The Bug-Drug-Host

Triad in the Era of Antibiotic Resistance: Focus on the Spectrum of ABSSSI

Supported by an educational grant from Melinta Therapeutics

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THE BUG: KNOWN AND HIDDEN CHALLENGES OF INFECTIONS WITH STAPHYLOCOCCUS AUREUS

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Brussels, Belgium

This presentation has been updated on Nov 3, 2016 (see slides 45-50)

With approval of the Belgian Common Ethical Health Platform – visa no. 16/V1/9365/084611

Disclosures

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  - the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  - The European Union for applied research on optimization of β-lactams treatments through on-line monitoring of free serum levels
  - *Université catholique de Louvain* for past personal support
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  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other relationships in relation to this talk

- Belgian Antibiotic Policy Coordination Committee,
- European Committee for Antibiotic Susceptibility Testing (EUCAST)
- European Medicines Agency (EMA)

Slides: http://www.facm.ucl.ac.be → Lectures

The Saga of *S. aureus*

The problems

- **the rise of resistance**
  - from penicillin-S to MDR
- **hidden habitats**
  - intracellular forms
- **unexpected forms**
  - the small colony variants
- **the communities**
  - biofilms

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  - disrupting the matrix ?

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The Staphylococcus *aureus* saga: 60 first years …

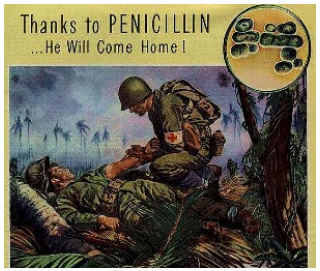
1881:
First observation of *staphylococci* in pus by Alexander Ogston

"Micrococci so deleterious when injected are seemingly harmless on the surface of wounds and ulcers".
Br Med J 1881;1:369e375

1884:
First distinction between *S. aureus* and *S. albus* by Friedrich Rosenbach

1914-1918:
Half of the casualties in the trenches of the First World War were due to septic wound infections with *S. aureus*.

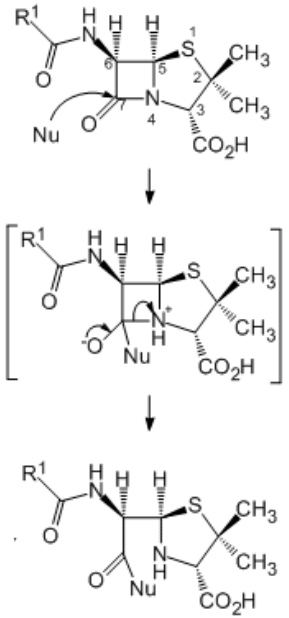
1940-45:
the production process for penicillin (then still universally active against the bacterium*) was a military secret



* the original observation of Fleming (1928) was made on *S. aureus*

The Staphylococcus *aureus* saga: the next 17 years …

1944:
First description of a β-lactamase in *S. aureus* *



Lee, S. (2008). State of C2/C3 substituents of ?-lactam antibiotics in the β-lactam ring cleavage by β-lactamases. *PHILICA.COM Article number 122.*

* The first description of a β-lactamase was made in 1940 in *E. coli* (Nature 146, 837 (28 December 1940)

1950-70:
almost all strains of *S. aureus produce a* β-lactamase

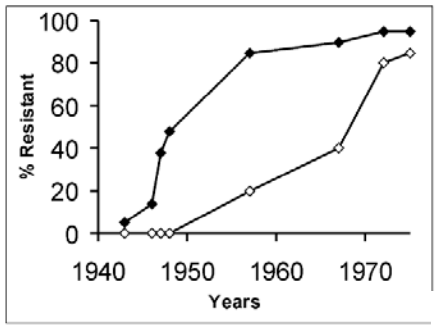


Figure. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *Staphylococcus aureus* in hospitals (closed symbols) and the community (open symbols).

1960:
introduction of methicillin … and emergence of resistance to methicillin in 1961

MICROBIOLOGICAL STUDIES ON SODIUM 6-(2,6 DIMETHOXYBENZAMIDO) PENICILLANATE MONOHYDRATE (BRL 1241) IN VITRO AND IN PATIENTS

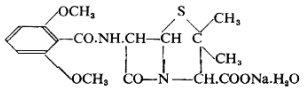
BY

G. T. STEWART, M.D., B.Sc.

With the Technical Assistance of
PATRICIA M. HARRISON, B.Sc., and
R. J. HOLT, F.I.M.L.T.

From Queen Mary's Hospital for Children and the Medical Research Council Laboratories, Carshalton, Surrey

A report in 1959 by Batchelor *et al.* on the isolation of 6-aminopenicillanic acid drew attention to the possibility of synthesizing new forms of penicillin by the introduction of side-chains. Derivatives prepared in this way may or may not possess antibacterial activity, but we were particularly impressed by the range and mode of action of one derivative, supplied to us in 1959 as BRL 1241 ("celbenin"). The compound—sodium 6-(2,6 dimethoxybenzamido)penicillanate monohydrate—may be represented by the following structural formula:



Methicillin-resistant staphylococci

MARY BARBER

From the Department of Bacteriology, Postgraduate Medical School of London

SYNOPSIS Eighteen strains of *Staph. pyogenes* (nine penicillin-sensitive and nine penicillin-destroying) were passaged 40 to 50 times on Celbenin[1] ditch plates.

All strains developed an increase in resistance to Celbenin and eight strains (four penicillin-sensitive and four penicillin-destroying) were able to grow in 100 μg/ml. or more Celbenin. Resistance was of the drug-tolerant type and none of the cultures inactivated Celbenin. There was an associated increase in tolerance to benzyl penicillin.

The highly Celbenin-resistant cultures isolated from penicillin-destroying staphylococci were in sharp contrast to those from penicillin-sensitive strains, as well as to penicillin G-tolerant staphylococci isolated *in vitro*, because they retained the cultural characteristics, coagulase and haemolytic activity, and mouse virulence of the parent strains, and the degree of resistance remained stable after repeated passage in the absence of Celbenin.

Three naturally occurring Celbenin-resistant strains of *Staph. pyogenes* isolated from infective processes were also studied. All three strains grew luxuriantly in concentrations of Celbenin up to 12·5 μg/ml. but very poorly in higher concentrations.

The possible significance of these findings is discussed.

The *Staphylococcus aureus* saga: from 1961 onwards…

1970's:
Spreading of methicillin resistance In hospitals

1980's:
Large scale re-introduction of vancomycin *

1997:
Strains with reduced susceptibility to vancomycin

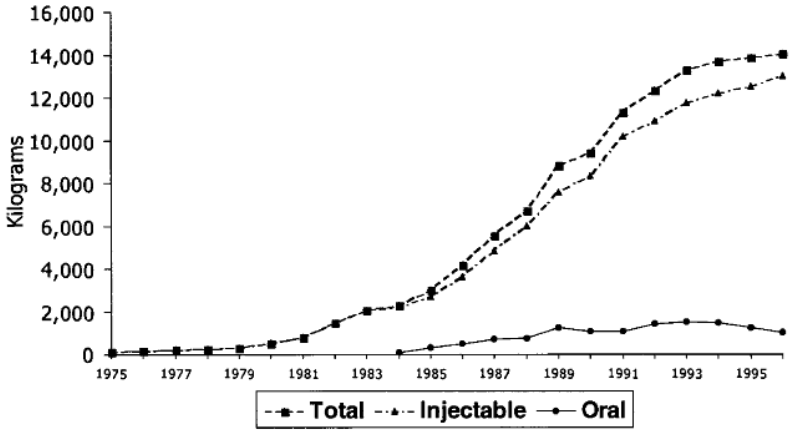


FIG. 1. Usage of vancomycin (in kilograms) in the United States, France, Italy, Germany, United Kingdom, and The Netherlands.

Kirst et al. Antimicrob Agents Chemother. 1998: 42:1303-4.

Journal of Antimicrobial Chemotherapy (1997) **40**, 135–146

Correspondence

Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility

J Antimicrob Chemother 1997; **40:** 135–136

K. Hiramatsu[a*], H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

[a]*Department of Bacteriology;* [b]*Department of Pedi - atrics, Juntendo University, Tokyo;* [c]*Clinical Labora - tory, Juntendo Hospital, Tokyo, Japan;* [d]*Nosocomial Pathogens Laboratory, Centers for Disease Control and Prevention, Atlanta, GA, USA*

* Vancomycin was described in 1955-57
(Antibiot Annu. 1955-1956;3:606-322 and 1956-57;4:75-122)

Staphylococcus aureus and linezolid

1996:
First description of linezolid

J. Med. Chem. **1996**, *39*, 673−679

Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potential Treatment of Multidrug-Resistant Gram-Positive Bacterial Infections

Steven J. Brickner,* Douglas K. Hutchinson, Michael R. Barbachyn, Peter R. Manninen, Debra A. Ulanowicz, Stuart A. Garmon, Kevin C. Grega, Susan K. Hendges, Dana S. Toops, Charles W. Ford, and Gary E. Zurenko

Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received December 22, 1995®

2002:
Resistance in *S. aureus* by target mutation

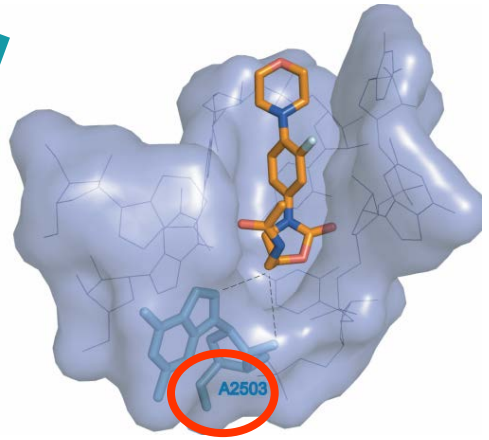
Linezolid Resistance in *Staphylococcus aureus:* Characterization and Stability of Resistant Phenotype

Satish K. Pillai,[1,3] George Sakoulas,[1,3] Christine Wennersten,[1] George M. Eliopoulos,[1,3] Robert C. Moellering, Jr.,[1,3] Mary Jane Ferraro,[2,3] and Howard S. Gold[1,3]

[1]*Division of Infectious Diseases, Beth Israel Deaconess Medical Center,* [2]*Departments of Pathology and Medicine, Massachusetts General Hospital, and* [3]*Harvard Medical School, Boston, Massachusetts*

Pillai et al. J Infect Dis. 2002;186:1603-7. PMID: 12447736.

2007:
Resistance in S. aureus by mehylation (*cfr*)



Toh et al. Mol Microbiol. 2007;64:1506-14
PMID: 17555436

2016:
first report of cfr in a pandemic MRSA clone (ST22) from patients

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

First Report of *cfr*-Carrying Plasmids in the Pandemic Sequence Type 22 Methicillin-Resistant *Staphylococcus aureus* Staphylococcal Cassette Chromosome *mec* Type IV Clone

Anna C. Shore,[a,b] Alexandros Lazaris,[a] Peter M. Kinnevey,[a] Orla M. Brennan,[a] Gráinne I. Brennan,[a,b] Brian O'Connell,[b,c] Andrea T. Feßler,[d] Stefan Schwarz,[d] David C. Coleman[a]

Microbiology Research Unit, Dublin Dental University Hospital, University of Dublin, Trinity College Dublin, Dublin, Ireland[a]; National MRSA Reference Laboratory, St. James's Hospital, Dublin, Ireland[b]; Department of Clinical Microbiology, School of Medicine, Trinity College Dublin, St. James's Hospital, Dublin, Ireland[c]; Institute of Farm Animal Genetics, Friedrich Loeffler Institut, Neustadt-Mariensee, Germany[d]

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Novel anti-MRSA antibiotics acting on resistant isolates *

*** not an exhaustive list**

- **already approved**
  - 2 β-lactams (ceftaroline / ceftobiprole [a])
  - 3 lipoglypopeptides (telavancin, dalbavancin, oritavancin)
  - 1 oxazolidinone: tedizolid [b]
- **In development**
  - fusidic acid [c]
  - radezolid [d]
  - plazomycin
  - new fluoroquinolones (delafloxacin, nadifloxacin, …) [e]
  - new topoisomerase type II inhibitors (gepotidacin, …)
  - fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …) [f]

[a] approved in Europe and other countries for pneumonia (CAP/HAP) - In discussion with FDA for ABSSSI and SAB
[b] active against *cfr+* linezolid resistant isolates
[c] development for use in the US
[d] currently in development for topical applications
[e] very low MICs (overcoming current mutation and efflux-mediated resistance mechanisms)
[f] very low MICs (typically 0.008 mg/L)

Novel anti-MRSA antibiotics acting on resistant isolates *

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  - 3
  - 1
- In c
  - fu
  - ra
  - pl
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  - new topoisomerase type II inhibitors (gepotidacin, …)
  - fatty acid synthesis inhibitors (AFN-1252/Debio 1452, …) f

> In comparison with other infectious agents, the antimicrobial pipeline for MRSA is potentiated with a number of agents under pre-clinical and clinical development. This is a hopeful sign that the IDSA's target might possibly be met by 2020.

