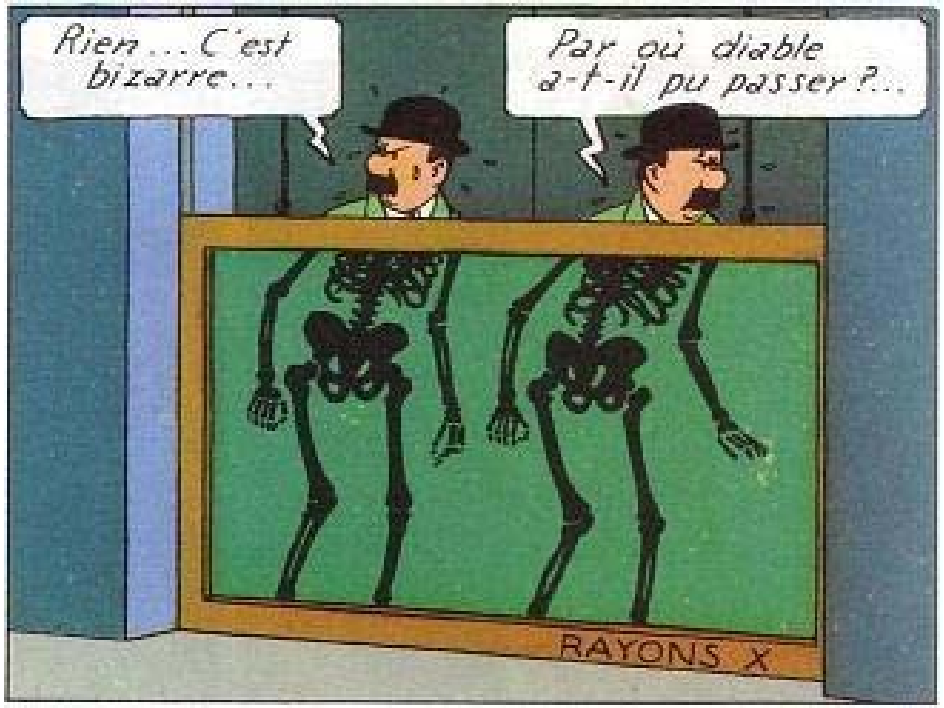
Antibiotic	In vitro (broth)	In the clinics*
cloxacillin, cefazolin	antagonism	= cloxacillin alone
vancomycin	synergy	= vancomycin alone
fluoroquinolone	antagonism	> fluoroquinolone alone
fusidic acid	indifference	= fusidic acid alone
clindamycin	synergy	90 % success
cotrimoxazole	antagonism	= cotrimoxazole alone
linezolid	indifference	90 % success
daptomycin	indifference	42 % success
cyclines	synergy	40 % failures

* different types of infection and evaluation criteria …

« checkerboard » not predictive of in vivo activity of combinations …

Coiffier et al., Revue du rhumatisme 2012; 79: 397–404

Specific forms of infection

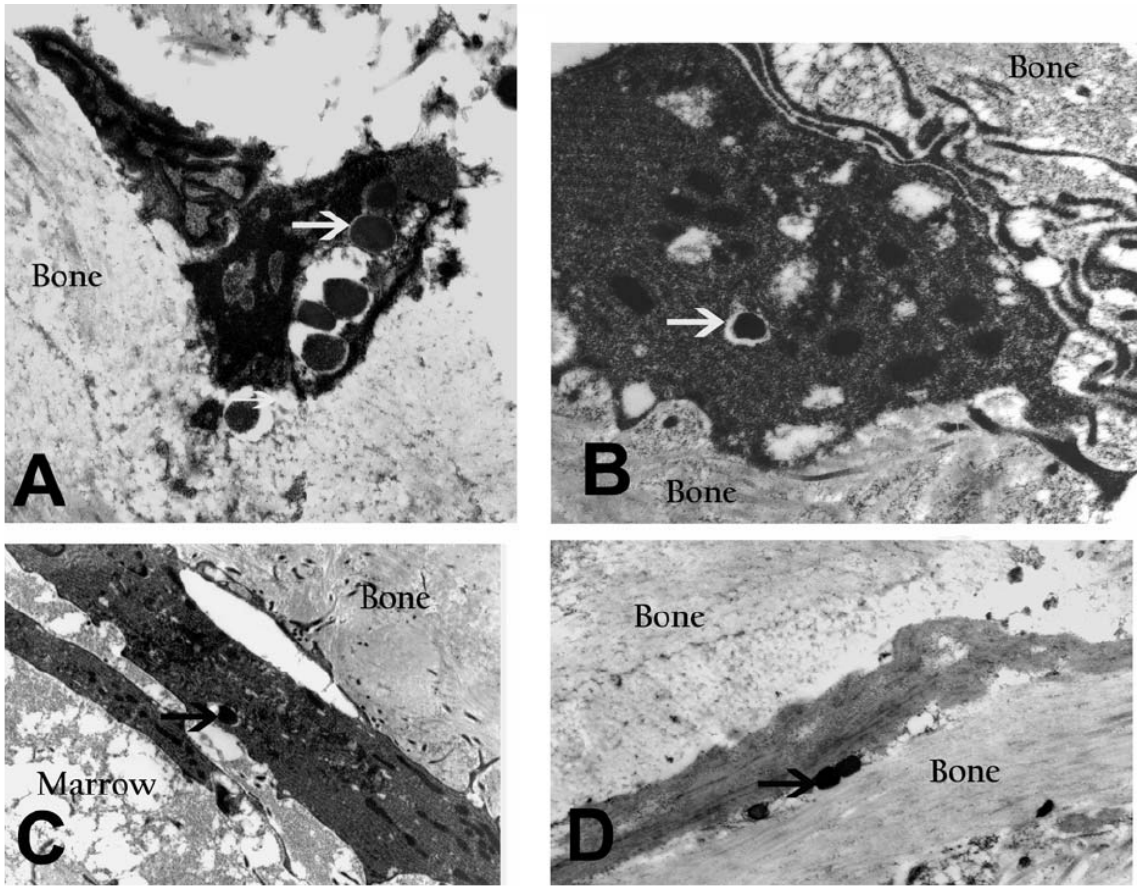


Hergé

http://24.media.tumblr.com/tumblr_m8q2lpiFtM1rq3prxo1_500.jpg

Intracellular survival

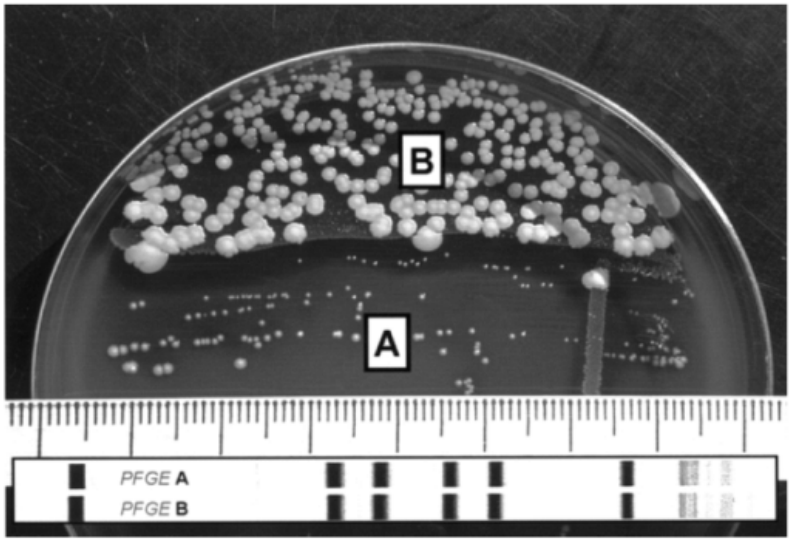
Evidence of an intracellular reservoir
in osteocytes (A,B), osteoblasts (C) and bone matrix
of a patient with recurrent osteomyelitis



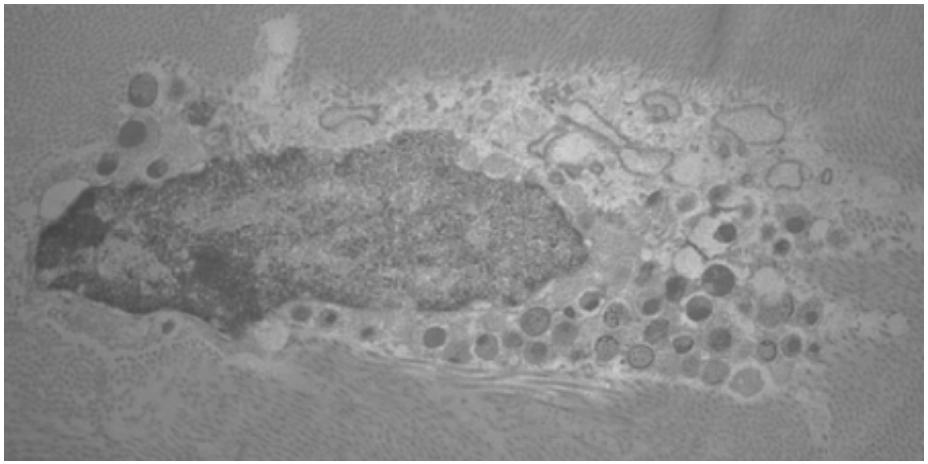
Bosse et al., J Bone Joint Surg Am. 2005; 87:1343-7

Small Colony Variants

Evidence of Small Colony Variants and of intracellular *S. aureus* after treatment failure * in patients with prosthetic joint infections



Small colony variant *(A)* and normal-phenotype *Staphylococcus aureus (B)* isolated from patient 1 on Columbia blood agar.

