Contribution of new antibiotics to current and future challenges of main Gram-positive infections

Paul M. Tulkens, MD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute,
Université catholique de Louvain,
Brussels, Belgium
http://www.facm.ucl.ac.be

ECCMID MSD Integrated Symposium
Are Gram-positive infections still a major concern to patients and Healthcare system?
Saturday 23 April 2018 – 16:00 – 18:00

UCL Université catholique de Louvain

LDRI LOUVAIN DRUG RESEARCH INSTITUTE

Disclosures

Research grants and Speaker's honoraria from

- Cempra Pharmaceuticals [1]
- Cerexa
- GSK
- Melinta Therapeutics [2]
- MerLion Pharmaceuticals
- Theravance
- Trius Therapeutics [3]
- Merck
- Bayer

Influenced by my participation to the

- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
- the Governance Body of DRIVE-AB (2014-2017)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

[1] merged in 2017 with and renamed as Melinta Therapeutics
[2] formerly RibX Pharmaceuticals
[3] acquired by Cubist (2014), which was then acquired by Merck (2016)

Learning objectives

- Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed
- Current duration of hospitalization: when could the patient go home ?
- Contribution of new therapeutic options:
  - review of some key available data
  - my personal views on specific/appropriate contribution of the new therapeutic options to both short and long term use and infection management

Common challenges when managing Gram positive infections

- Clinical management challenges with various :
  - clinical entities,
  - site of infections,
  - involved Gram positive pathogens
  - antibiotic therapeutic options and duration

- **Resistance challenges**

- **BJI and Biofilms challenges to antibiotic treatment**

- intracellular forms / persisters /small colony variants

Resistance challenges (in *S. aureus*)

β-lactams	**glycopeptides**	**fluoroquinolones**	**oxazolidinones** (linezolid)	**macrolides lincosamides**	**lipopeptides** (daptomycin)	**fusidic acid**	**trimethoprim**	**sulfamethoxazole**
penicillinase	thick cell wall	gyrA mutations	*cfr*	*erm*	*mprF*	*fusA*	*dfrA*	*dpsA*
PBP2a	*van A* *van H*	*norA* (efflux)	ribosomal mutations	*mrsA* (efflux)				

Adapted from Que & Moreillon, Staphylococcus aureus. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., Elsevier (chapter 196 [updated 2016]; available on line at https://expertconsult.inkling.com)

This has considerably reduced our potential arsenal, with full or partial demise of

- conventional β-lactams (except the recent anti-MRSA cephalosporins [ceftaroline, …])
- most currently EU-approved fluoroquinolones
- currently approved macrolides and lincosamides
- fusidic acid (in Europe) and sulfamethoxazole/trimethoprim

and even menacing

- vancomycin (for isolates with MIC > 1.5 mg/L (EUCAST "R" breakpoint is > 2 mg/L)
- linezolid -

Alternatives treatments include

- quinupristin/dalfopristin *(availability ?)*
- tigecycline *(efficacy ?)*

and <u>newly EU-approved drugs</u>

- oritavancin, dalbavancin
- tedizolid
- ceftarolline….

Are MRSA still of concern ?