Kumar & Chopra. J Antimicrob Chemother. 2013;68:1465-70. PMID: 23429643

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[b] active against *cfr*+ linezolid resistant isolates
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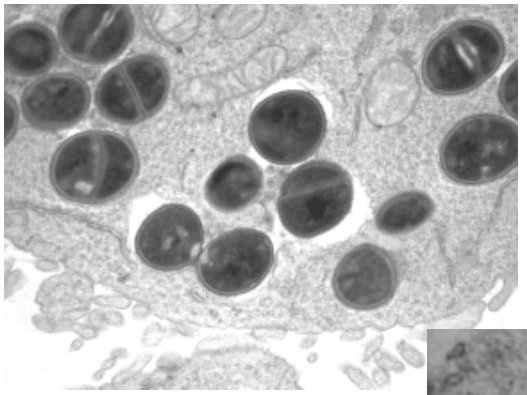
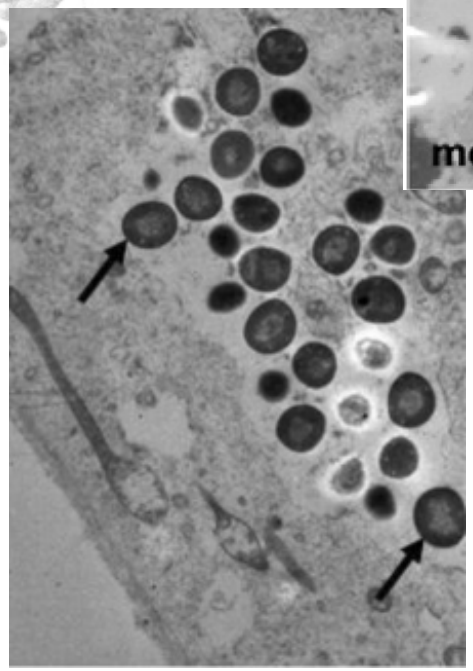
S. aureus as an intracellular parasite

S. aureus in THP-1 macrophages



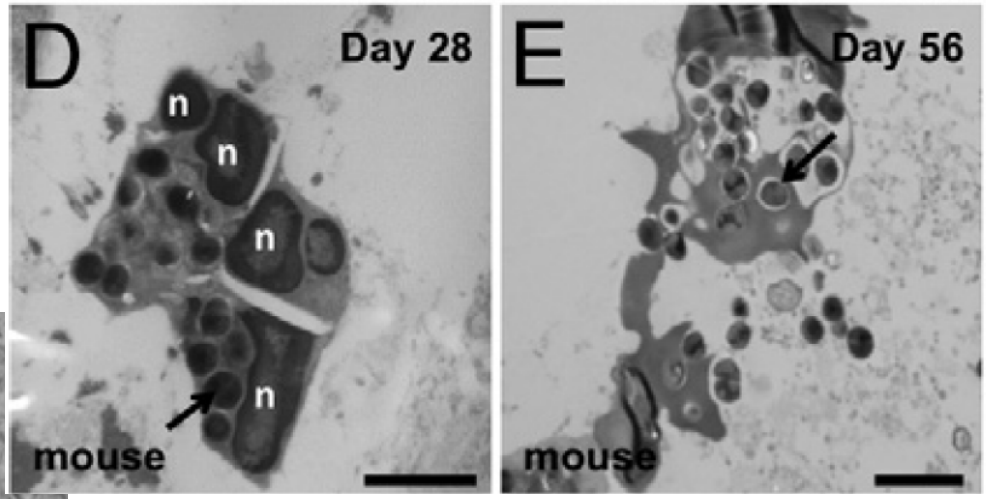
Van Bambeke & Tulkens
unpublished

S. aureus in
human osteoblasts



Kalinka *et al.*, Int J Med Microbiol. 2014;
304:1038-49 - PMID: 25129555

S. aureus in and released from neutrophils in a mouse osteomyelitis model



Horst *et al.* Am J Pathol 2012;181:1206–1214 - PMID: 22902429

intracellular *S. aureus*

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A simple view in 1991

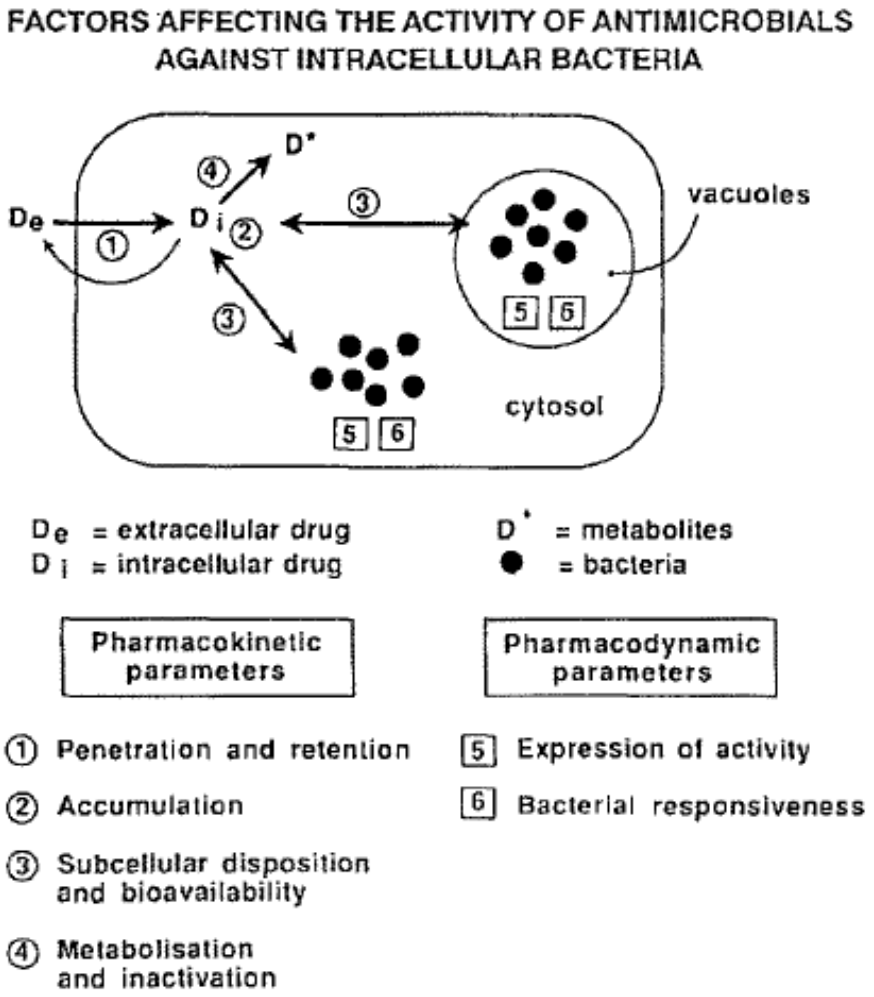
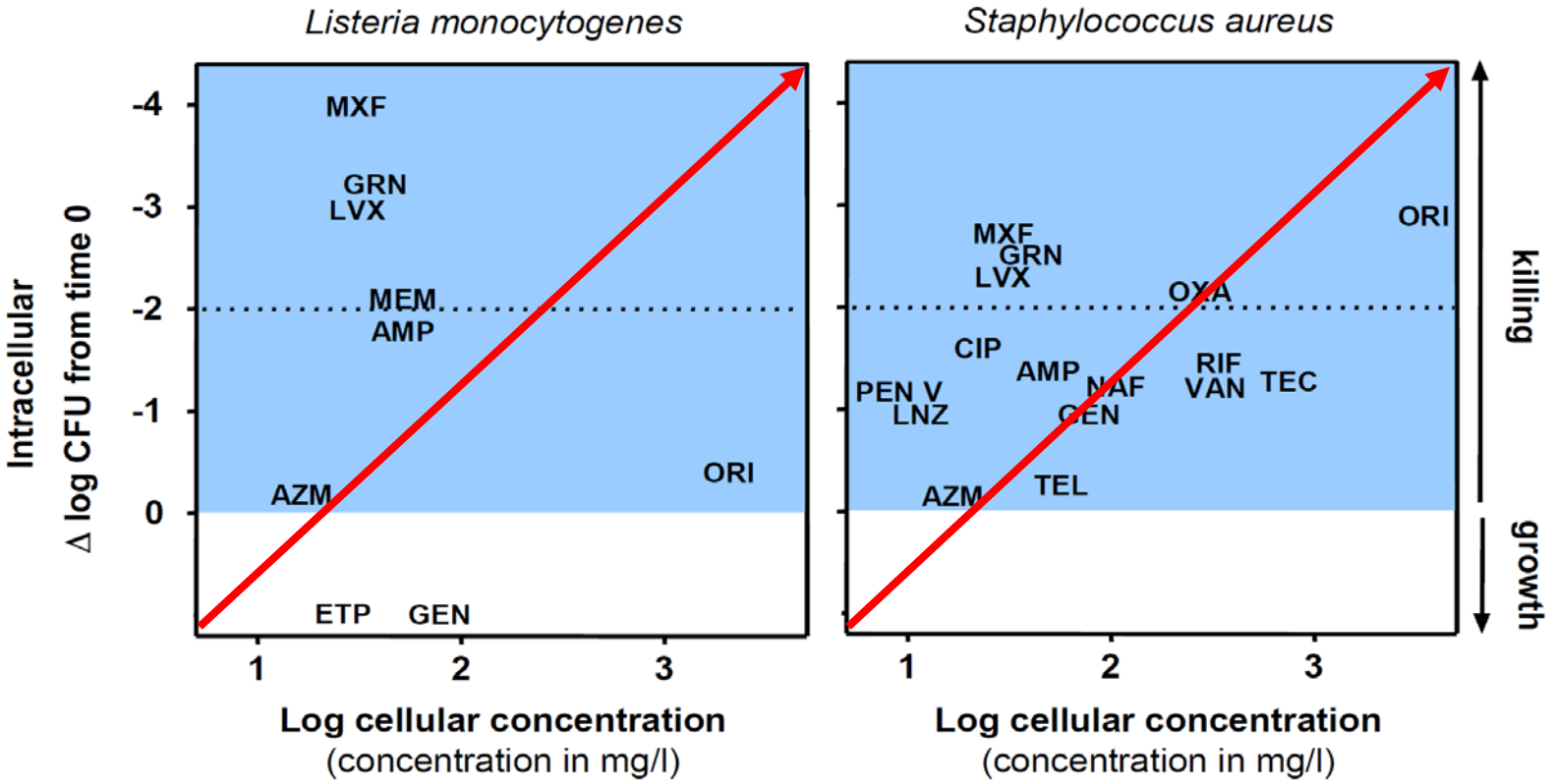


Figure 1: Pharmacokinetic and pharmacodynamic parameters involved in the activity of antimicrobial drugs against intracellular microorganisms.

Tulkens PM. Eur J Clin Microbiol Infect Dis. 1991 10:100-106. PubMed PMID: 1864271.

Intracellular activity is not directly correlated to accumulation

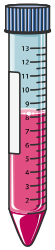


AMP=ampicillin; AZM=azithromycin; CIP=ciprofloxacin; ETP=ertapenem; GEN=gentamicin; GRN=garenoxacin; LNZ=linezolid; LVX=levofloxacin; MEM=meropenem; MXF=moxifloxacin; NAF=nafcillin; ORI=oritavancin; OXA=oxacillin; PEN V=penicillin V; RIF=rifampicin; TEC=teicoplanin; TEL=telithromycin; VAN=vancomycin

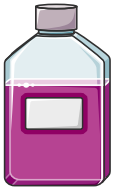
Adapted from Van Bambeke *et al.*, Curr Opin Drug Discov Devel 2006;9:218-230 – PMID: 16566292

24h pharmacodynamic dose-effect model

1. Cell exposure to a a wide range of extracellular concentrations of the antibiotic



Opsonization (45', 37° c)
9 mL RPMI +
1 mL human serum



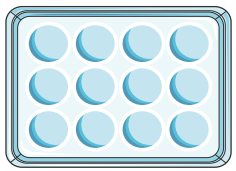
500,000 THP-1 cells/mL

4 cfu/cell (MOI = 4)

Phagocytosis (1 h)

Extracellular Wash
GEN 50 µg/mL
(45 min)

Typical post-phagocytosis inoculum:
5 to $7x10^5$ CFU/mg prot.