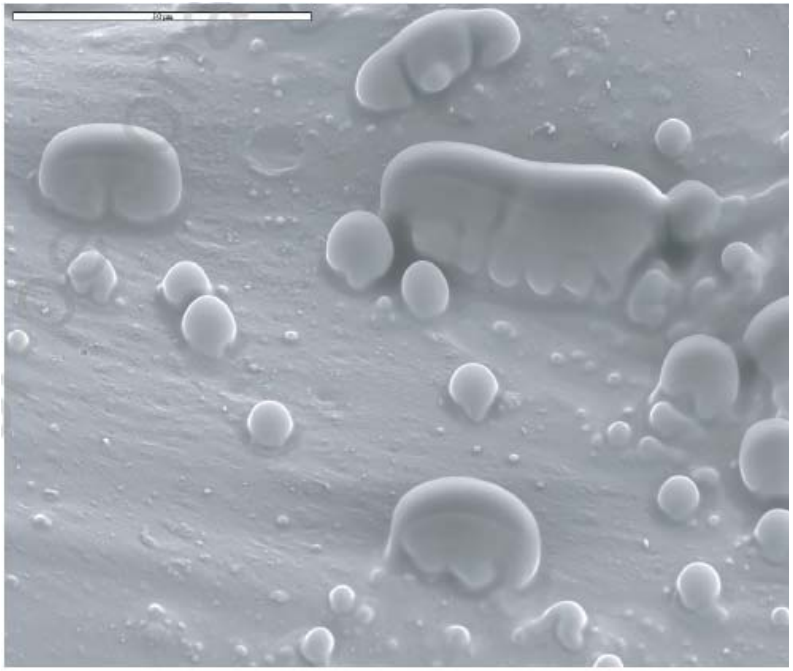


* Fluclox, CIP+ RIF, VAN + FEP

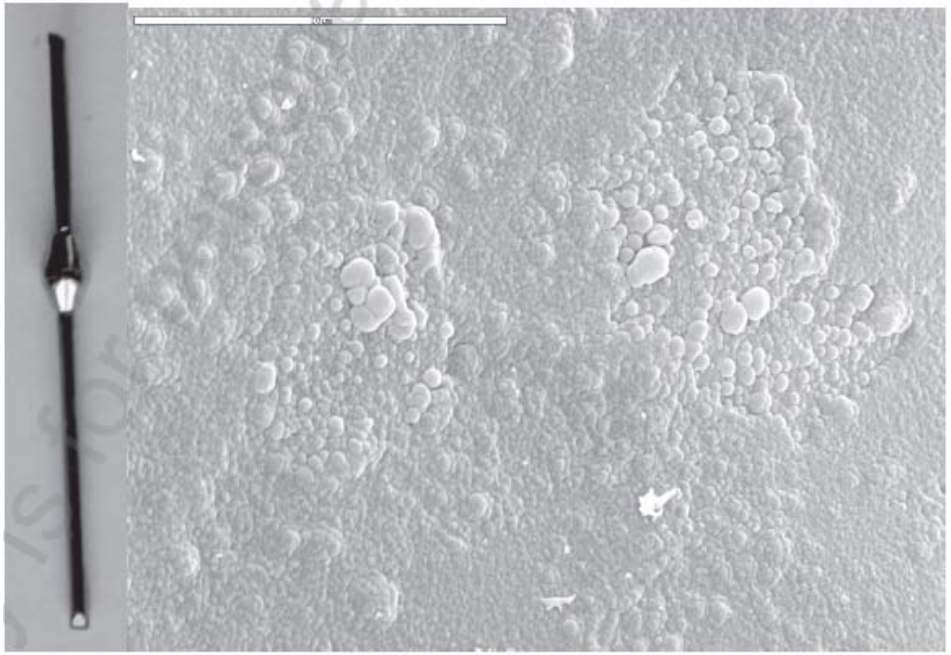
Sendi et al., Clin Infect Dis. 2006; 43:961-7

Biofilms

biofilm observed in electron microscopy on a bone sequester obtained from a patient with bone necrosis (*Enterobacter* sp.)

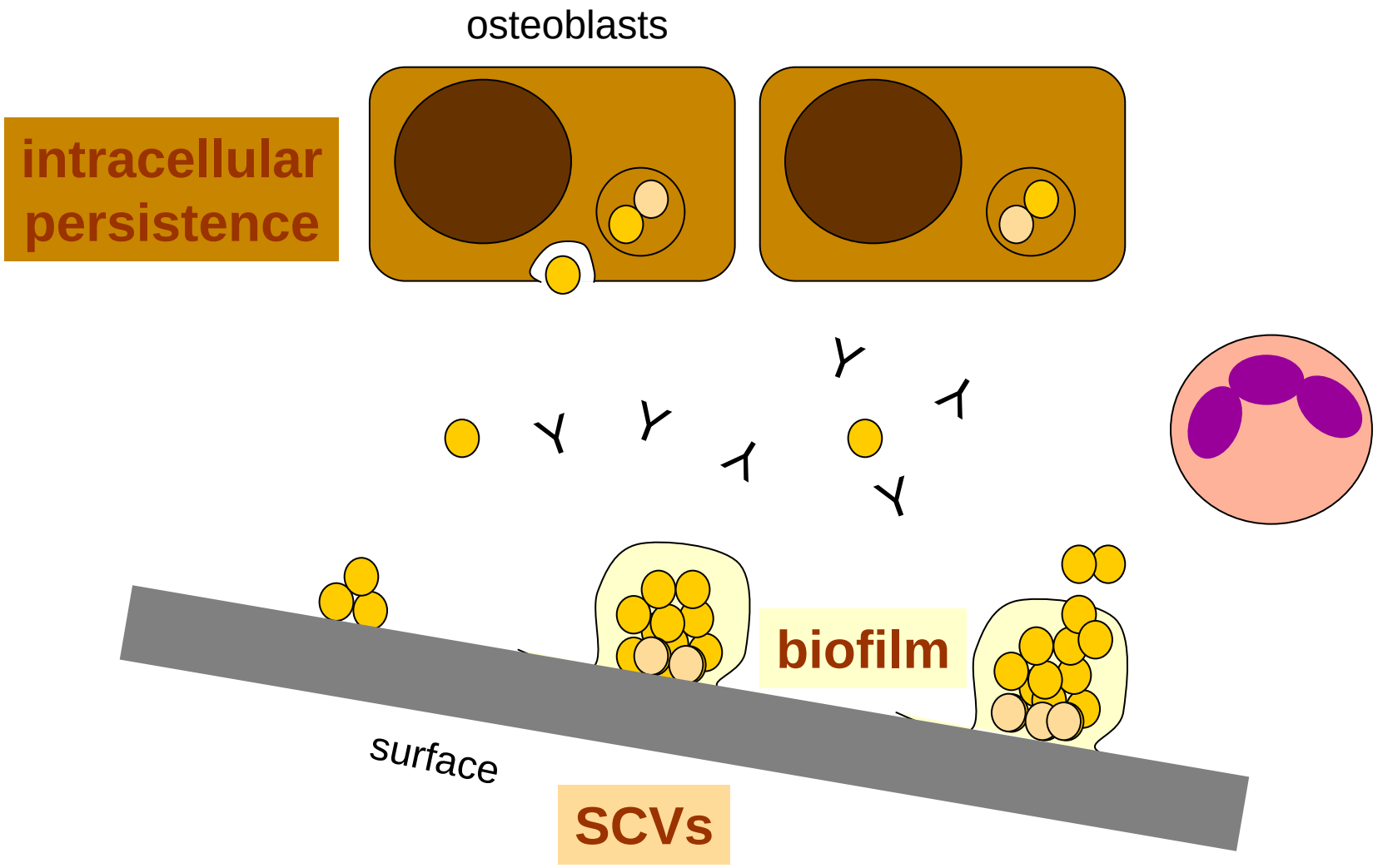


biofilm observed in electron microscopy on a steel component of an Ilizarov device obtained from a patient with clinical infection (*S. aureus*)