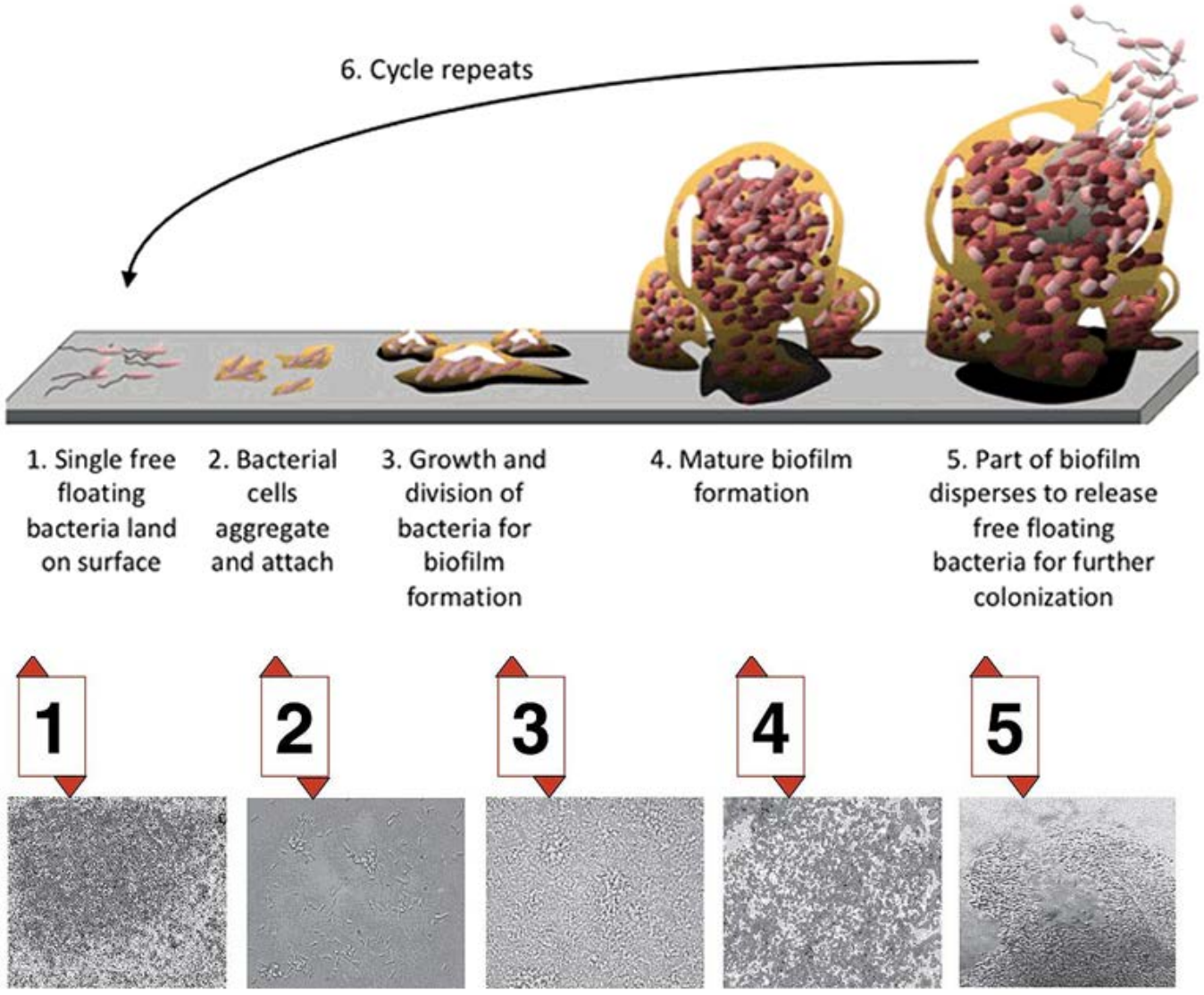
Table 3. Prevalence of MRSA in various regions based on surveillance programs.

Region	*S. aureus* (N)	MSSA (%)	MRSA (%)	Testing period	Reference
US	43,331	53.6	**46.4**	2011–2014	57
Canada	2539	80.2	**19.8**	2010–2012	58
Europe	40,414	82.6	**17.4**	2013	59
China	6656	51.1	**48.9**	2004–2011	60
Asia	4117	47.5	**52.5**	2004–2006	61
Asia Pacific	1971	38.1	**61.9**	2012	62
Latin America	1066	41.7	**58.3**	2012	63
Middle East/ North Africa	NR	NR	**42.1**	Before 2014	25

MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-sensitive *Staphylococcus aureus*; NR, not reported.