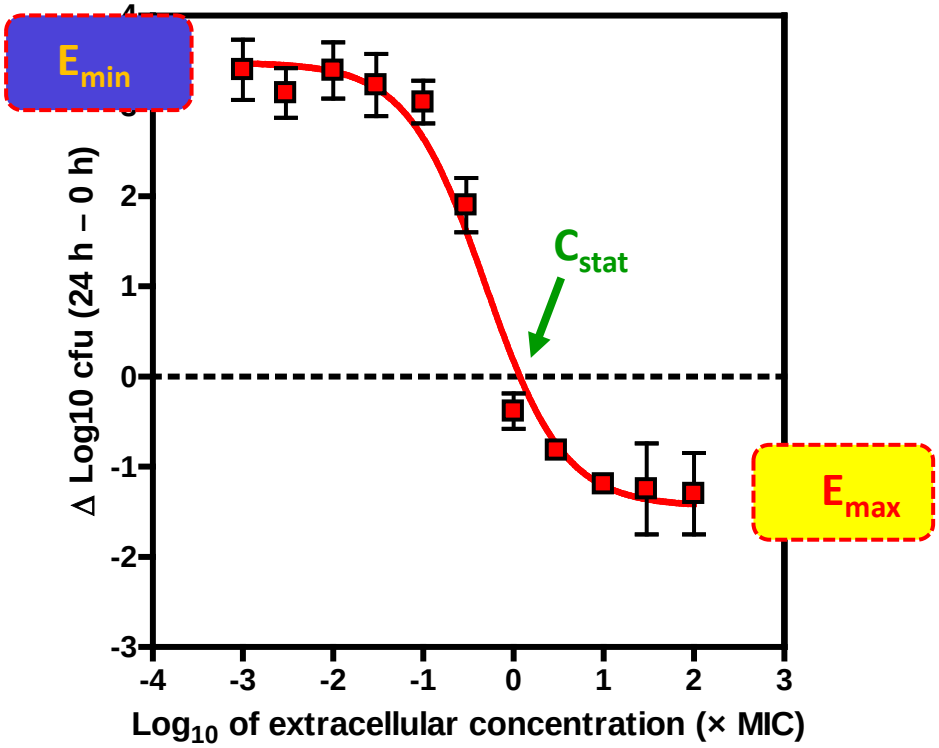
Incubation (with ATB)
(T0, T24 h)

- Cell washing, collection, and lysis
- Cell-associated CFUs counting
- Cell Protein content determination

Buyck et al. In vitro Models for the Study of the Intracellular Activity of Antibiotics;
In "Bacterial Persistence", Molecular Biology Laboratory Protocols Series, J. Michiels and M. Fauvart, editors, 2016, p 147-157 - DOI: 10.1007/978-1-4939-2854-5

Interpretation of the results of the 24h dose-effect model

2. Analysis of the response



E_{min}: cfu increase (in log_{10} units) at 24 h from the corresponding initial inoculum as extrapolated for an infinitely low antibiotic concentration

Static concentration (C_{stat}): extracellular concentration resulting in no apparent bacterial growth (number of cfu identical to the initial inoculum)

E_{max}: cfu decrease (in log_{10} units) at 24 h from the corresponding initial inoculum as extrapolated from infinitely large antibiotic concentration

Reference: Barcia-Macay M, Seral C, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activity of antibiotics against *Staphylococcus aureus* in a model of THP-1 macrophages. Antimicrobial Agents and Chemotherapy (2006) 50:841-851 – PMID: 16495241

Interpretation of the results of the 24h dose-effect model

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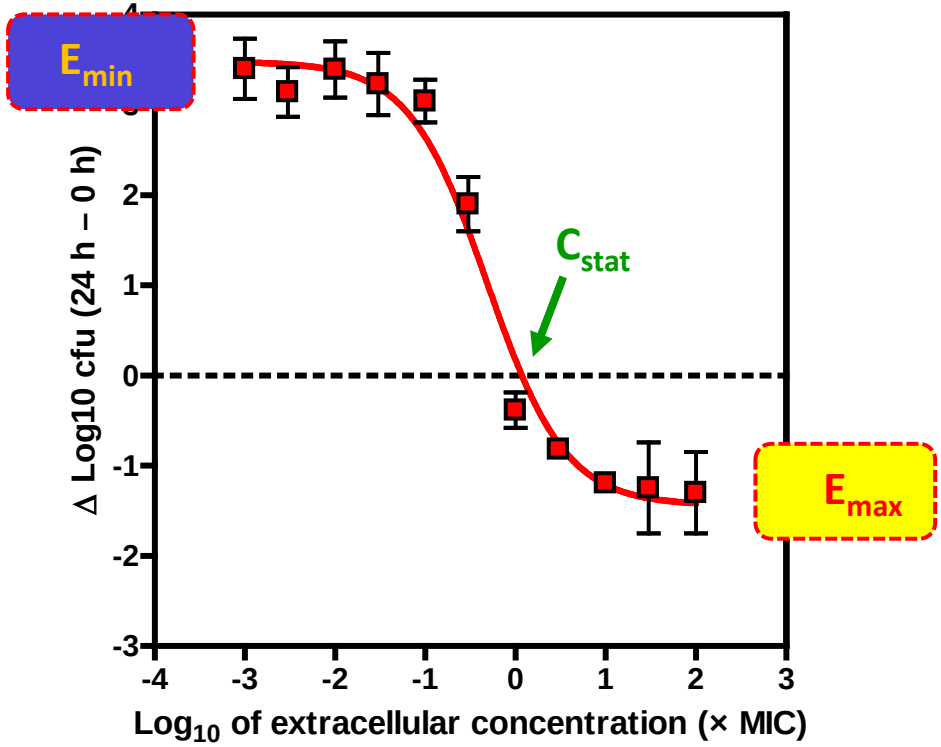


E_{min}: cfu increase (in log_{10} units) at 24 h fr itial inoculu h infinite concentration

Bacteria!

Static concentration (C_{stat}): extrac ulting in no a h (numb initial inoculum)

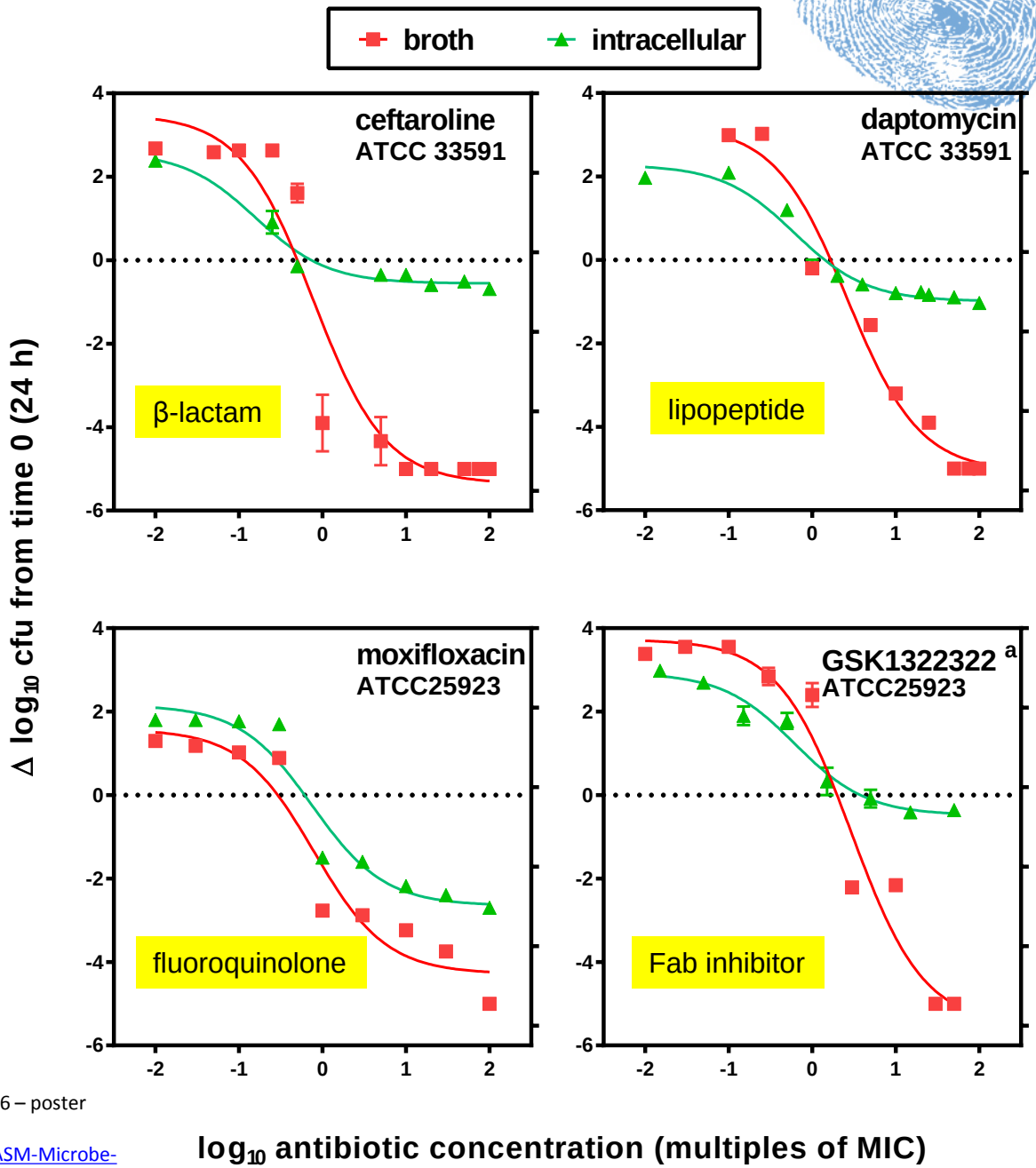
Potency!

E_{max}: cfu decrease (in log_{10} units) at concentration

Maximal effect

Reference: Barcia-Macay M, Seral C, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activity of antibiotics against *Staphylococcus aureus* in a model of THP-1 macrophages. Antimicrobial Agents and Chemotherapy (2006) 50:841-851 – PMID: 16495241

Most antibiotics show a much lower E_{max} against intracellular bacteria than against bacteria in broth



Van Bambeke & Tulkens, ASM Microbe 2016 – poster SATURDAY 571 – Session 188
http://www.facm.ucl.ac.be/posters/2016/ASM-Microbe-2016/VanBambeke-Tulkens-Poster-SATURDAY-571-ASM-Microbe-2016.pdf

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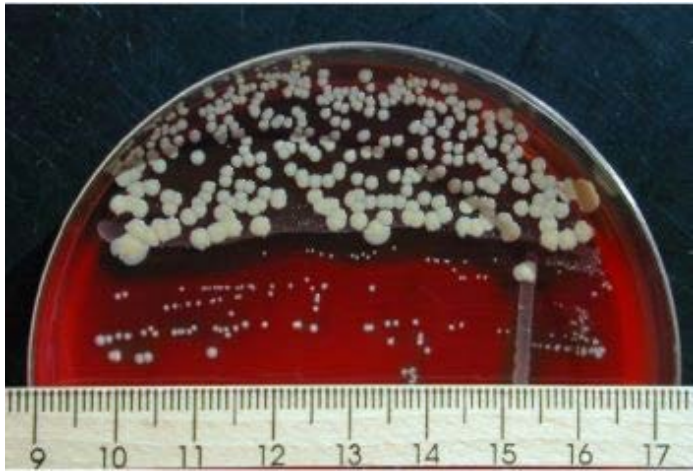
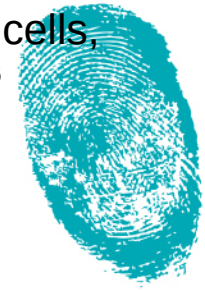
Small Colony Variants



http://infekt.ch/2006/10/small-colony-variants-von-staphylococcus-aureus-schwierig-zu-behandelnde-infektionen/
Klinik für Infektiologie/Spitalhygiene, St Gallen, Switzerland
Last visited 09/10/2016

- tiny colonies difficult to see by naked eye and often mistakenly disregarded as contaminants [1]
- usually recovered from protracted, difficult-to-treat infections (osteomyelitis, infected prostheses, cystic fibrosis…) [2]
- slow grow **(wait for 72h…)**
- deficit in metabolic pathways (→ menadione, hemin, or thymine dependence) [3]
- selected by antibiotics … and, consequently, poor susceptibility to most antibiotics [4]
- equally or more infective than their fast-growing parents [5]
- particularly prone to invade eukaryotic cells, persist therein and display resistance [6]



[1] Proctor et al. Infect Agents Dis (1994) 3:302-312 - PMID: 7889317
[2] Besier et al. J Clin Microbiol (2007) 45:168-172 -PMID:17108072
[3] Garcia et al, J Antimicrob Chemother (2013) 68:1455-1464 PMID: 23485724
[4] Baumert et al. Microb Drug Resist. 8:253-260 2002 PMID 12523621
[5] Jonsson et al. Microb Pathog (2003) 34:73-79 - PMID: 12623275 Bates et al. J Infect Dis (2003) 187:1654-1661 - PMID: 12721946
[6] Proctor et al. Infect Agents Dis (1994) 3:302-312 - PMID: 7889317 Tuchscherr et al. J Antimicrob Chemother (2016) 71:438-448 - PMID: 26589581

SCVs are a cause of resistance

J Antimicrob Chemother 2016; **71**: 438–448
doi:10.1093/jac/dkv371 Advance Access publication 20 November 2015

Journal of Antimicrobial Chemotherapy

Staphylococcus aureus develops increased resistance to antibiotics by forming dynamic small colony variants during chronic osteomyelitis