Bartoszewicz et al; Orttopediia Traumatologia Rehabilitacja 2007; 9:310-8

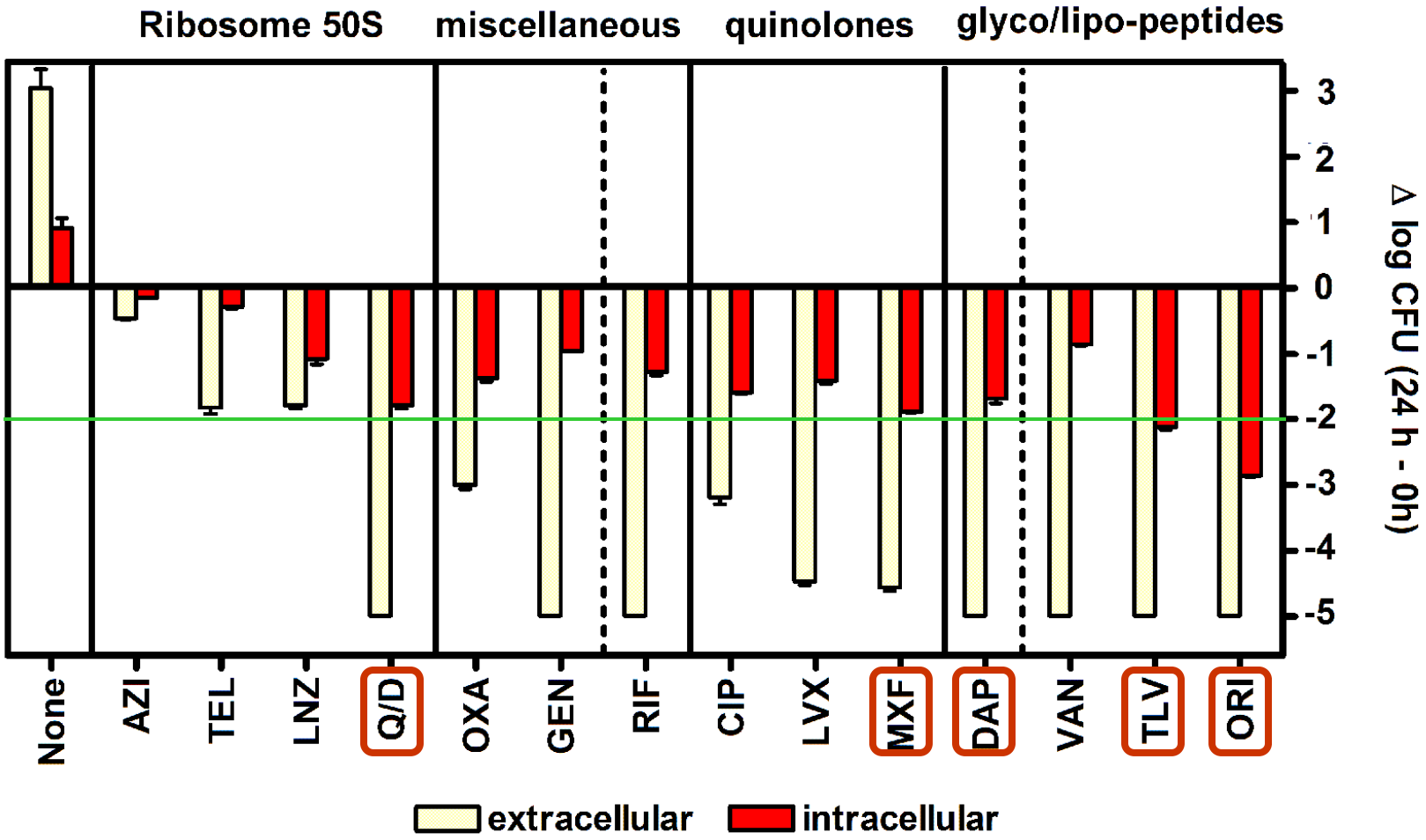
Three forms of persistent infections …



Based on Coiffier et al., Revue du rhumatisme 2012; 79: 397–404

Extracellular vs intracellular activity at Cmax

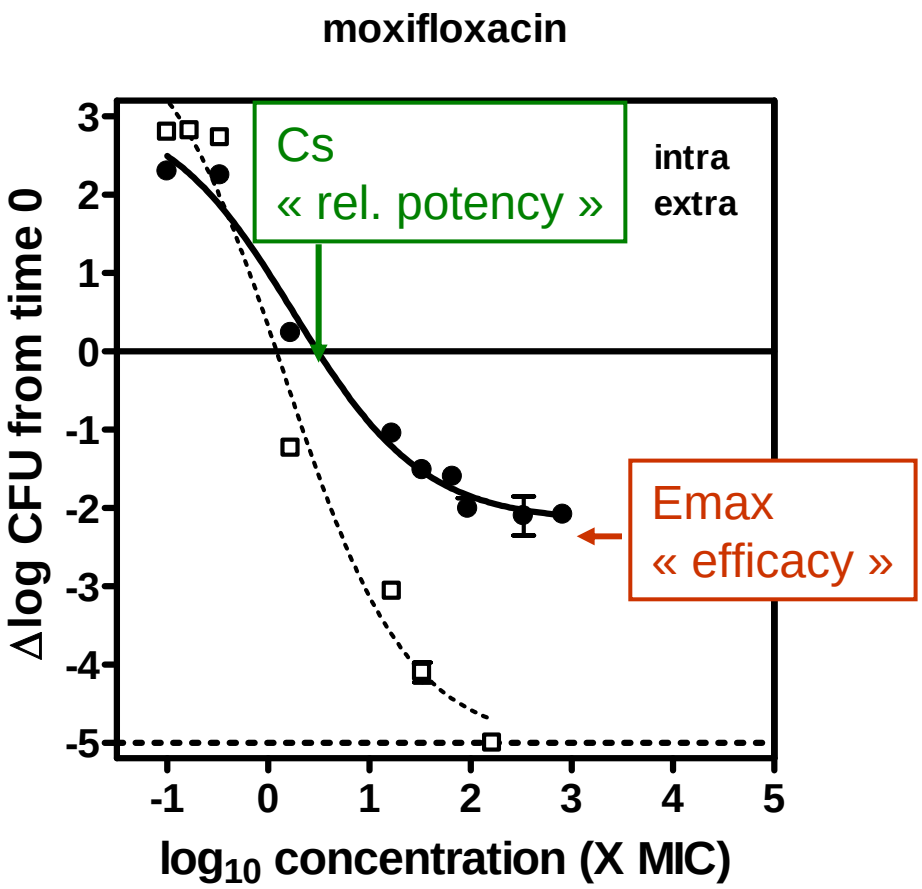
All antibiotics show reduced activity intracellularly against *S. aureus*



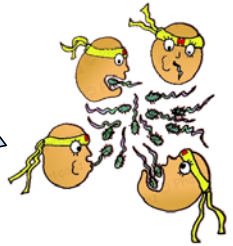
THP-1 monocytes,24 h, MSSA ATCC25923

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

A pharmacodynamic model to assess antibiotic intracellular activity



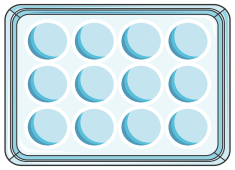
Opsonization
Culture medium +
human serum



Phagocytosis

Extracellular Wash
(Gentamicin 100 X MIC; ~1 h)

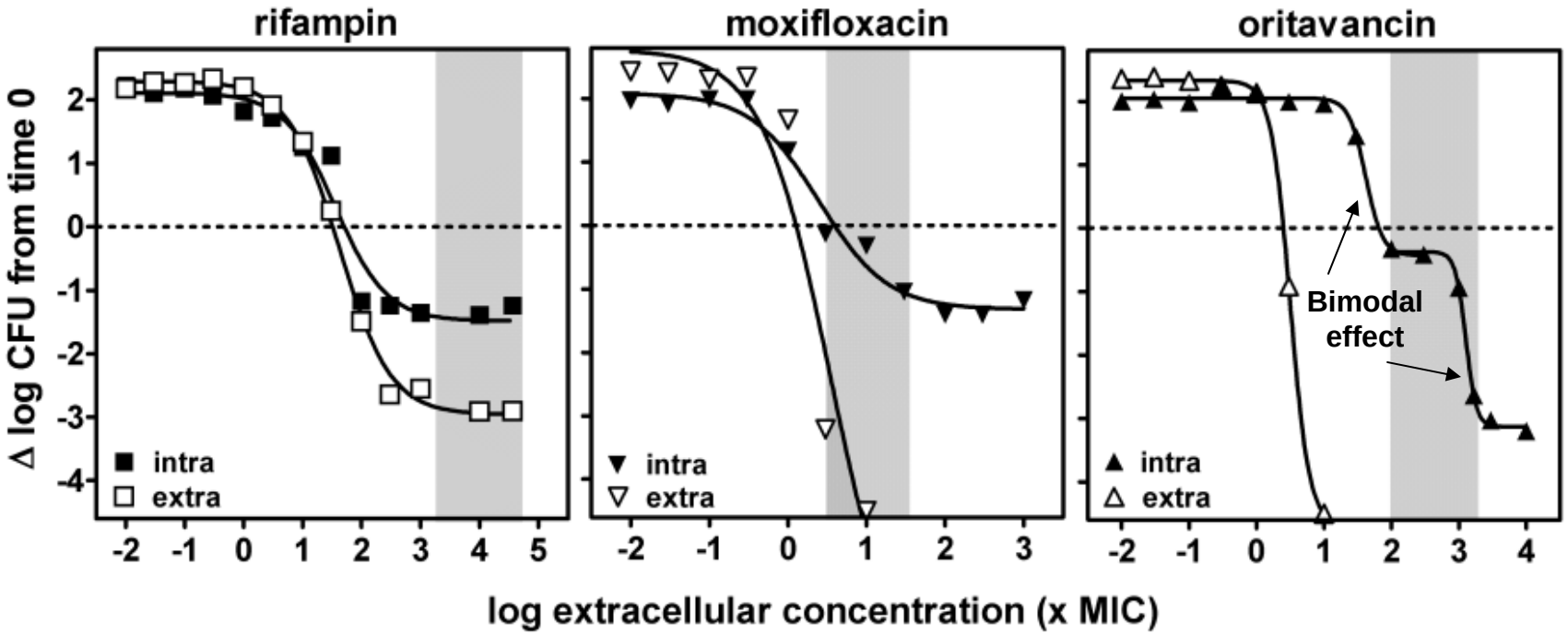
5 -10 x10^5 CFU/mg prot.
Time 0



Incubation (with antibiotics)
For up to 24 h
(control: Gentamicin 0.5 X MIC)

Lemaire et al., JAC 2011; 66:596-607

Dose-response curves of the 3 most active antibiotics against extra- and intracellular SCV (24 h of exposure)