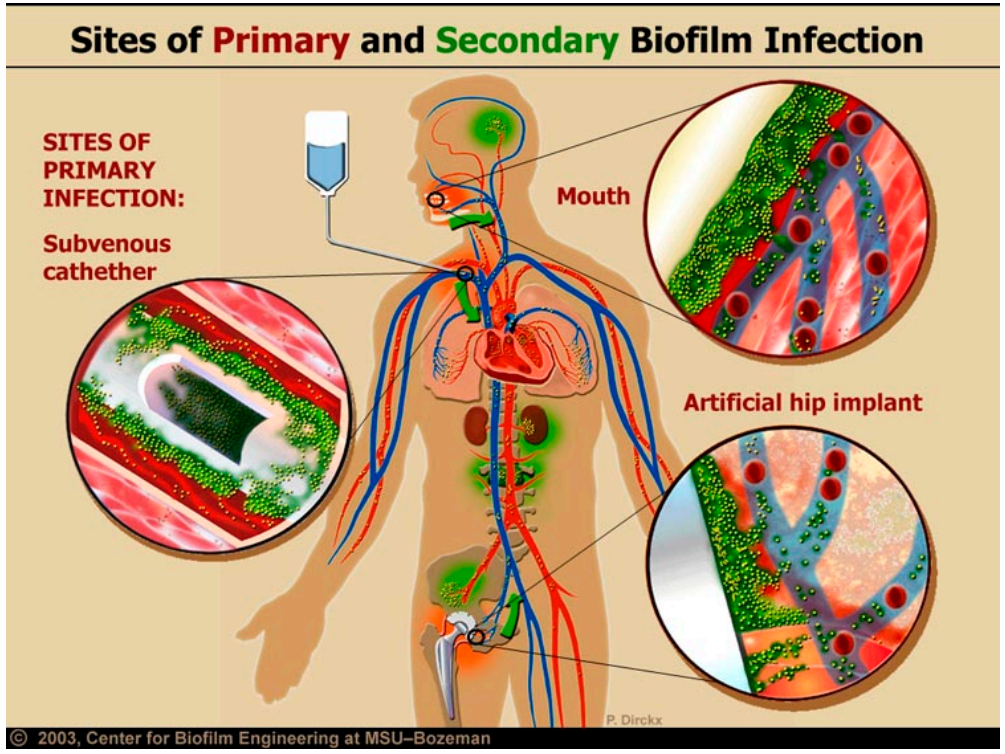
Pulido-Cejudo et al. Ther Adv Infect Dis. 2017;4:143-161 - PMID: 28959445

Biofilms challenges



http://www.bayarealyme.org/blog/straight-talk-biofilms-new-answer-treating-lyme-disease/ Last visited: 28 Sep 2017

Biofilms are associated to 65[a]-80[b] % of human infections and can colonize virtually all organs …



[a]CDC 1999; [b]Lewis et al, Nat Rev Microbiol. 2007; 5:48-56

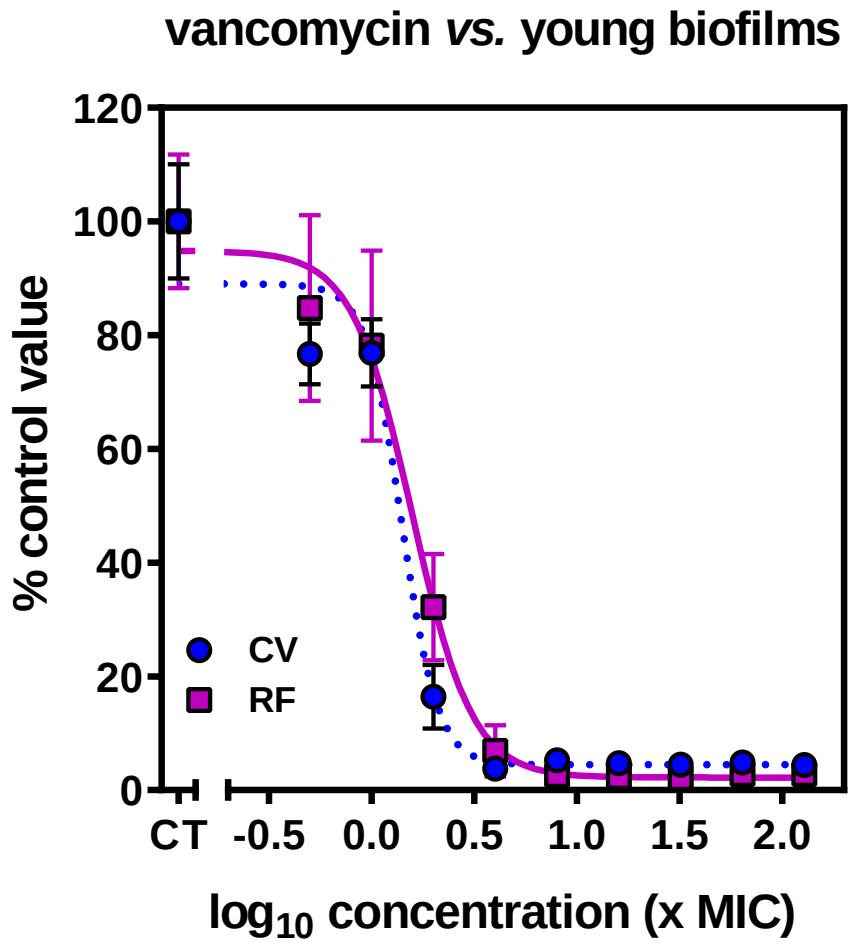
Biofilms are recalcitrant to antibiotics once formed and mature