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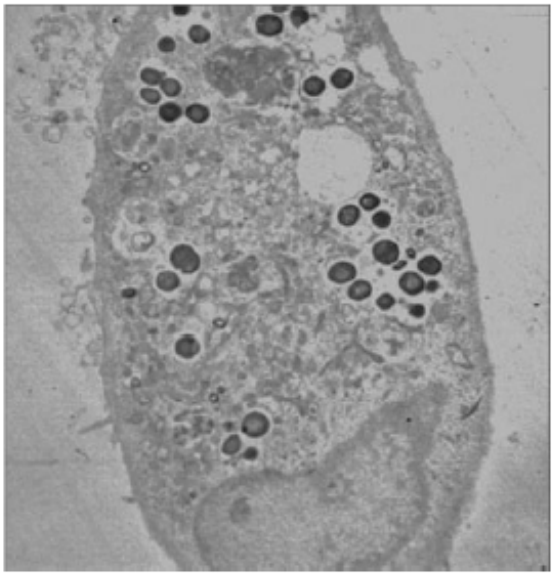
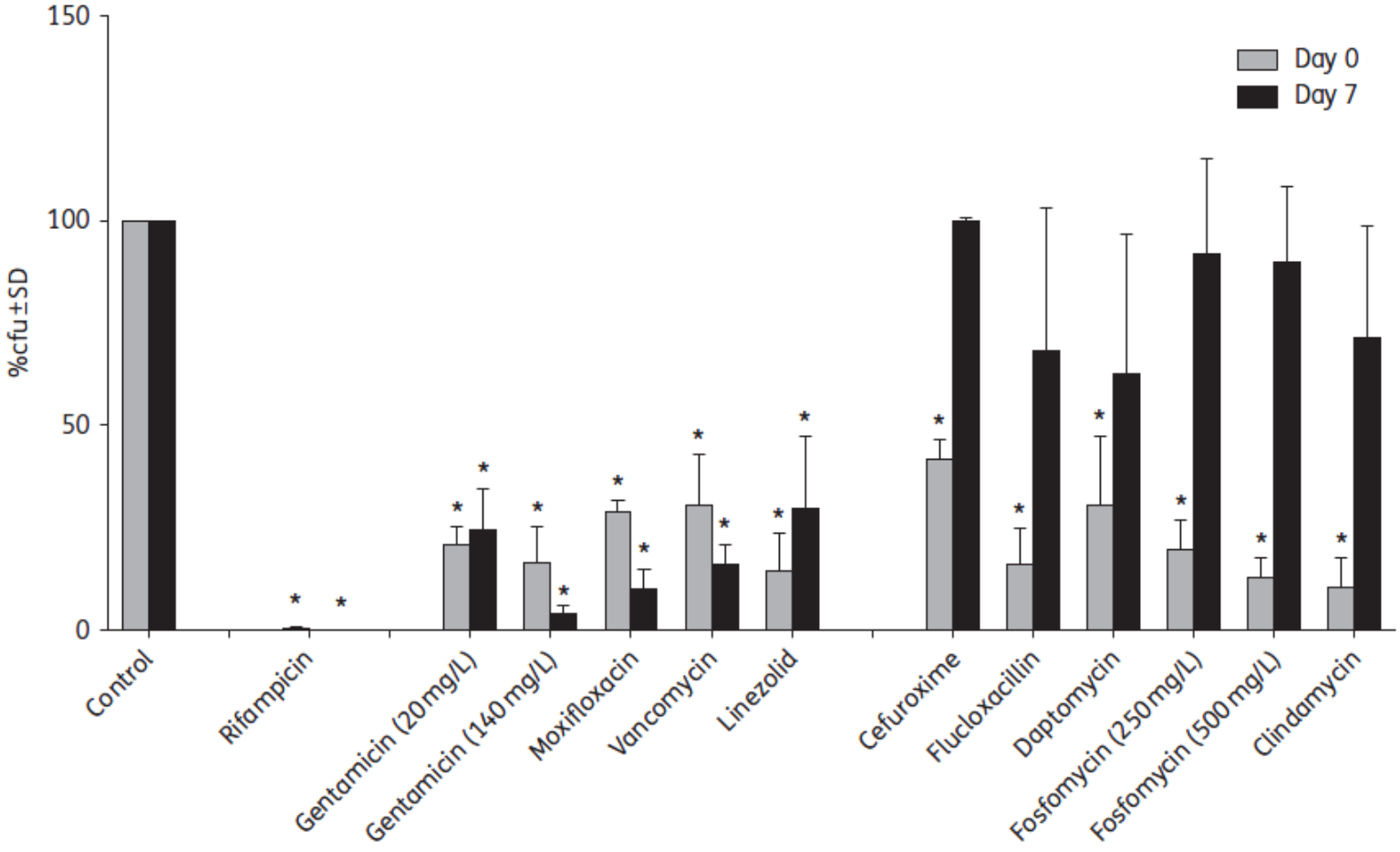
Tuchscherr et al. J Antimicrob Chemother (2016) 71:438-448 - PMID: 26589581



osteoblast infected with S. aureus SCV

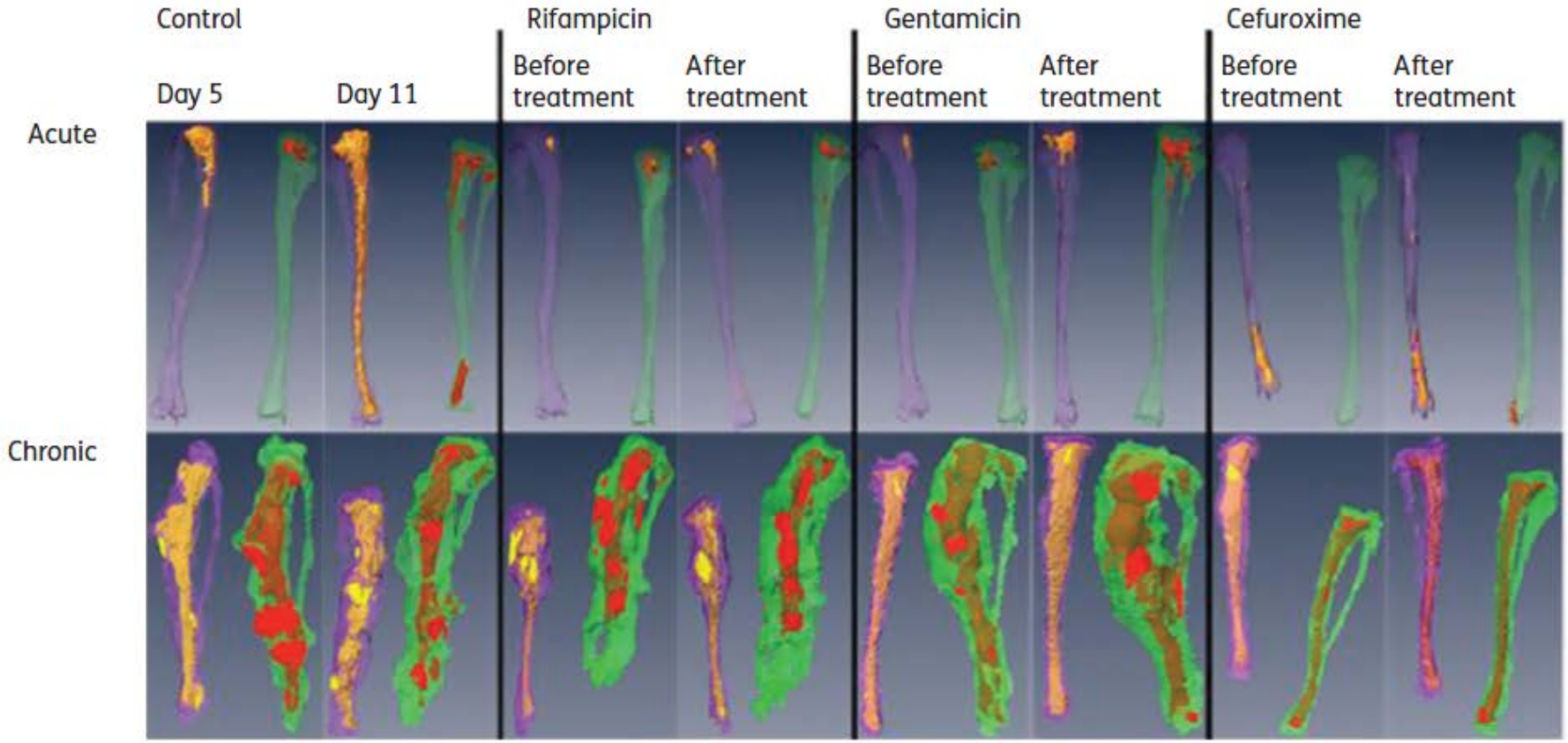
SCVs are not easily eradicated from osteoblasts in vitro (7 days model)



Osteoblasts infected with S. aureus SCVS and exposed to antibiotics: surviving bacteria

Tuchscherr et al. J Antimicrob Chemother (2016) 71:438-448 - PMID: 26589581

SCVs are not easily eradicated from osteoblasts in vivo (chronic infection)

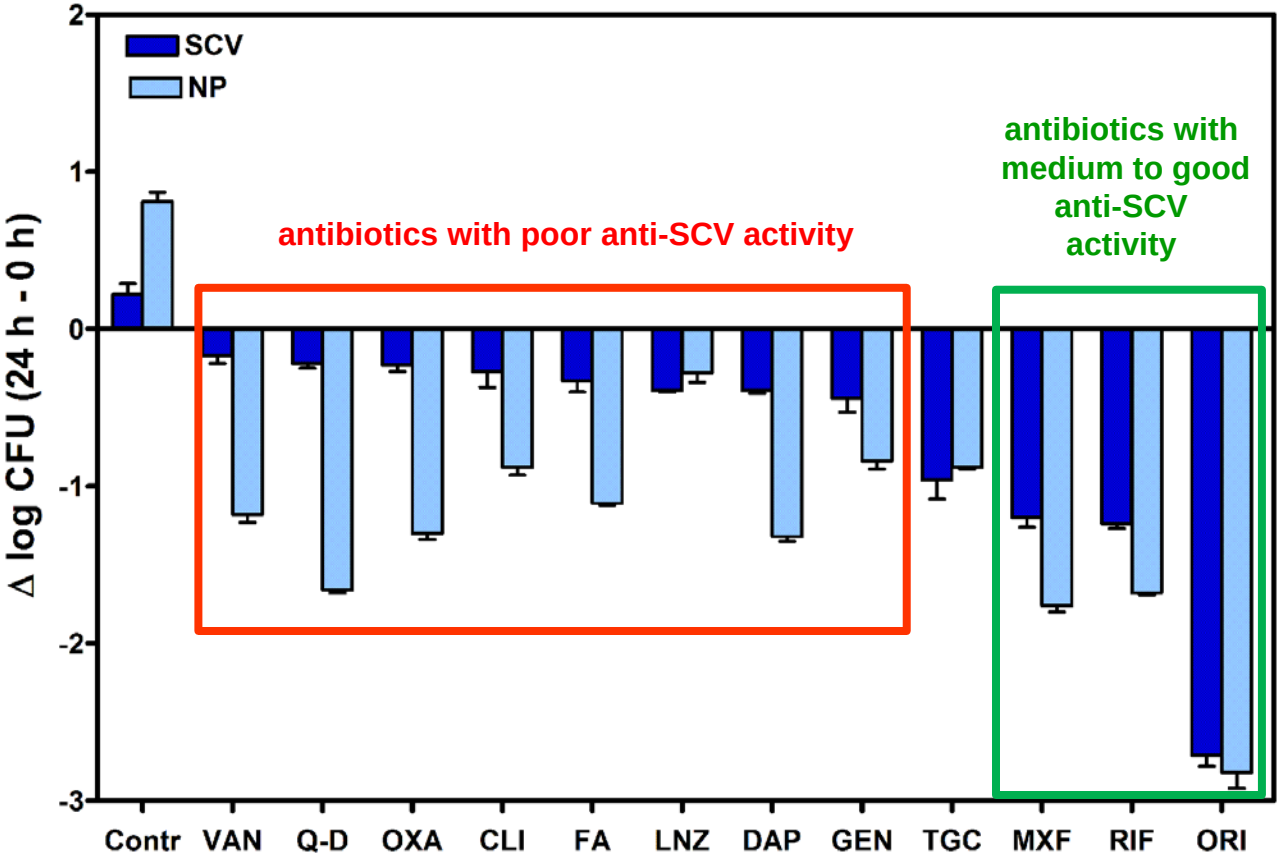


Magnetic resonance imaging showing osteomyelitis progression with and without therapeutic treatment

- Inflammatory lesions: orange and yellow (left) and red and brown (right)
- Non-inflamed area: magenta (left) and green (right)

Tuchscherr et al. J Antimicrob Chemother (2016) 71:438-448 - PMID: 26589581

A direct comparison of antibiotic efficacies between intracellular SCV and their isogenic fast growing parents (NP)



Contr: control
VAN: vancomycin
Q-D: quinupristin/ dalfopristin
OXA: oxacillin
CLI: clindamycin
FA: fusidic acid
LNZ: linezolid
DAP: daptomycin
GEN: gentamicin
TGC: tygecyclin
MXF: moxifloxacin
RIF: rifampin
ORI: oritavancin

Efficacy lower against SCV, possibly related to slower metabolism ?

Nguyen et al. Antimicrob Agents Chemother (2009) 53:1434-1442 – PMID: 19188393

Dose-effect studies comparing extracellular and intracellular SCVs

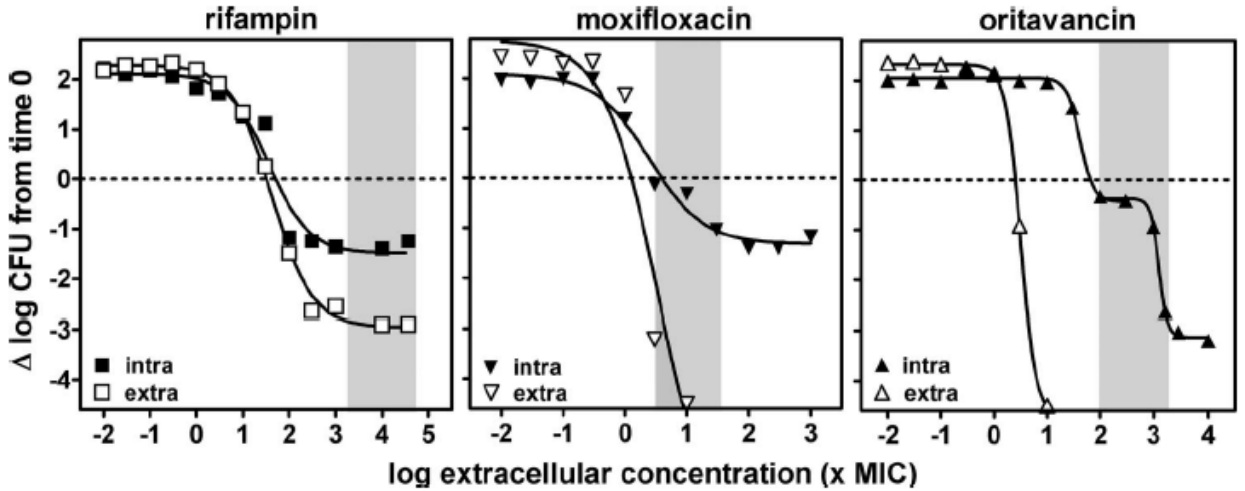


FIG. 6. Dose-response curves of the three most active antibiotics against extracellular and intracellular SCVs. The graphs show the change in the number of CFU (Δlog CFU from the initial inoculum) per ml of broth (extracellular [extra]) or per mg of cell protein (intracellular [intra]) in THP-1 macrophages after a 24-h incubation at the extracellular concentrations (total drug) shown in the abscissa. Curves were constructed by sigmoidal regression using the Hill equation (Table 2 gives the regression parameters); for oritavancin, for which a bimodal curve is clearly seen intracellularly, two successive sigmoidal regressions with variable slopes were used to fit the data. The zone highlighted in gray corresponds to the clinically relevant concentration range (total drug). Data are means ± standard deviations ($n = 3$); most error bars are smaller than the symbols.