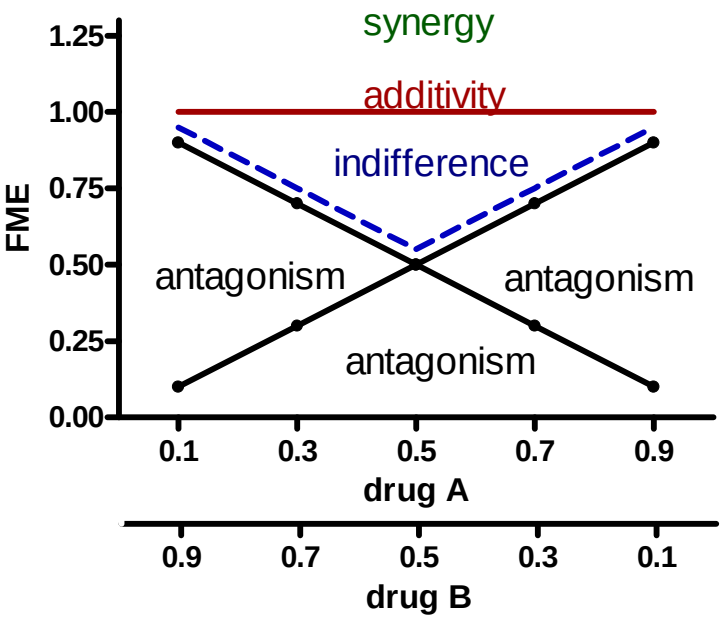


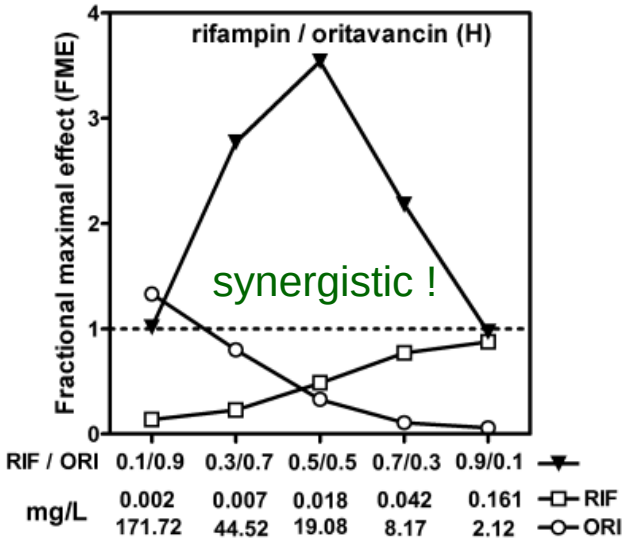
Gray zones: clinically-relevant range of concentrations

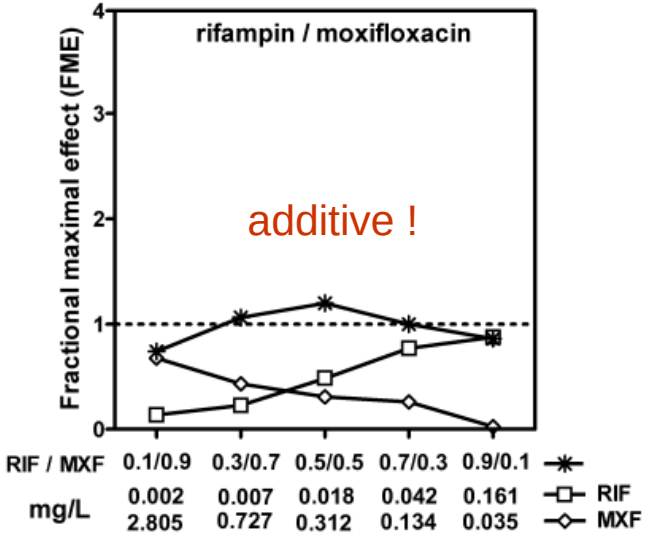
- **Extracellular activity:**
  - all drugs show concentration-dependent bacteridal effects
- **Intracellular activity:**
  - RIF and MXF show markedly reduced activity
  - ORI shows a bimodal effect with maximal activity ≈ 3 log

Nguyen et al., AAC 2009; 53:1434-42

Antibiotic combinations against intracellular SCVs





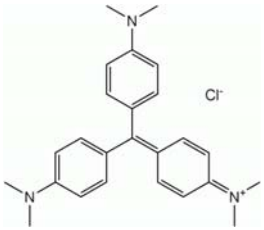


Nguyen et al., AAC 2009; 53:1443-49

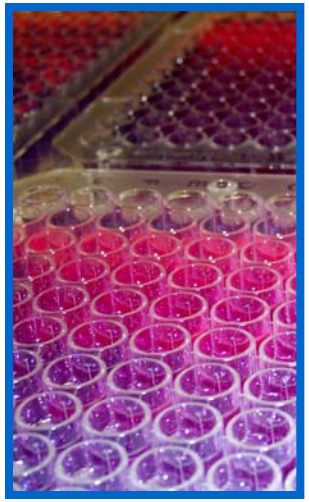
A pharmacodynamic model to assess antibiotic activity against biofilms