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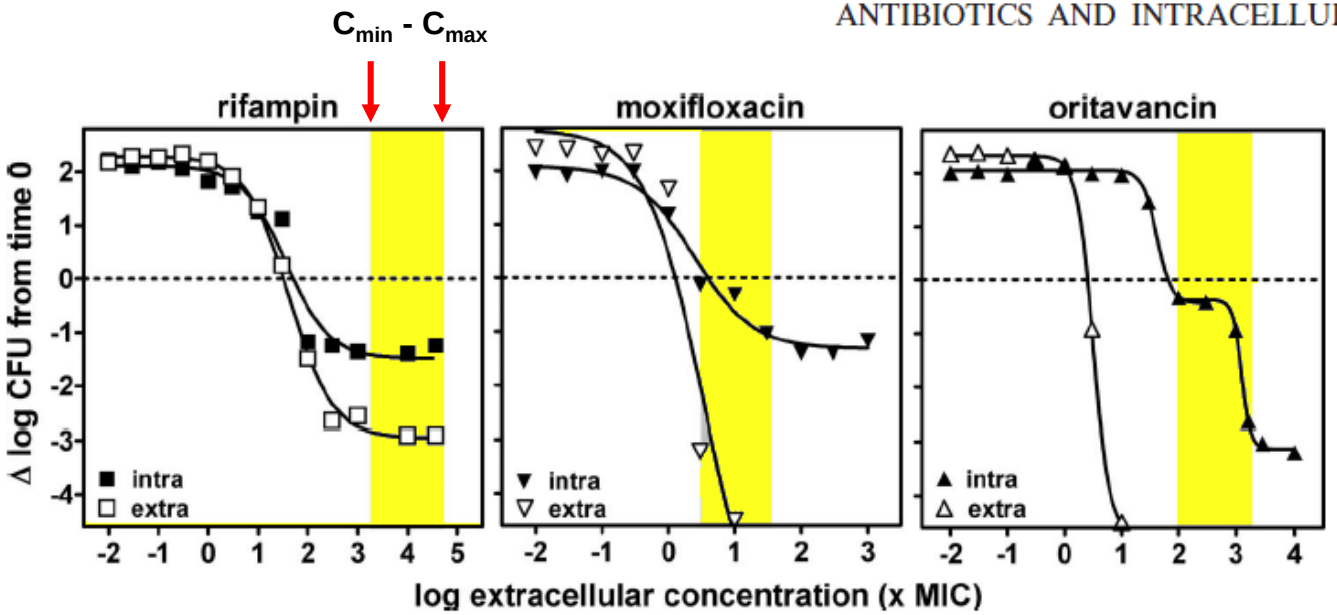

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The Saga of *S. aureus*

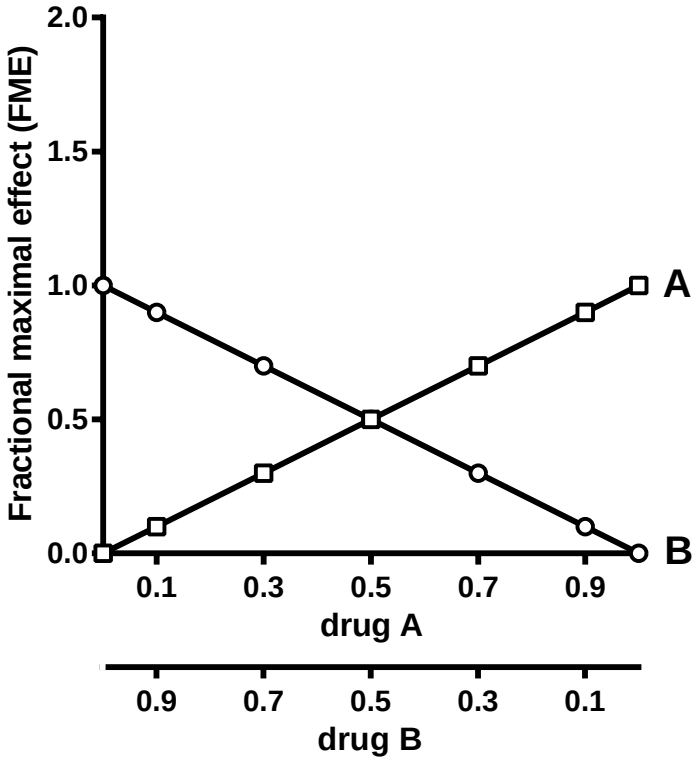
The problems

- the rise of resistance
  - from penicillin-S to MDR
- hidden habitats
  - intracellular forms
- **unexpected forms**
  - **the small colony variants**
- **the communities**
  - **biofilms**

Towards solution(s)

- the antibiotics
  - success of the 10 x '20 initiative ?
- driving antibiotic into cells
  - is accumulation helping ?
- **antibiotic combinations**
  - **overcoming poor susceptibility ?**
- **improving antibiotic penetration**
  - **disrupting the matrix ?**

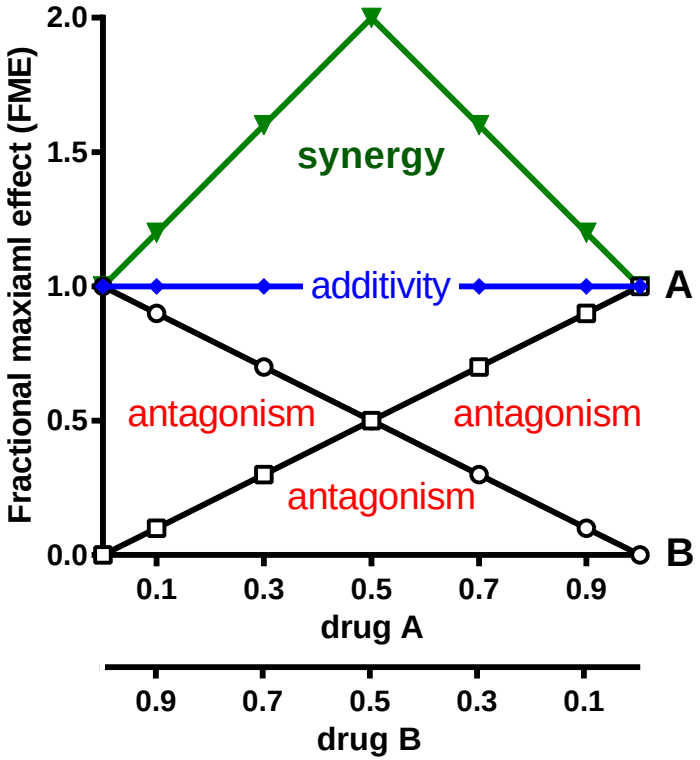
Antibiotic combinations may be a solution



Let us vary the ratio of A to B

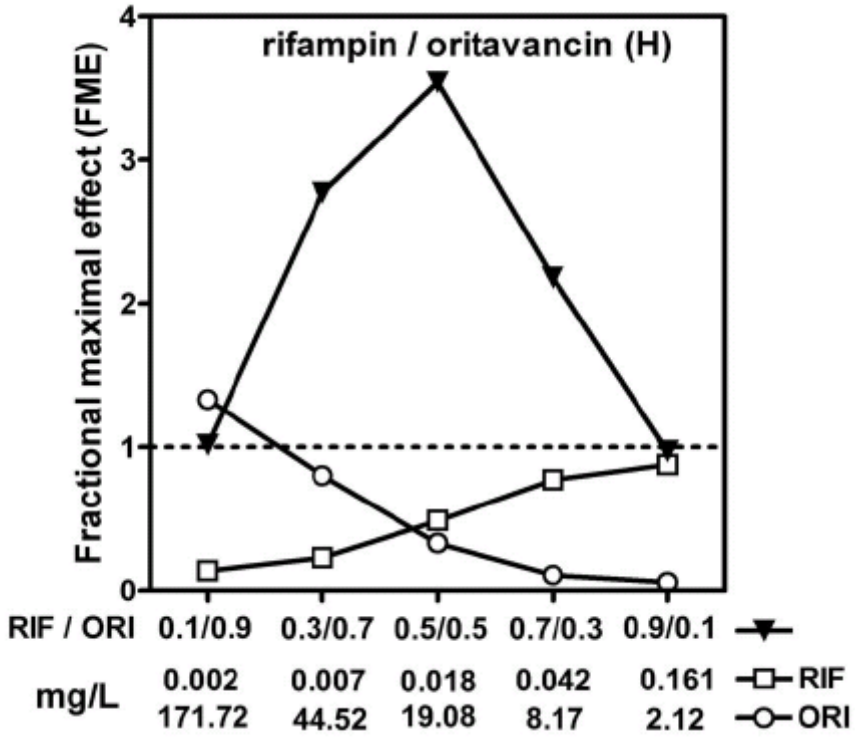
Li et al. Antimicrob. Agents Chemother (1993) 37:523–531 - PMID: 8460921
Desbiolles et al. Agents Chemother (2001) 45:3328–3333 - PMID:11709304

Antibiotic combinations may be a solution



Here is what you expect !

Li et al. Antimicrob. Agents Chemother (1993) 37:523–531 - PMID: 8460921
Desbiolles et al. Agents Chemother (2001) 45:3328–3333 - PMID:11709304

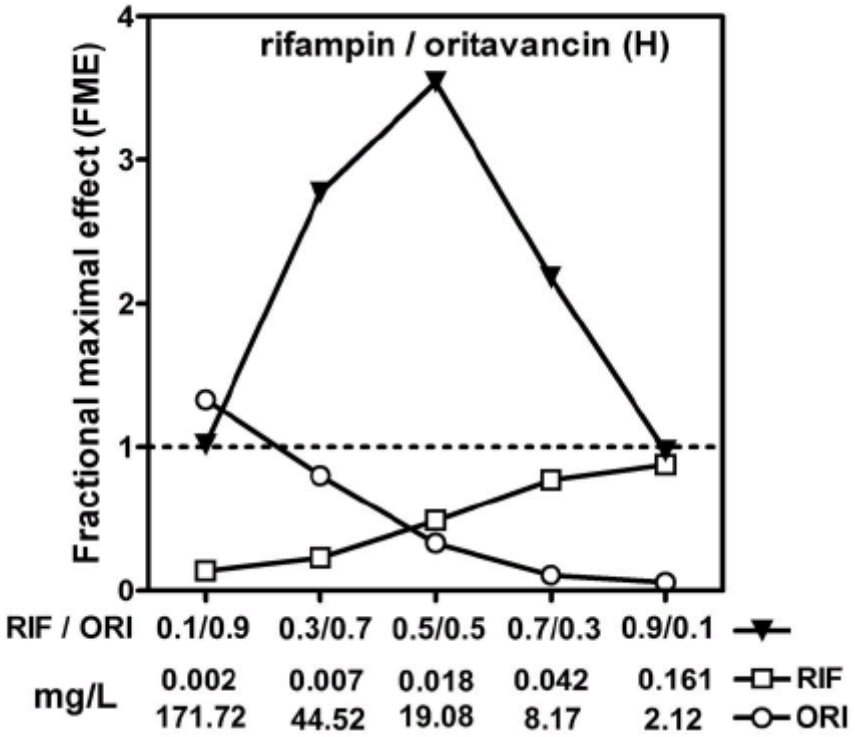


and this is what we saw !

Nguyen et al. Antimicrob Agents Chemother (2009) 53:1434-1442 – PMID: 19188393

Antibiotic combinations may be a solution

https://de.wikipedia.org/wiki/Heinrich_von_Opel
Last visited: 22 Oct 2016



More combinations must be studied …

and this is what we saw !

Nguyen et al. Antimicrob Agents Chemother (2009) 53:1434-1442 – PMID: 19188393

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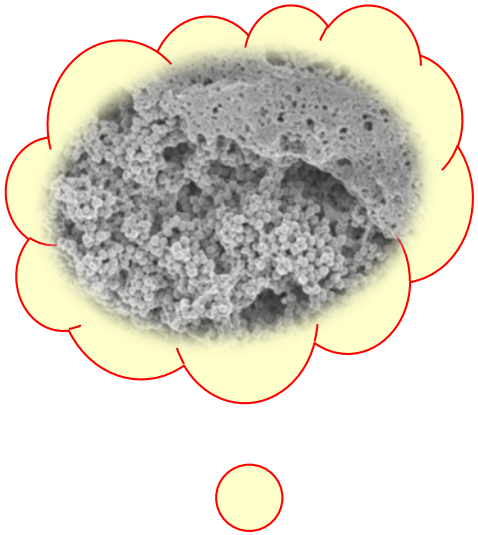
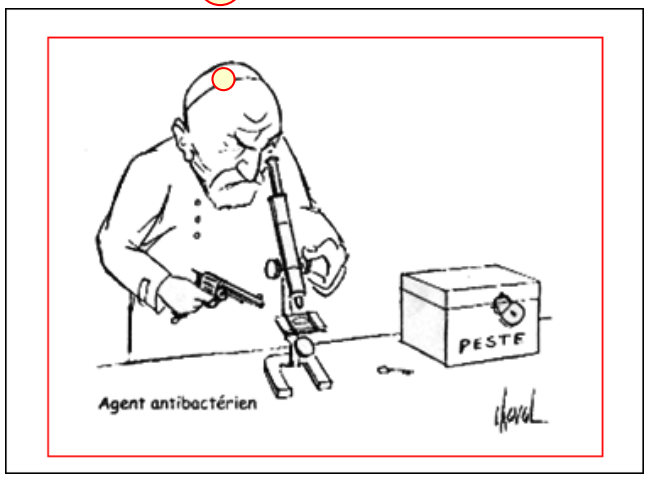
- improving antibiotic penetration
  - disrupting the matrix ?

Biofilms (microbial communities)



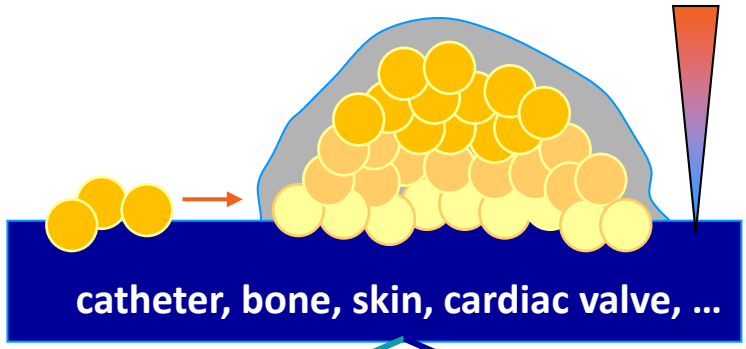
University of Gothenburg, Gohtenburg, Sweden
http://phys.org/news/2015-11-technique-dangerous-biofilms-catheters.html



- ancient multicellular life forms [1] with key pathogenic roles in up to 80 % of infections processes (first recognized with *P. aeruginosa* [2])
- structured aggregation of surface-attached microcolonies **encased in an extracellular matrix** and separated by fluid-filled channels [3]
- substratum conditioned by host matrix proteins (fibrinogen, fibronectin, and collagen) [4]
- resistance mediated through a dormant phenotype (anoxic environment and nutrient deprivation) with cell division occurs very slowly, producing **persister cells** [5]

1 Henrici AT J Bacteriol (1933) 25:277–87 - PMID: 16559616
2 Lam et al. Infect Immun (1980) 28:546–56 -PMID: 6772562
3 O'Toole et al. Annu Rev Microbiol (2000) 54:49-79. PMID: 11018124
4 François et al. J Lab Clin Med (2000) 135:32–42 -PMID: 10638692
5 Lewis K Annu Rev Microbiol (2010) 64:357-372 - PMID: 20528688

Biofilms: the problems



pharmacokinetics

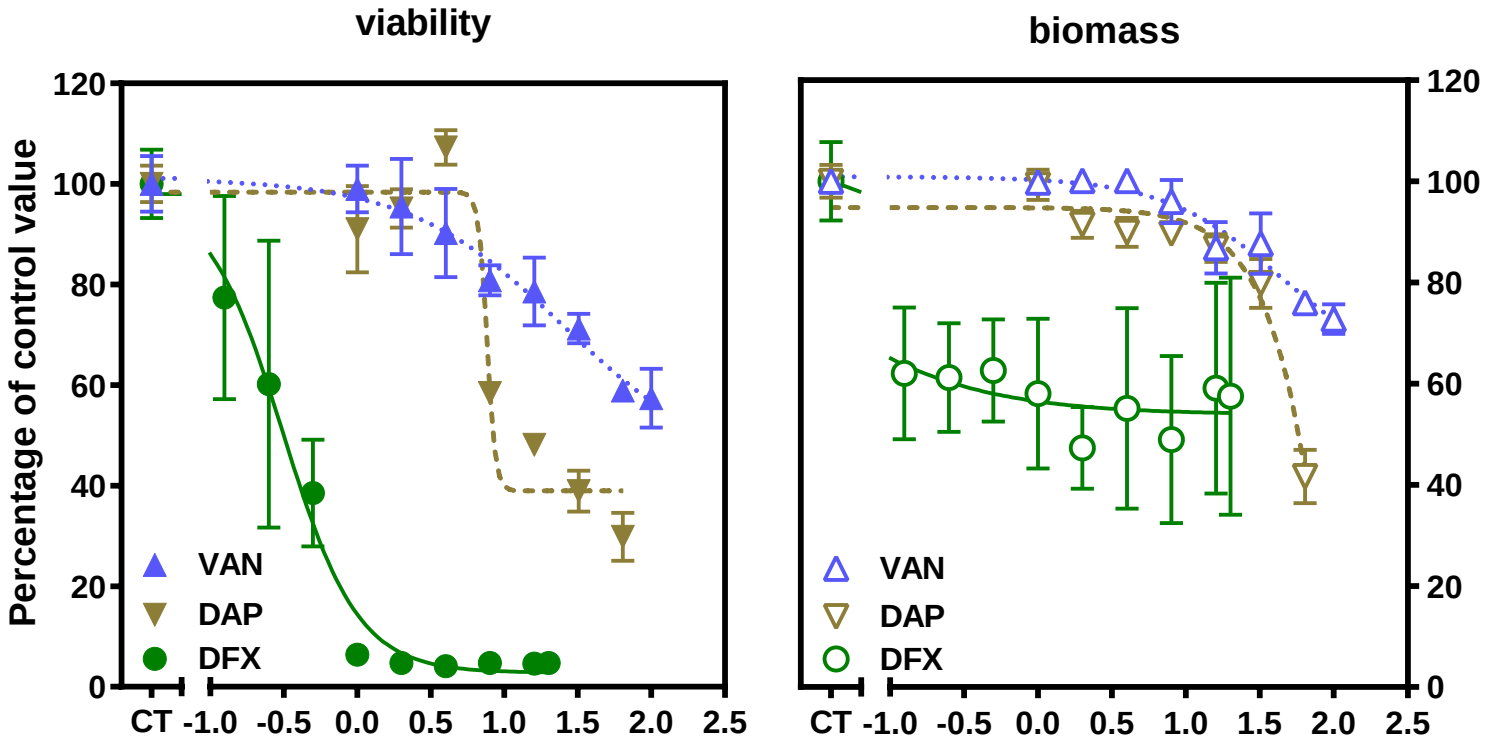
- diffusibility through the matrix
- bioavailability within the biofilm
- access to bacteria
- efflux out of bacteria

pharmacodynamics

- bacterial responsiveness (metabolic activity of bacteria)
- antibiotic expression of activity (local environment [O_2, pH, ..])

From F. Van Bambeke: Anti-staphylococcal activity of antibiotics in biofilm and host cell.
ESCMID Postgraduate educational course, Lyon, France, 2016
http://www.facm.ucl.ac.be/conferences/2016/06-Lyon-ESCMID/Vanbambeke-ESCMID-intra-biofilm.pdf
Last visited: 10 Oct 2016

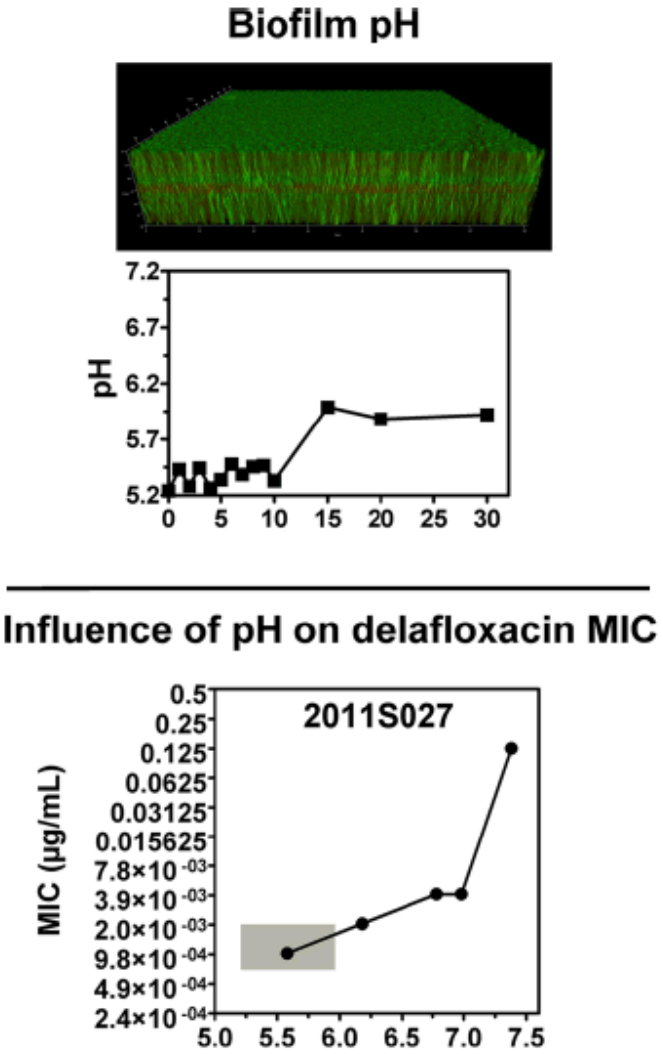
Biofilms respond poorly to many antibiotics… but not all…



Activities of antibiotics against biofilms. Concentration-response activities of antibiotics against 24-h biofilms of strain 2011S027 incubated with increasing concentrations of antibiotics for 48 h (**DFX, delafloxacin**; **DAP, daptomycin**; **VAN, vancomycin**).

Siala et al. Antimicrob Agents Chemother (2014) 58:6385-6398 – PMID: 25114142

Delafloxacin activity in biofilms is boosted by acid pH

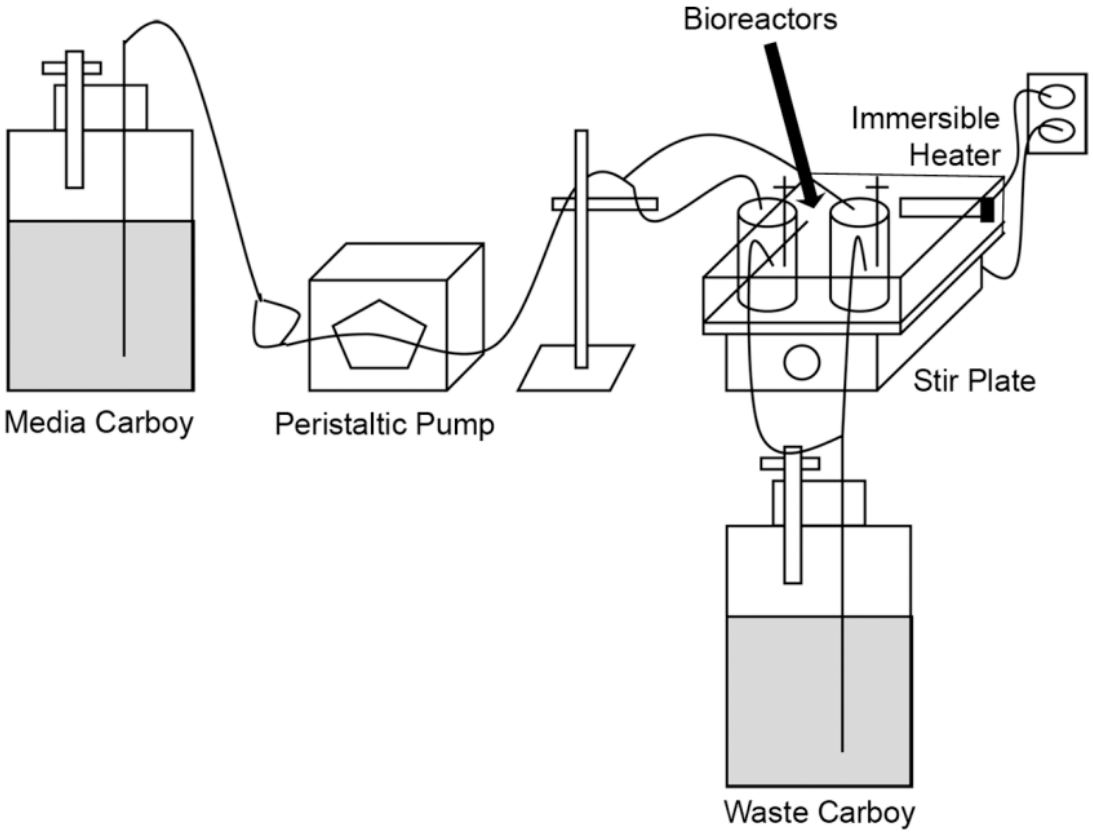


Micro-pH in biofilms and influence on delafloxacin activity

- Top: micro-pH within biofilms using C-SNARF-4 as a pH-sensitive probe (fluorescence emitted shifting from red to **green** upon acidification).
- Middle: micro-pH in the depth of the biofilm.
- Lower: influence of pH on the MIC of delafloxacin in MHB. The gray squares highlight the range of pH measured in the corresponding biofilm.