biofilm mass

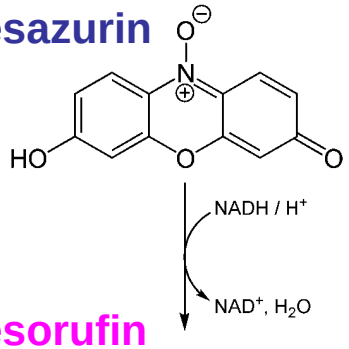
crystal violet



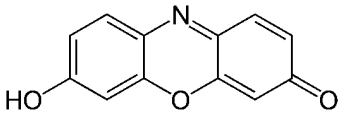
viability



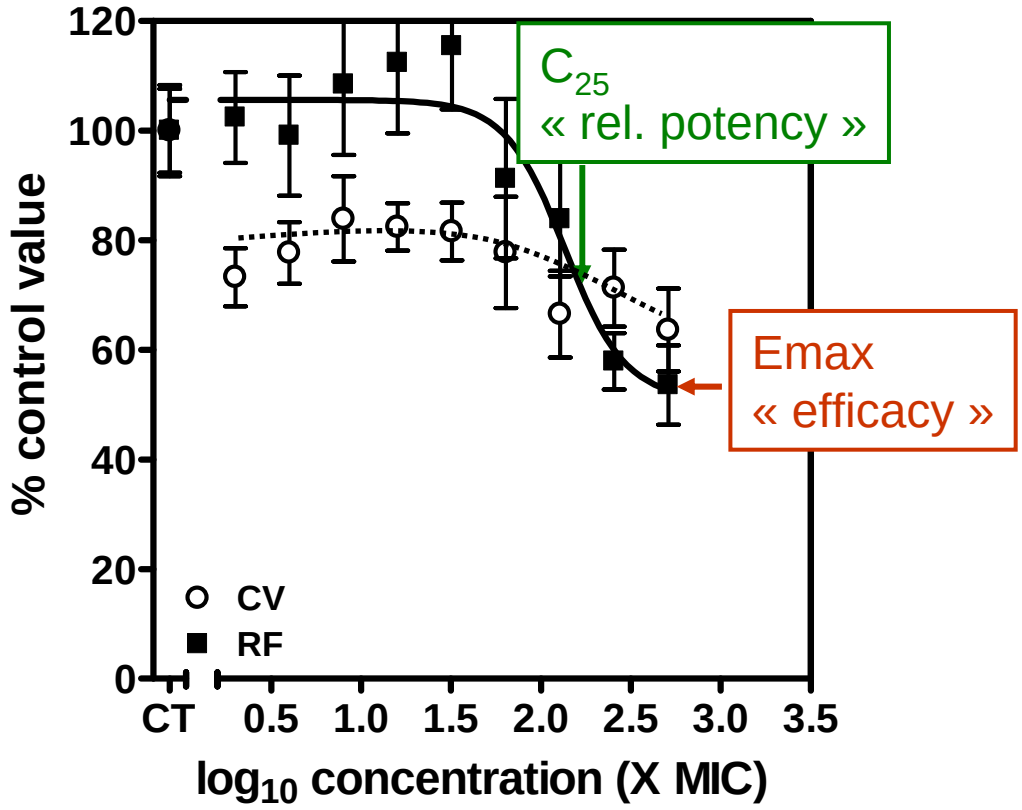
resazurin



resorufin

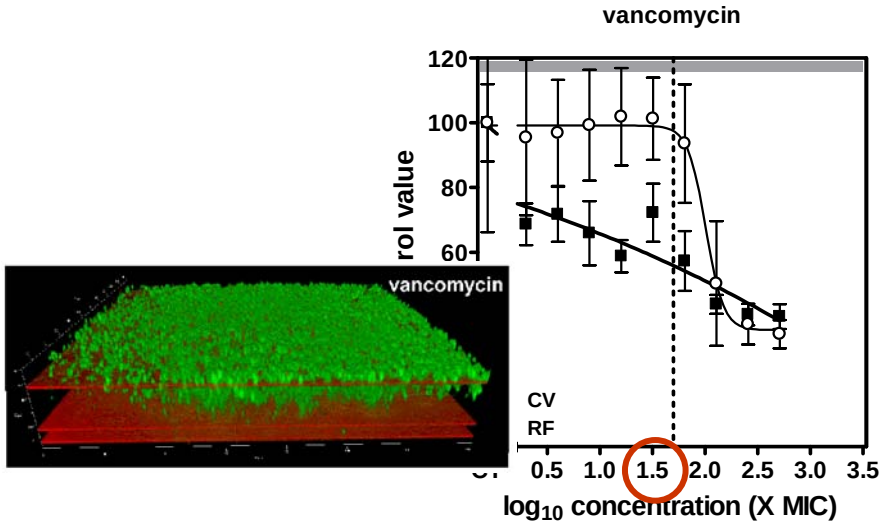


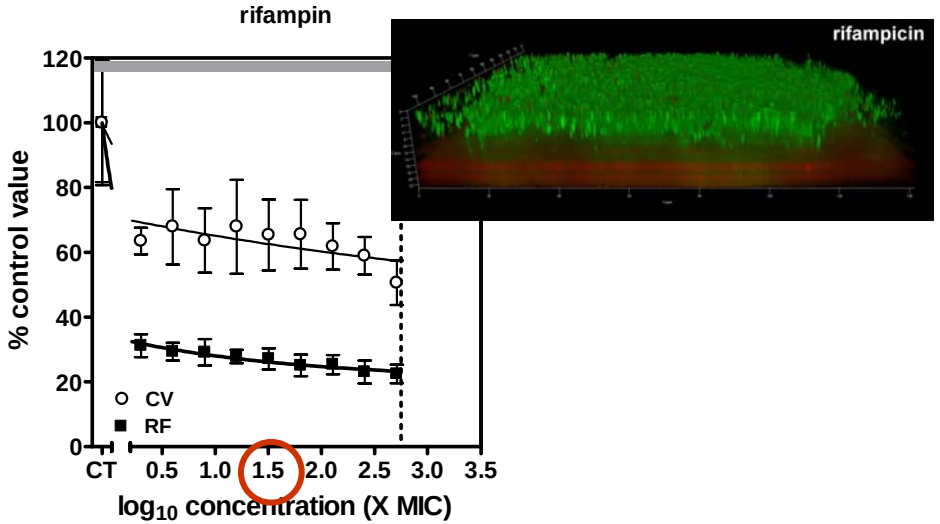
moxifloxacin

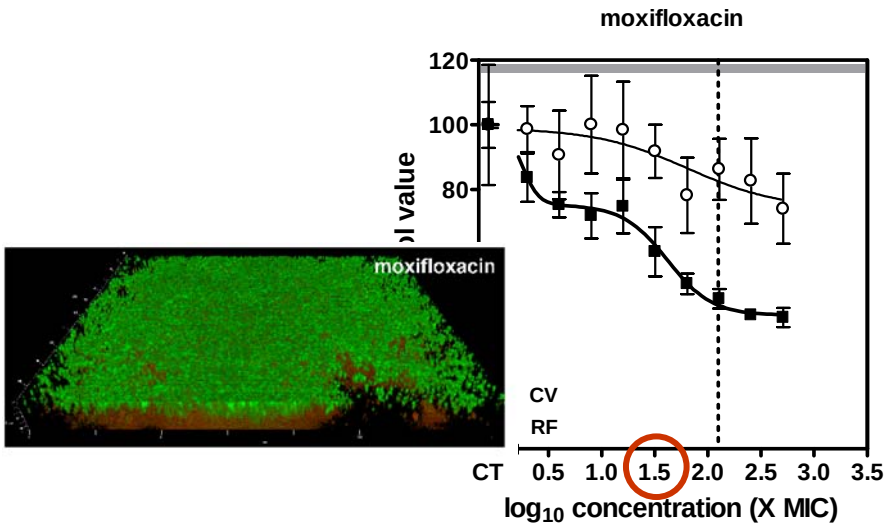


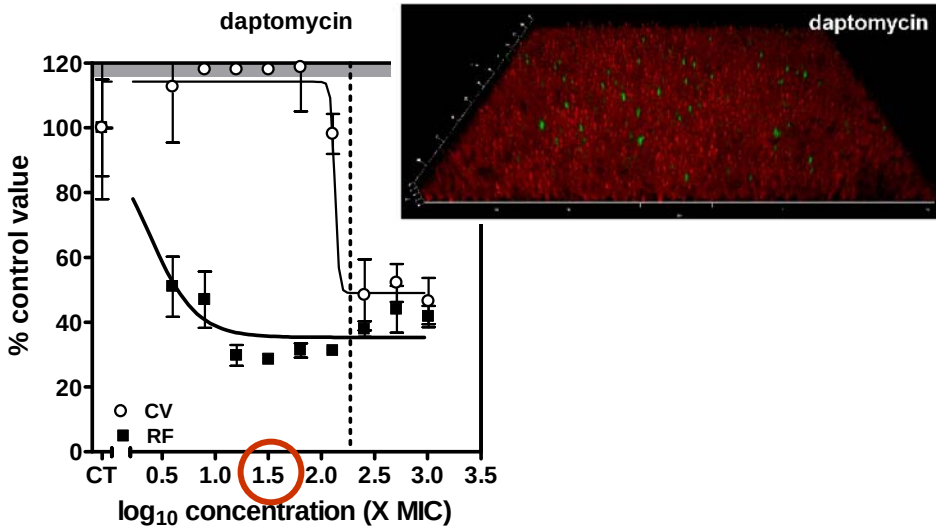
Bauer, Siala et al., AAC 2013, Epub, PMID: 23571532

Antibiotic activity against biofilms- MRSA





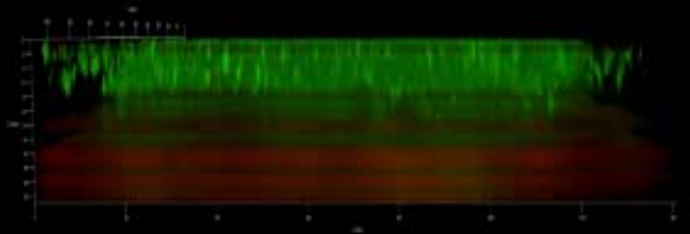




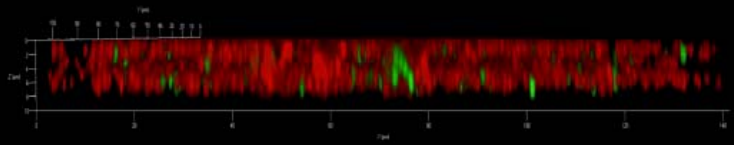
Bauer, Siala et al., AAC 2013; Epub PMID: 23571532

Antibiotic activity against biofilms

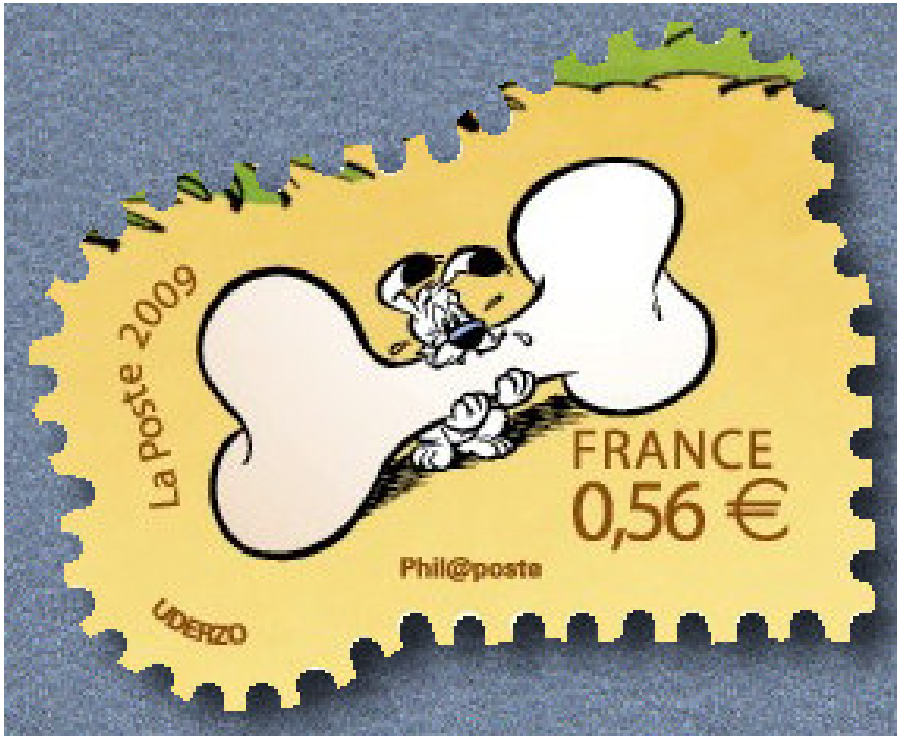
RIFAMPICIN



DAPTOMYCIN



Safety profile



Main problems associated with antibiotics in bone infections

A summary of the main antibiotics used in the treatment of MRSA soft tissue and bone infections

Antibiotic	Route of administration	Main benefits	Main problems
Erythromycin	PO (main) & IV	Widespread experience of use	Comparatively poor oral absorption, GI side effects
Clindamycin	PO (main) & IV	Excellent bone penetration No monitoring required	Risk of *Clostridium difficile* diarrhoea
Linezolid	PO (main) & IV	Excellent bioavailability & tissue penetration Resistance rare	Haematological side effects limit use for long courses
Daptomycin	IV	Once daily administration Resistance rare	Necessitates IV dosing
Vancomycin	IV	Widespread experience of use	Nephrotoxicity – monitoring required Increasing resistance concerns
Teicoplanin	IV	Less nephrotoxic than vancomycin Once daily administration	Monitoring required
Doxycycline	PO	Once daily administration	GI side effects
Tigecycline	IV	Use in polymicrobial infection	
Rifampicin	PO (main) & IV	Excellent tissue penetration	Must be used in combination Extensive interations
Fusidic acid	PO (main) & IV	Excellent tissue penetration	Must be used in combination

PO, by mouth; IV, intravenous, GI, gastrointestinal.

resistance ?

safety ?

efficacy ?