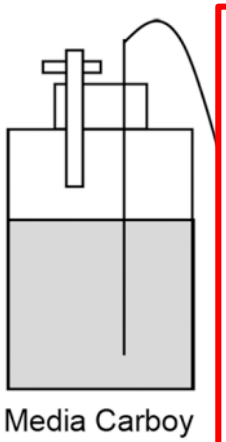
Siala et al. Antimicrob Agents Chemother (2014) 58:6385-6398 – PMID: 25114142

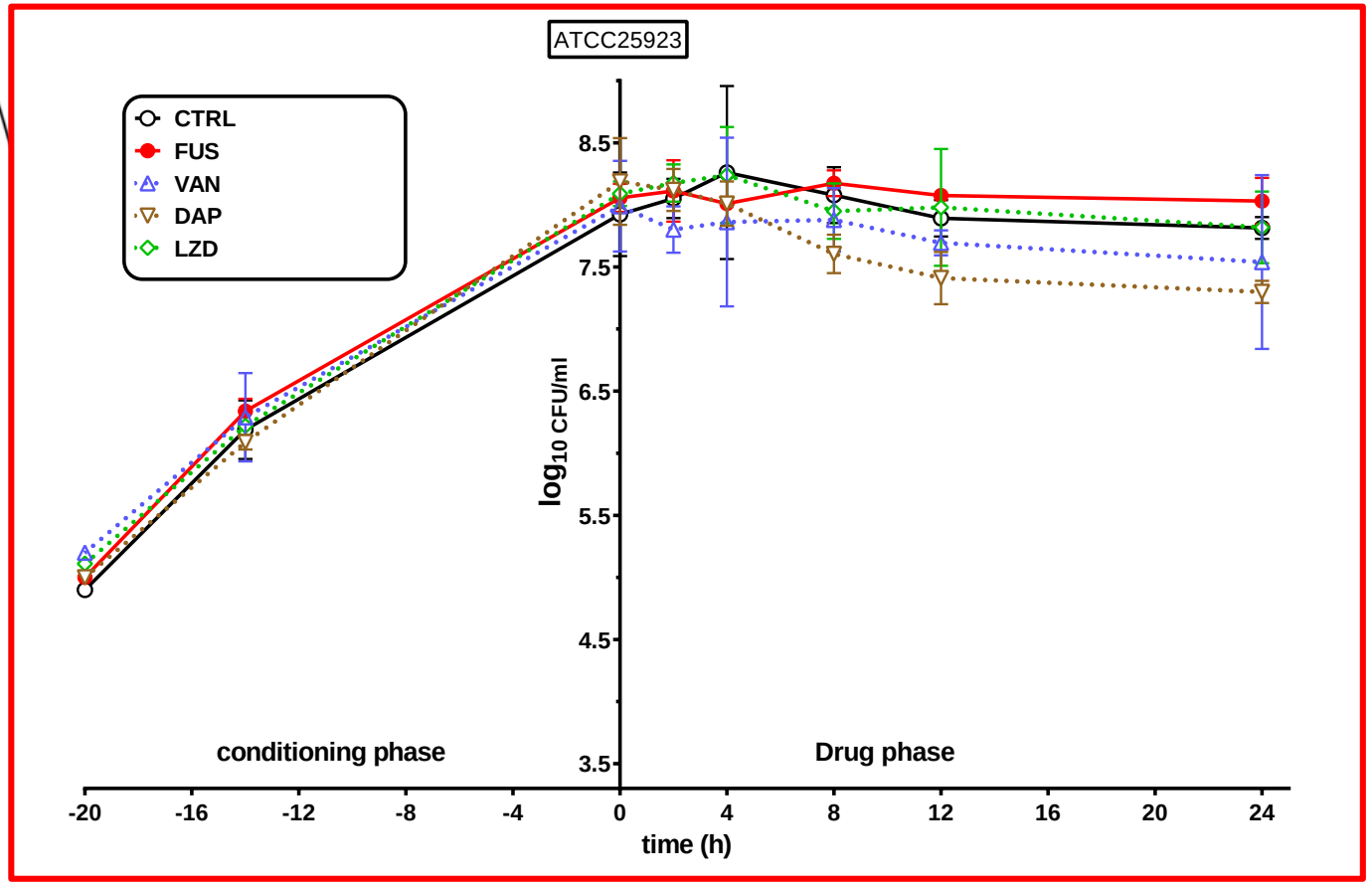
Moving to a dynamic model…



Stewart et al. PLoS One. 2012;7(11):e50560 - PMID: 23185637

Combinations may be the way to go for biofilms…





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Siala et al. Antimicrobial resistance in microbial biofilms and options for treatment ESCMID Course, 5-7 Oct 2016, Ghent, Belgium

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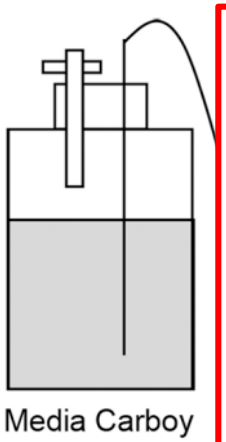

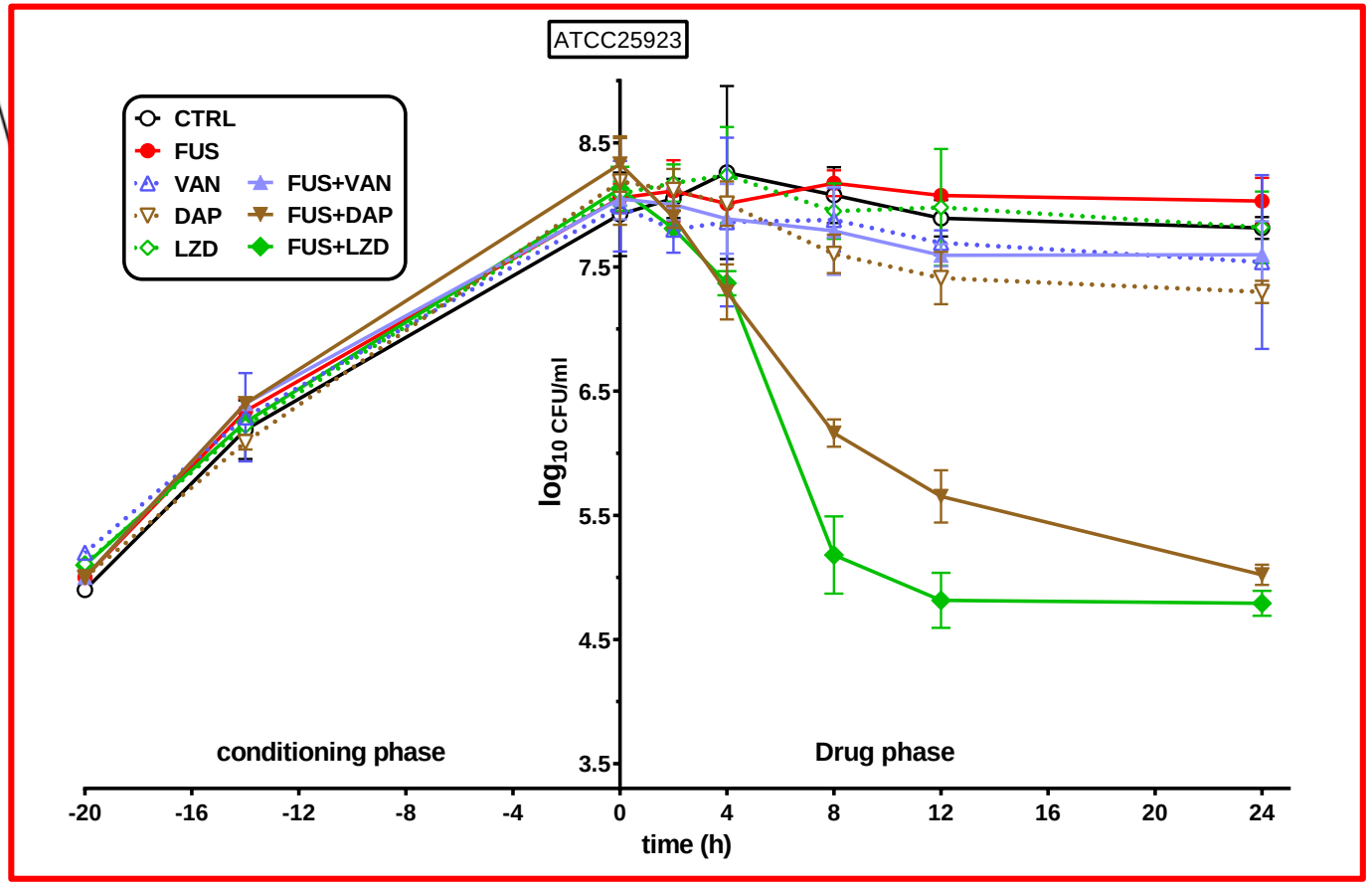

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Disrupting the Matrix ?

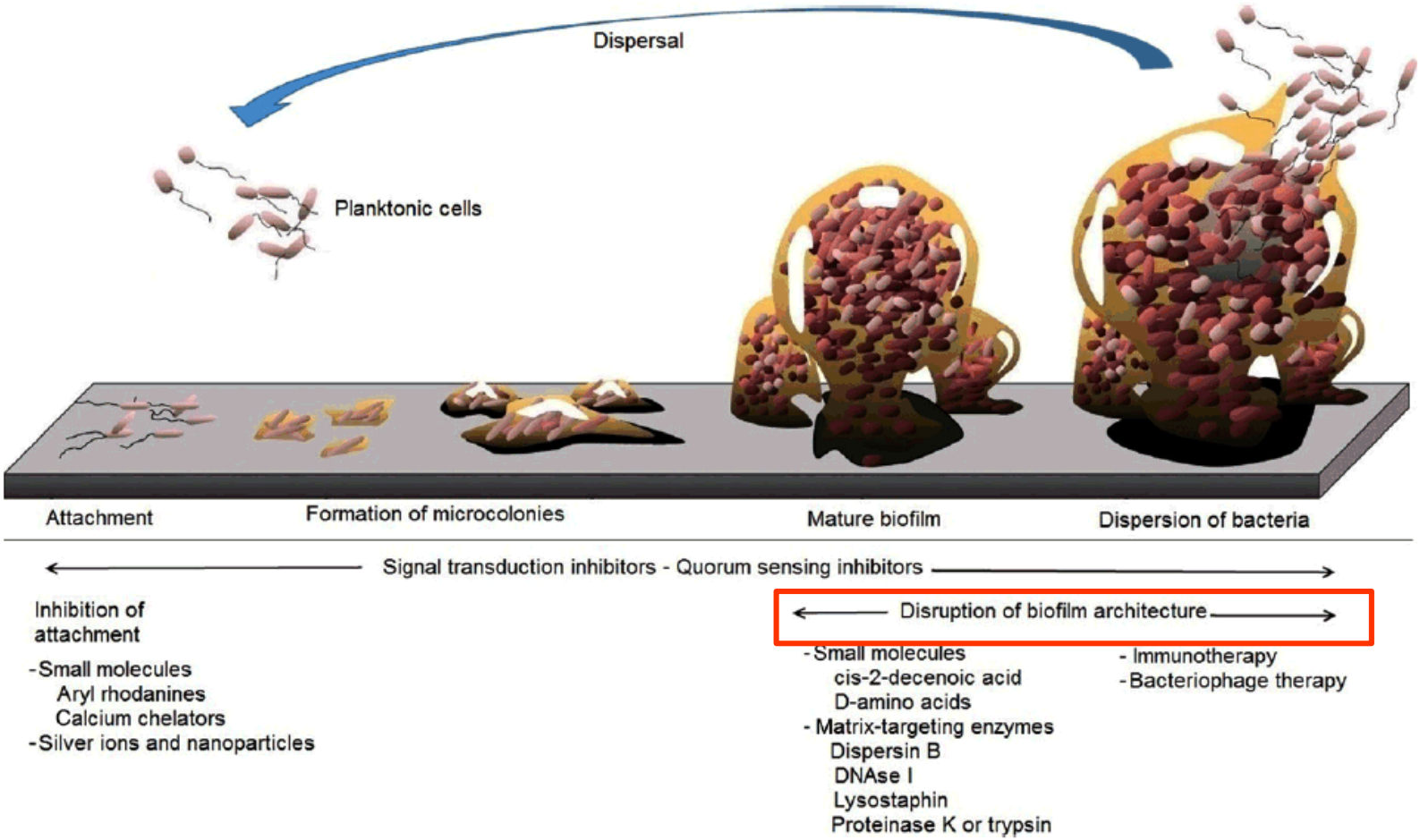
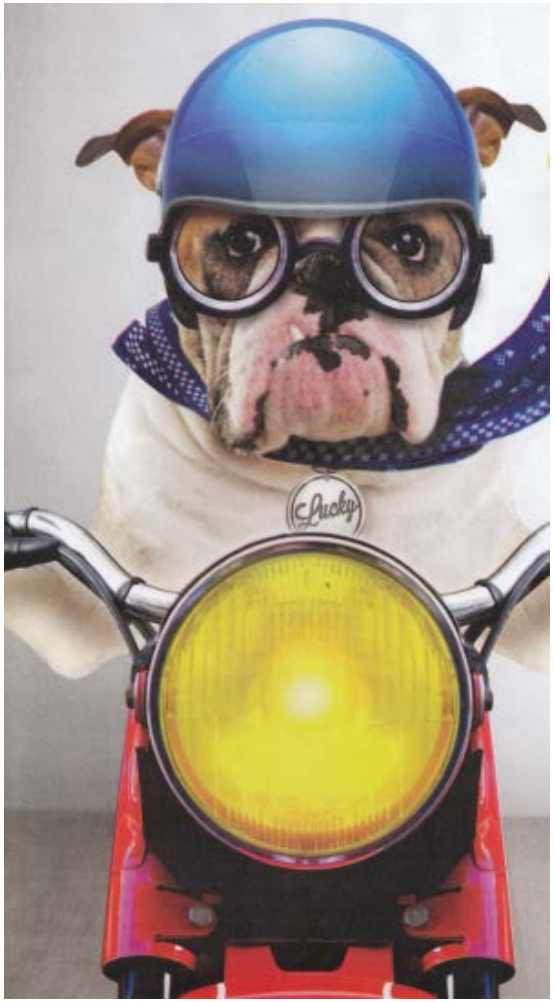


Fig. 2 Strategies in the management of biofilms (adapted from wikipedia.org/wiki/File:Biofilm.jpg).