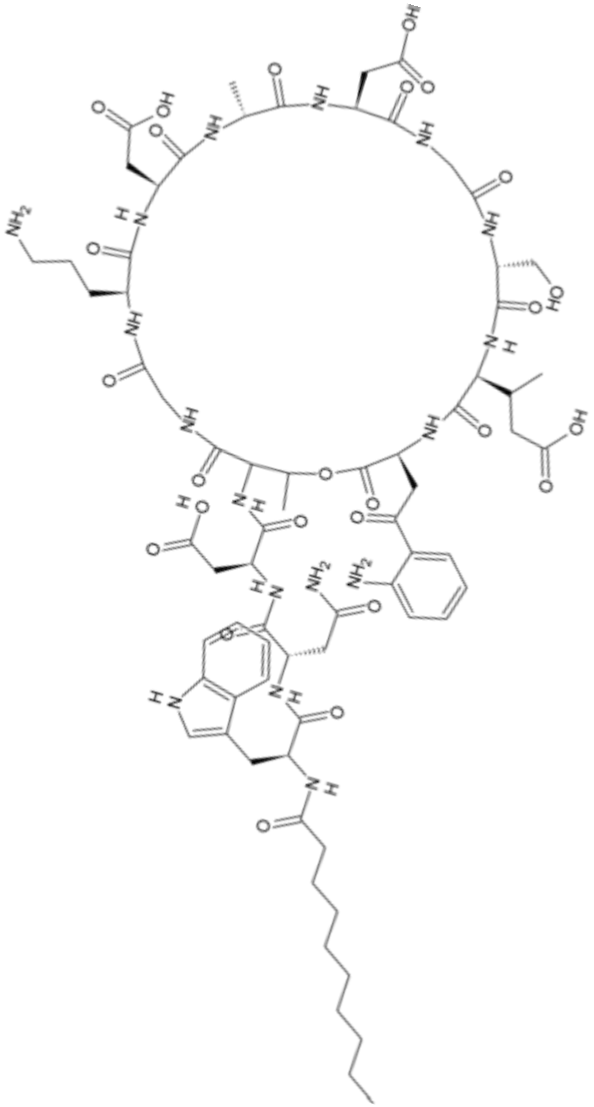
Thompson & Townsend, Injury, Int. J. Care Injured 42 (2011) S5, S7–S10

Perspectives for improvement in the future ?

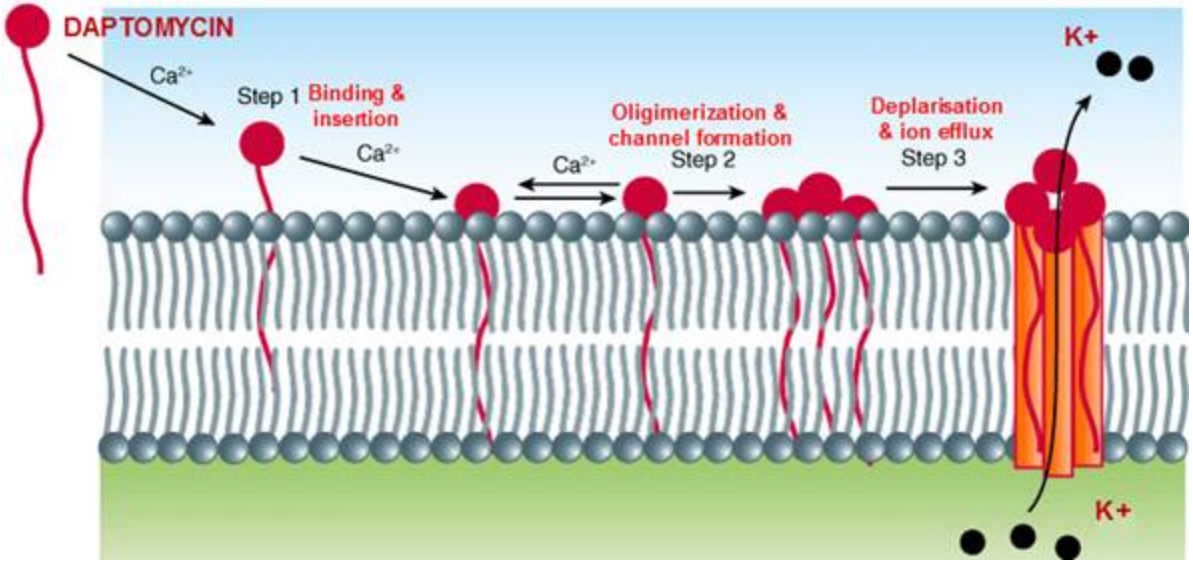
P. Delvaux

http://ginette-villeneuve.forumactif.com/t5780-un-squelette-age-chausse-ses-lunettes

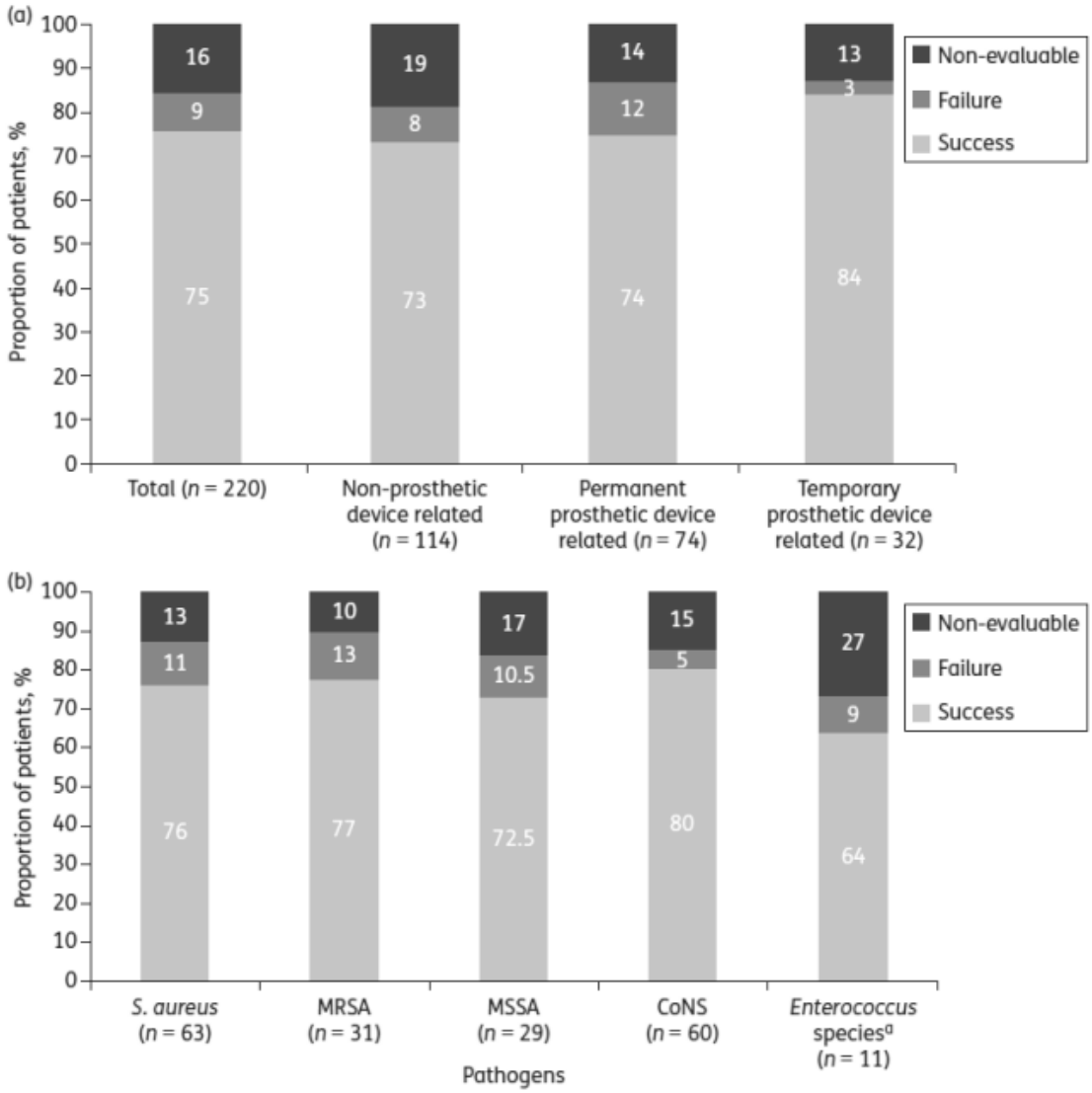
Daptomycin



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



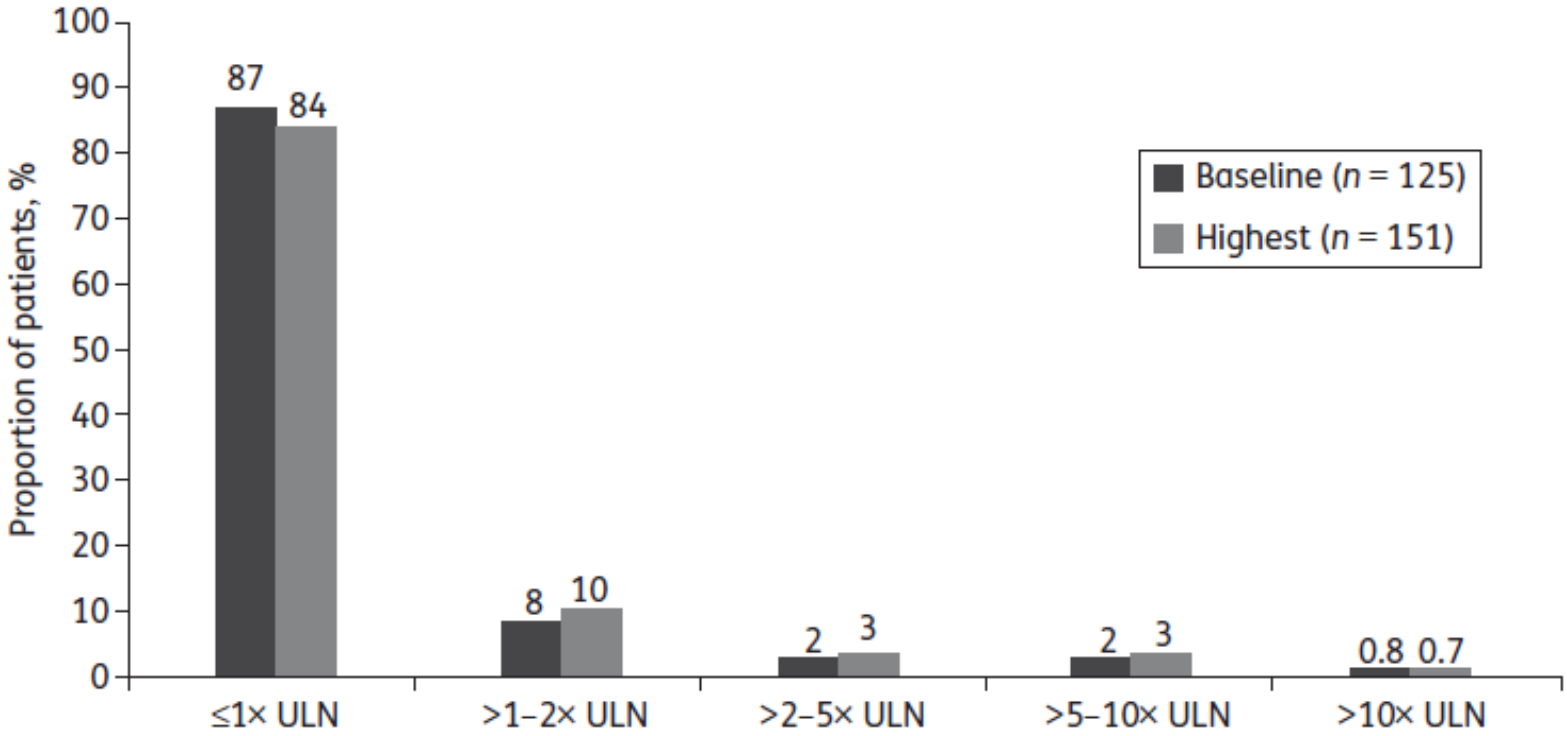
Daptomycin efficacy in osteomyelitis



Seaton et al., JAC 2013 Epub PMID: 23515247

Daptomycin safety in osteomyelitis

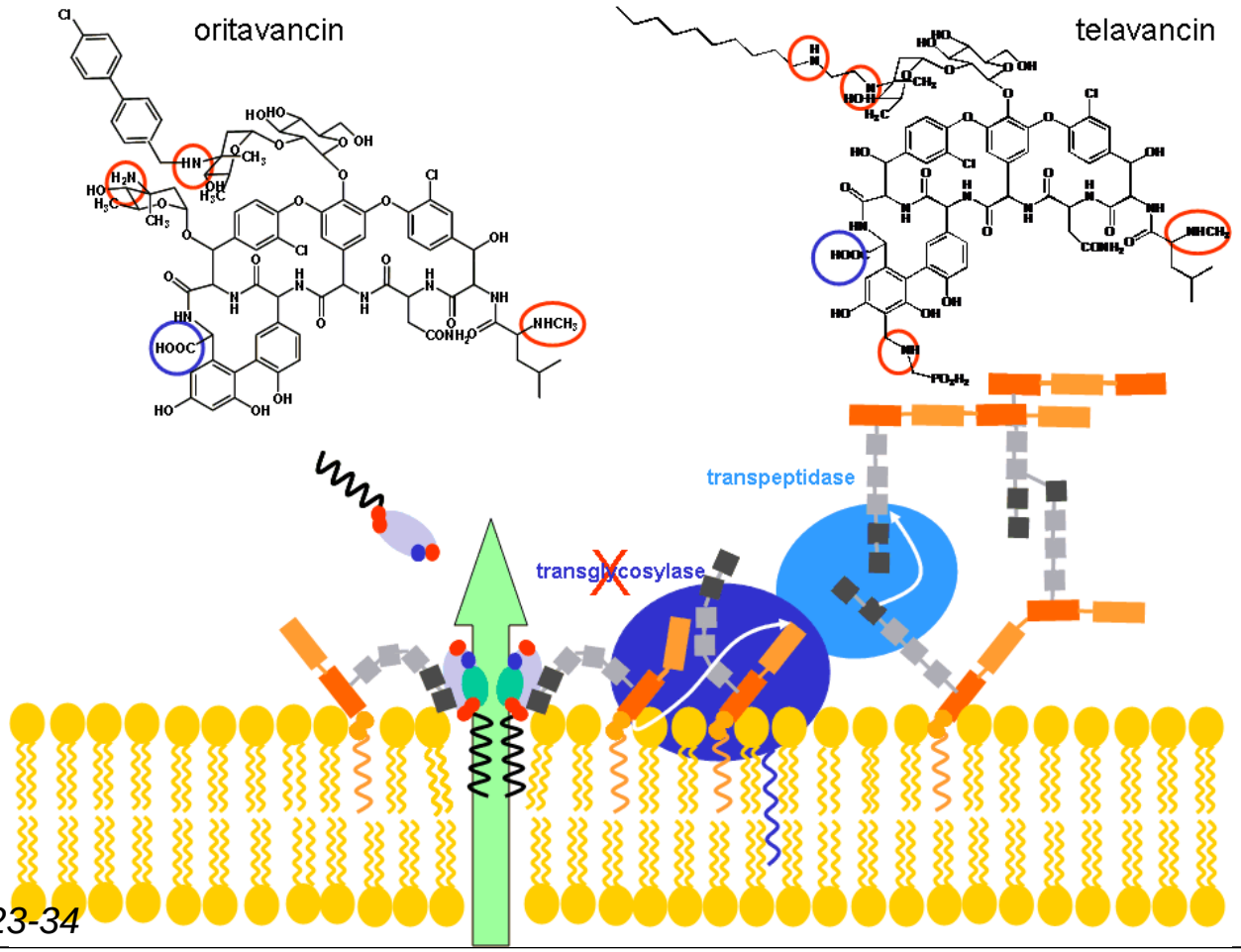
Creatinine phosphokinase levels



Seaton et al., JAC 2013 Epub PMID: 23515247

Lipoglycopeptides

- very bactericidal towards Gram (+) organisms through dual mode of action
- oritavancin highly active intracellularly and on biofilms



Van Bambeke et al., TIPS 2008; 29:123-34

Telavancin efficacy in osteomyelitis

A few encouraging case reports ….

J Antimicrob Chemother 2011
doi:10.1093/jac/dkr329
Advance Access publication 10 August 2011

Telavancin for the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis

Jennifer D. Twilla[1,2], Michael S. Gelfand[1,3], Kerry O. Cleveland[1,3]* and Justin B. Usery[1,2]

J Antimicrob Chemother 2012
doi:10.1093/jac/dks165
Advance Access publication 27 April 2012

Successful treatment of methicillin-resistant *Staphylococcus epidermidis* prosthetic joint infection with telavancin

Rajit Kaushal[1] and Ali Hassoun[2]*

Successful Treatment of Polymicrobial Calcaneal Osteomyelitis with Telavancin, Rifampin, and Meropenem

Mary Beth Brinkman, Kaili Fan, Renee L Shivelev, and Lucinda J Van Anglen

The Annals of Pharmacotherapy ▪ *2012 June, Volume 46* ▪ **e15**

Antibiotic-loaded beads

Campoccia et al., Biomaterials 2010; 31:6363-77

Antibiotic-loaded beads

Summary of clinical studies of gentamicin–polymethylmethacrylate (PMMA) beads.

Reference	Type of infection	No. of patients and treatment administered	Duration of follow-up (years)	Infection control rate	Recurrence rate
Randomised studies					
Blaha et al., 1993 [10]	Chronic osteomyelitis	190 i.v. antibiotics vs. 145 i.v. antibiotics, gentamicin–PMMA beads vs. 49 gentamicin–PMMA beads	1	–	24% vs. 43%* vs. 29%
Nelson et al., 1993 [12]	Infected hip and knee arthroplasties	13 debridement, i.v. antibiotics vs. 15 debridement, gentamicin–PMMA beads	0.5–5.6	–	30% vs. 15% (N/S)
Shih et al., 2005 [13]	Subacute osteomyelitis	10 i.v. antibiotics over 2 weeks, followed by oral antibiotics for 4 weeks vs. 13 gentamicin–PMMA beads	4.6	100% vs. 100%	0%
Observational studies					
Klemm, 1979 [16]	Chronic osteomyelitis	128 debridement, gentamicin–PMMA beads	2	91.4%	11.6%
Majid et al., 1985 [19]	Chronic osteomyelitis	50 debridement, gentamicin–PMMA beads and i.v. antibiotics for 48 h, followed by oral antibiotics for an average of 3 months	1.2	91% of 43 analysed	N/A
Jerosch et al., 1995 [15]	Post-traumatic osteomyelitis	102 debridement, gentamicin–PMMA beads	4–10	89.2%	10.8%
Walenkamp et al., 1998 [17]	Chronic osteomyelitis ($n = 66$), combined with arthritis ($n = 18$) or with pseudarthrosis ($n = 3$) and other forms of osteomyelitis ($n = 13$)	100 debridement, gentamicin–PMMA beads	1–12	92%	17%
Mohanty et al., 2003 [20]	Chronic osteomyelitis of different aetiologies (infected osteosynthesis, infected open fractures and haematogenous osteomyelitis)	45 debridement, antibiotic-loaded PMMA beads and i.v. antibiotics over 7 days	3.7	87%	13%
Kelm et al., 2004 [18]	Orthopaedic MRSA infections associated with osteosynthetic material	10 debridement, vancomycin- and gentamicin-containing PMMA beads	0.4–4.6	100%	0%
Chang et al., 2007 [14]	Chronic osteomyelitis	40 debridement vs. 25 debridement + Osteoset T pellets	6	60% vs. 80% (N/S)	N/A

i.v., intravenous; N/S, not significant; MRSA, meticillin-resistant *Staphylococcus aureus*; N/A, not available.