Chung & Toh. Pathog Dis (2014) 70:231-239 - PMID: 24453168

Disrupting the Matrix ?



see how …

https://www.shutterstock.com/search/russell+terrier
Last visited: 22 Oct 2016

Disrupting the Matrix ?

nature COMMUNICATIONS

ARTICLE

Received 23 Feb 2016 | Accepted 20 Sep 2016 | Published 3 Nov 2016

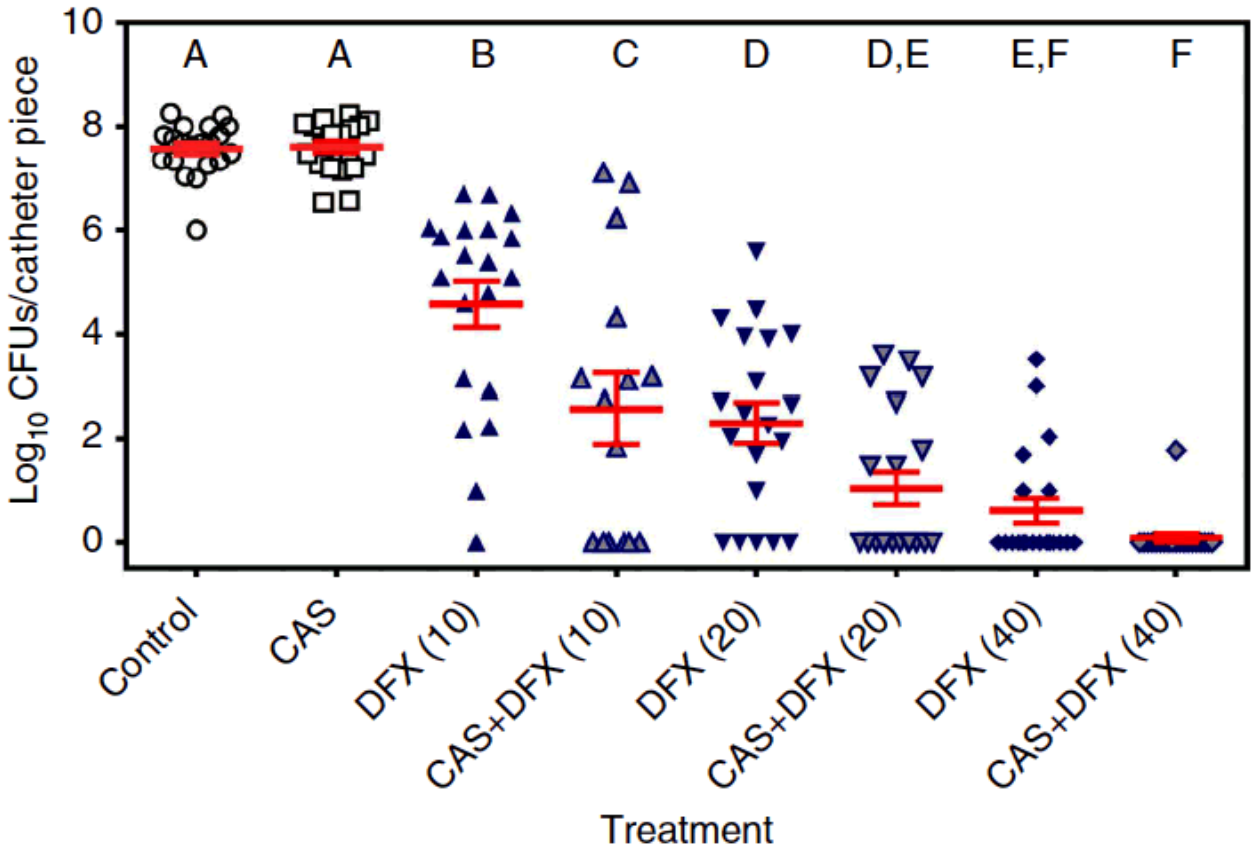
DOI: 10.1038/ncomms13286 OPEN

The antifungal caspofungin increases fluoroquinolone activity against *Staphylococcus aureus* biofilms by inhibiting *N*-acetylglucosamine transferase

Wafi Siala[1], Soňa Kucharíková[2,3], Annabel Braem[4], Jef Vleugels[4], Paul M. Tulkens[1], Marie-Paule Mingeot-Leclercq[1], Patrick Van Dijck [2,3] & Françoise Van Bambeke[1]

http://www.nature.com/articles/ncomms13286

Disrupting the Matrix ?

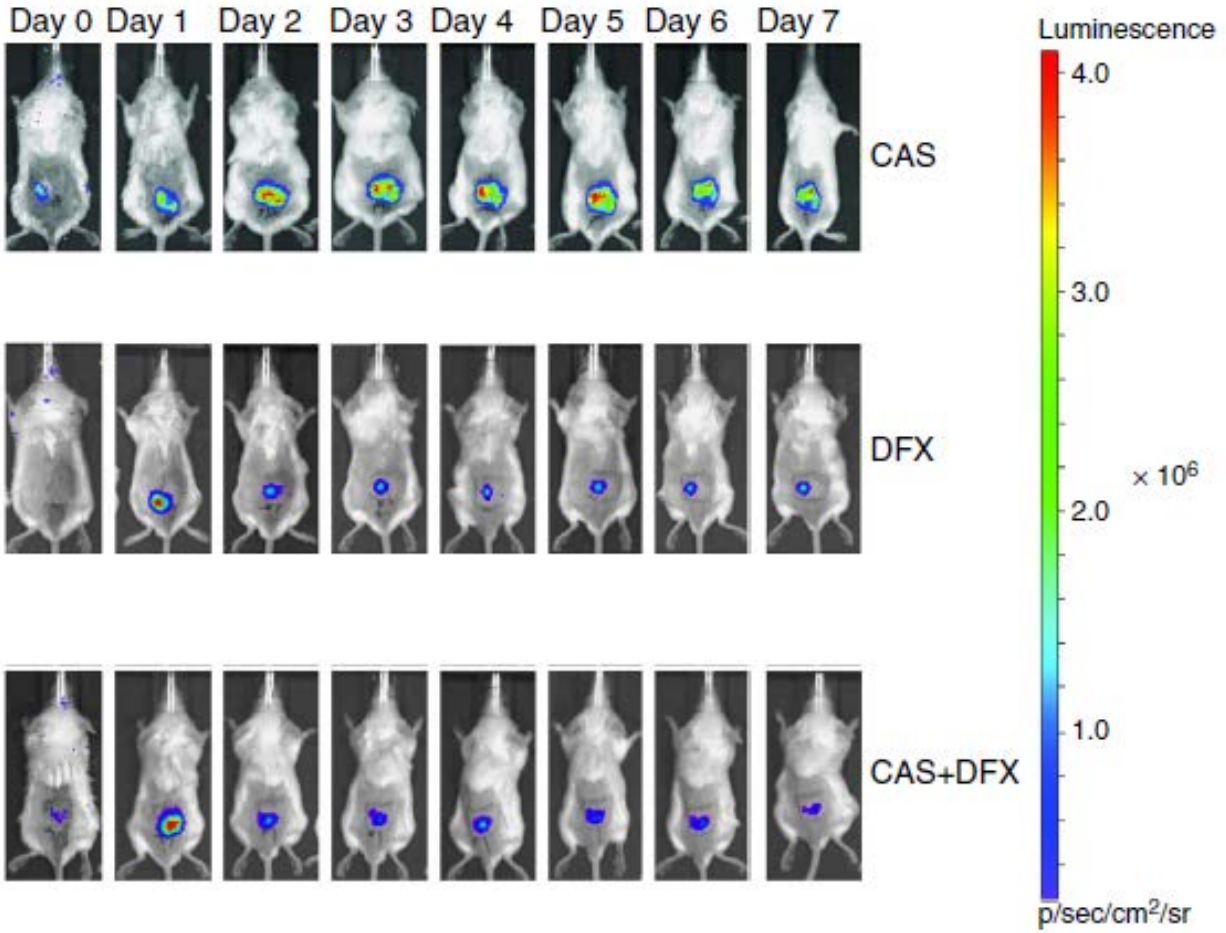


Activity (dose response) of delfloxacin alone or combined with caspofungin on S. aureus biofilms in vivo: (mouse subcutaneous biofilm model). Animals were treated for 7 days with caspofungin (CAS; 4 mg/kg of body weight) once daily, delafloxacin twice daily, or with delafloxacin at each of these doses combined with caspofungin Statistical analysis (one-way ANOVA; Tukey post-hoc test): groups with different letters are significantly different from one another (P<0.05).

http://www.nature.com/articles/ncomms13286

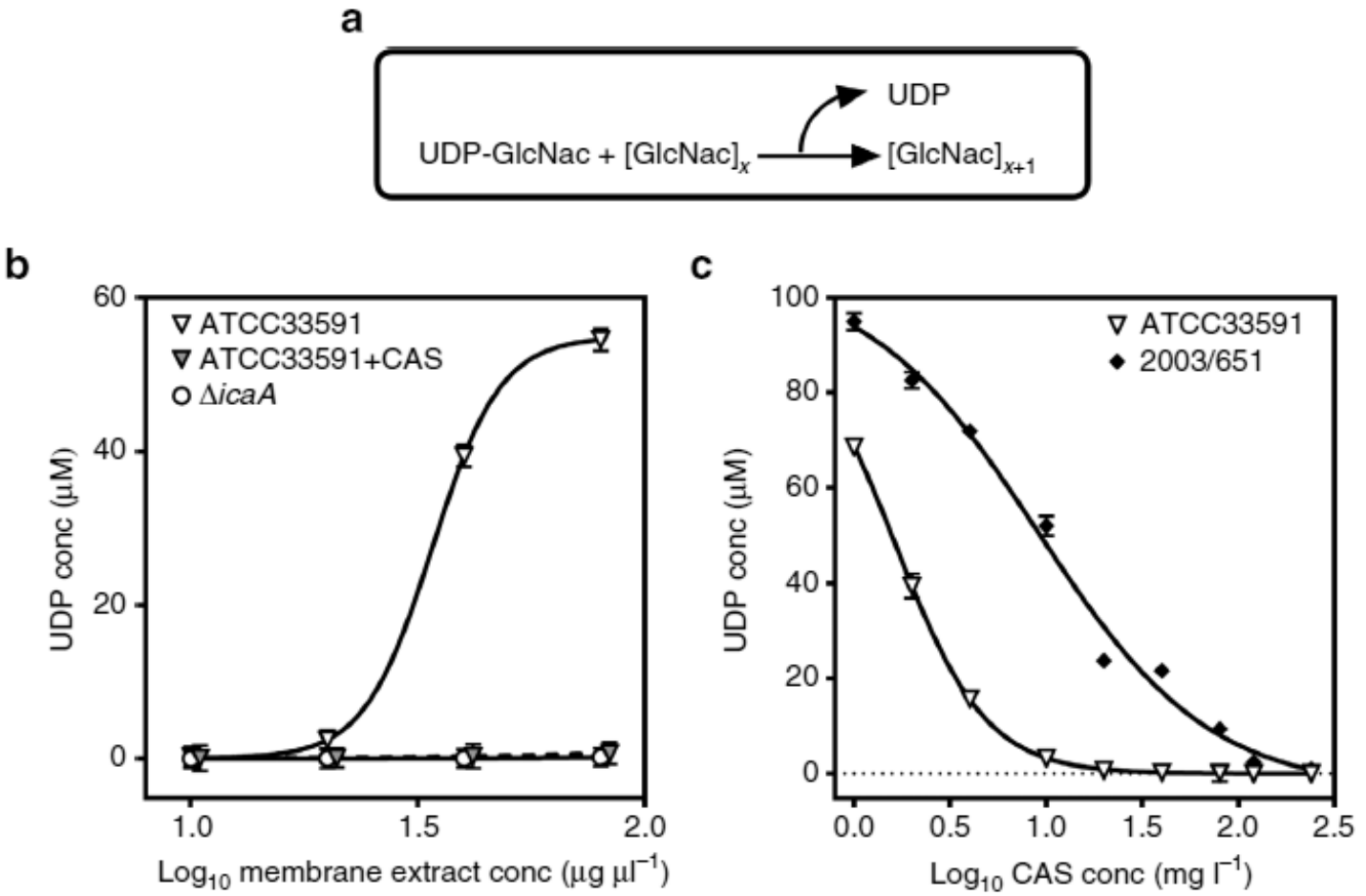
Disrupting the Matrix ?

http://www.nature.com/articles/ncomms13286



Activity of delafoxacine alone or combined with caspofungin against the bioluminescent strain Xen36 in vivo. Bioluminescent signal emitted from catheters infected by Xen36, implanted at day 0 in the back of mice treated 24 h after implantation and for the next 7 days with caspofungin (CAS) (4mg/kg/of body weight once daily), or delafloxacin (DFX) (40 mg/kg of body weight twice daily) or with a delafloxacin and caspofungin (each injected separately and according to its own schedule; Intensity of the transcutaneous photon emission represented as a pseudocolor image.

Disrupting the Matrix ? Here is why …



Ica A (N-acetylglucosamine transferase) activity and its inhibition by caspofungin. (a) Reaction catalyzed by IcaA. (b) Activity of IcaA in membrane protein extracts from strain ATCC33591 and its *ΔicaA* mutant. Activity was evaluated by the amount of UDP liberated in the reaction medium.

http://www.nature.com/articles/ncomms13286

Messages

- *S. aureus* (and other *staphylococci*) have been of medical concern for many years…
- Resistance was long considered as the first danger … but may have been put under (provisional) control by the wave of new drugs *(success of the 10 x 20's initiative ?)*
- Intracellular forms, SCV's, and biofilms still require much attention as current therapies are often inadequate…
  - Novel drugs need to be tested for activity against these recalcitrant forms of infection
  - Fluoroquinolones (delafloxacin in particular) and caspofungin may cooperate for biofilm elimination
    (through bacterial killing and matrix disruption)