* Significant difference between i.v. antibiotics alone (24%) and combination therapy (i.v. antibiotics + beads; 43%), with a more favourable outcome in the i.v. antibiotics-only group.

Barth et al., IJAA 2011; 38:371–75

Release of antibiotics from spacers and beads

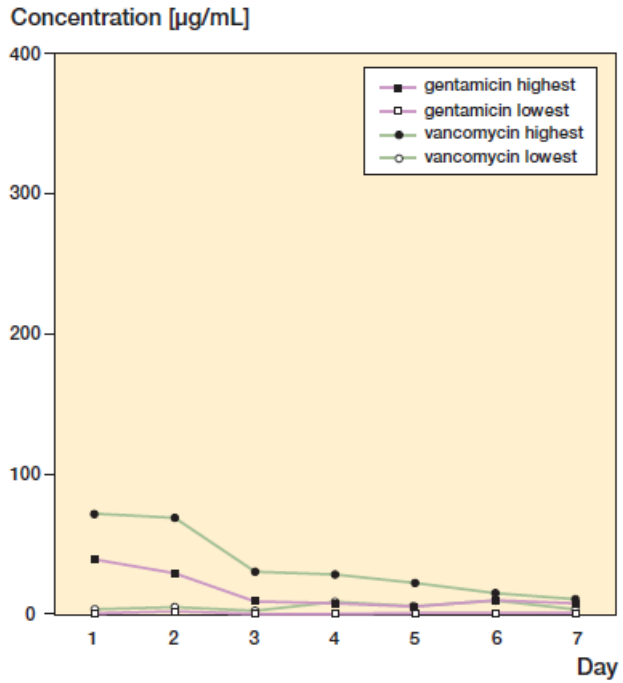


Figure 4. The elution from the spacers showed substantial inter-individual variability in the peak amounts of antibiotic released during the first postoperative days.

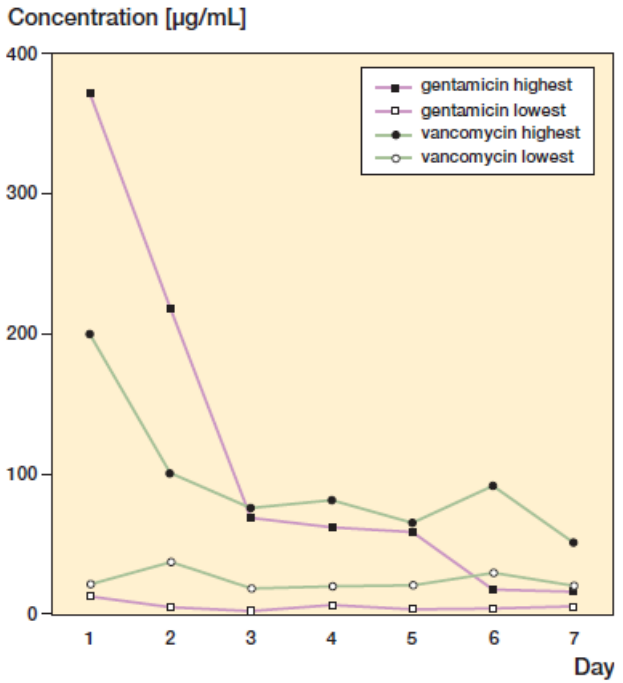


Figure 5. The release of antibiotic from beads also showed substantial inter-individual variability for both agents regarding the peak amounts of antibiotic released during the first postoperative days.

Anagnostakos et al., Acta Orthopaedica 2009; 80: 193–7

Antibiotic bone cements

Interest in total joint arthroplasty

Endpoint in the analyses	THAs	Revisions	12-year revision (%)	RR [a]	95% CI	P-value
Infection	56,275	252				
Uncemented THAs	5,259	20	0.7	1	–	–
THAs with antibiotic in cement	35,214	126	0.6	1.2	0.7–2.0	0.5
THAs without antibiotic in cement	15,802	106	0.9	1.8	1.0–3.1	0.04
Aseptic loosening	56,275	1,906				
Uncemented THAs	5,259	302	16.9	1	–	–
THAs with antibiotic in cement	35,214	559	6.1	0.6	0.5–0.7	< 0.001
THAs without antibiotic in cement	15,802	1,045	10.6	1.3	1.1–1.6	< 0.001
All reasons for revision	56,275	2,789				
Uncemented THAs	5,259	559	27.6	1	–	–
THAs with antibiotic in cement	35,214	929	7.9	0.5	0.4–0.6	< 0.001
THAs without antibiotic in cement	15,802	1,301	12.7	0.9	0.8–1.0	0.01

[a] Adjusted in the Cox model for sex, age, systemic antibiotic prophylaxis, type of operating room, and duration of operation

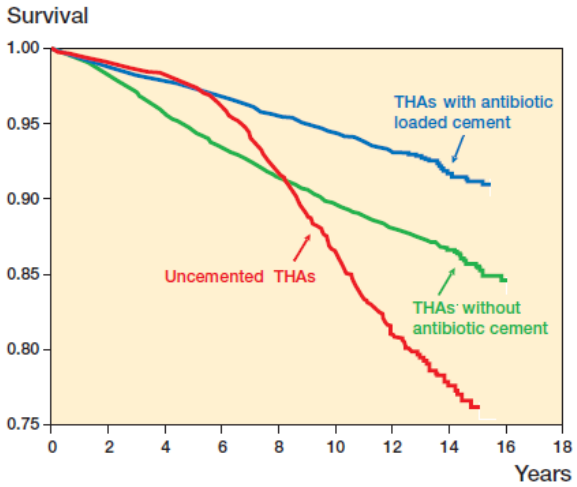


Figure 4. Cox-adjusted survival curves with all reasons for revision as endpoint for uncemented arthroplasties, for cemented hip arthroplasties with antibiotic-loaded cement, and for cemented hip arthroplasties without antibiotic cement.

Engeseater et al., Acta Orthop 2006;77:351-8.

Bone cements

Study by Arthroplasty Site	Study Period	Patients, No./ Joints, No.	Spacer Antibiotic Content (Dose, g/40 g Cement)	Infection Eradication Rate[a]		
				By Review	As Reported by Authors	Death
Knee						
[43]	Not reported	12/12	Tobramycin (4.8) + vancomycin (4)	12/12 (100)	12/12 (100)	0
[17][c]	1995–2002	29/31	Tobramycin (4.6) + vancomycin (4)	25/31 (81)	29/31 (93)	0
[15][d]	1998–2005	102/102	Tobramycin (3.6) + vancomycin (4)	47/102 (46)	70/96 (73)	0
[20]	1986–1994	48/48	Tobramycin (3.6) + vancomycin (2)	43/48 (90)	44/48 (92)	0
[13][d]	1997–1999	58/58	Tobramycin (3.6) + vancomycin (1.5)	48/58 (83)	45/47 (96)	NA[e]
[44]	1998–2001	24/24	Tobramycin (2.4) + vancomycin (1)	22/24 (92)	22/24 (92)	0
[45]	1996–2001	28/28	Tobramycin (1.2) or gentamicin (1) + vancomycin (1)	25/28 (89)	25/28 (89)	0
[46]	2000–2005	36/36	Piperacillin-tazobactam (4.5) + vancomycin (2) + erythromycin (1)	32/36 (89)	32/36 (89)	0
[18]	1989–2001	50/50	Tobramycin (4.8)	44/50 (88)	44/50 (88)	NA
[22]	1994–2002	44/44	Tobramycin (4.8)	43/44 (98)	43/44 (98)	0
[14][d]	1986–1999	40/40	Tobramycin (1.2)	36/40 (90)	36/40 (90)	0
[19]	1989–1993	69/69	Tobramycin (1)	60/69 (87)	61/69 (88)	0
[47][f]	1998–2003	48/48	Vancomycin (1)	30/48 (63)	42/48 (88)	0
Hip						
[17][c]	1995–2002	16/23	Tobramycin (4.6) + vancomycin (4)	18/23 (78)	22/23 (96)	0
[48]	Not reported	12/12	Tobramycin (3.6) + vancomycin (1)	12/12 (100)	12/12 (100)	0
[12][d]	1998–2001	22/22	Tobramycin (2.4) + vancomycin (1)	20/22 (90)	20/20 (100)	2 (9)
[10][d]	1993–1997	24/24	Gentamicin (1) + vancomycin (1) + cefotaxime (1)	21/24 (88)	21/22 (95)	2 (8)
[16][d,f]	1998–2003	43/44	Gentamicin (0.25) + vancomycin (2)	35/44 (80)	38/41 (93)	3 (7)
[11][d]	1991–2001	42/42	Tobramycin (4.8)	26/42 (62)	26/27 (96)	8 (19)
[9][g]	1996–2003	38/38	Vancomycin (1)	32/38 (84)	34/38 (89)	2 (5)
[23][h]	2001–2006	40/40	Gentamicin (0.76)	38/40 (95)	39/40 (97.5)	0

Iarikov et al., CID 2012; 55:1474-80

Unanswered questions …

- Bone concentrations are lower than serum concentrations, but what about PD paramaters (AUC/MIC, T > MIC) ?
- Combinations help preventing resistance, but are there really synergistic ?
- Specific lifestyles may affect antibiotic efficacy (intracellular, biofilm, SCV), how to act upon these ?
- Treatment should be long, any safety concern ?