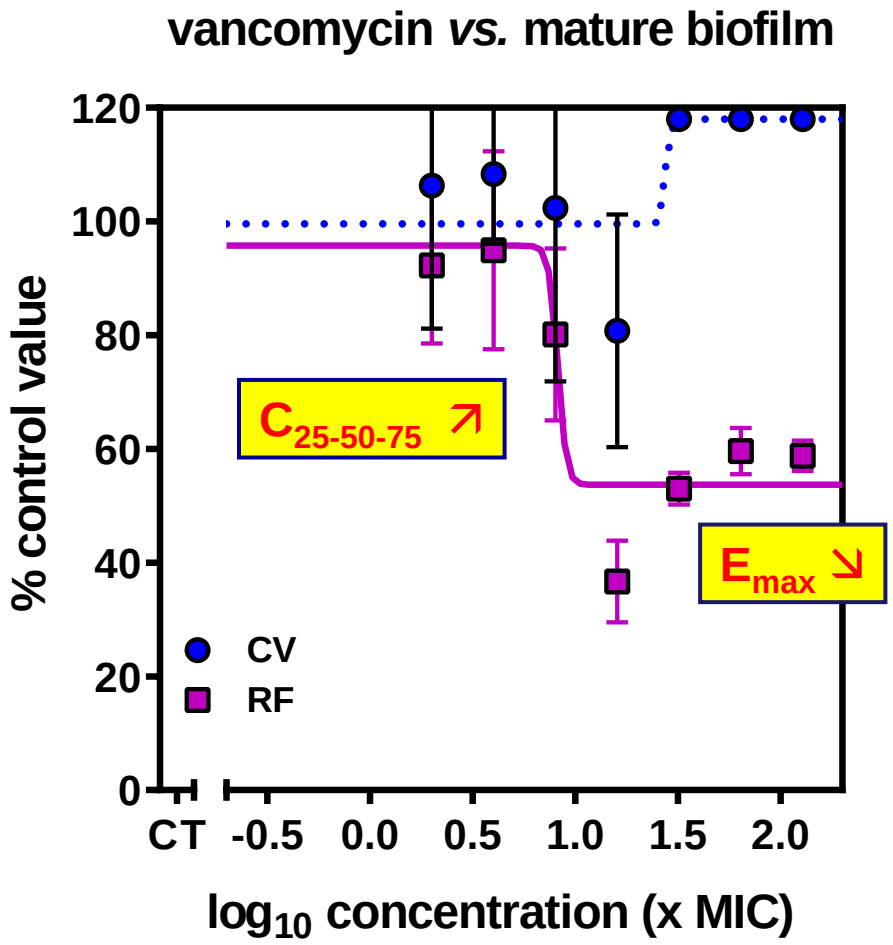
MSSA

24 h incubation

biomass (crystal violet [CV])

viability (resorufin [RF])



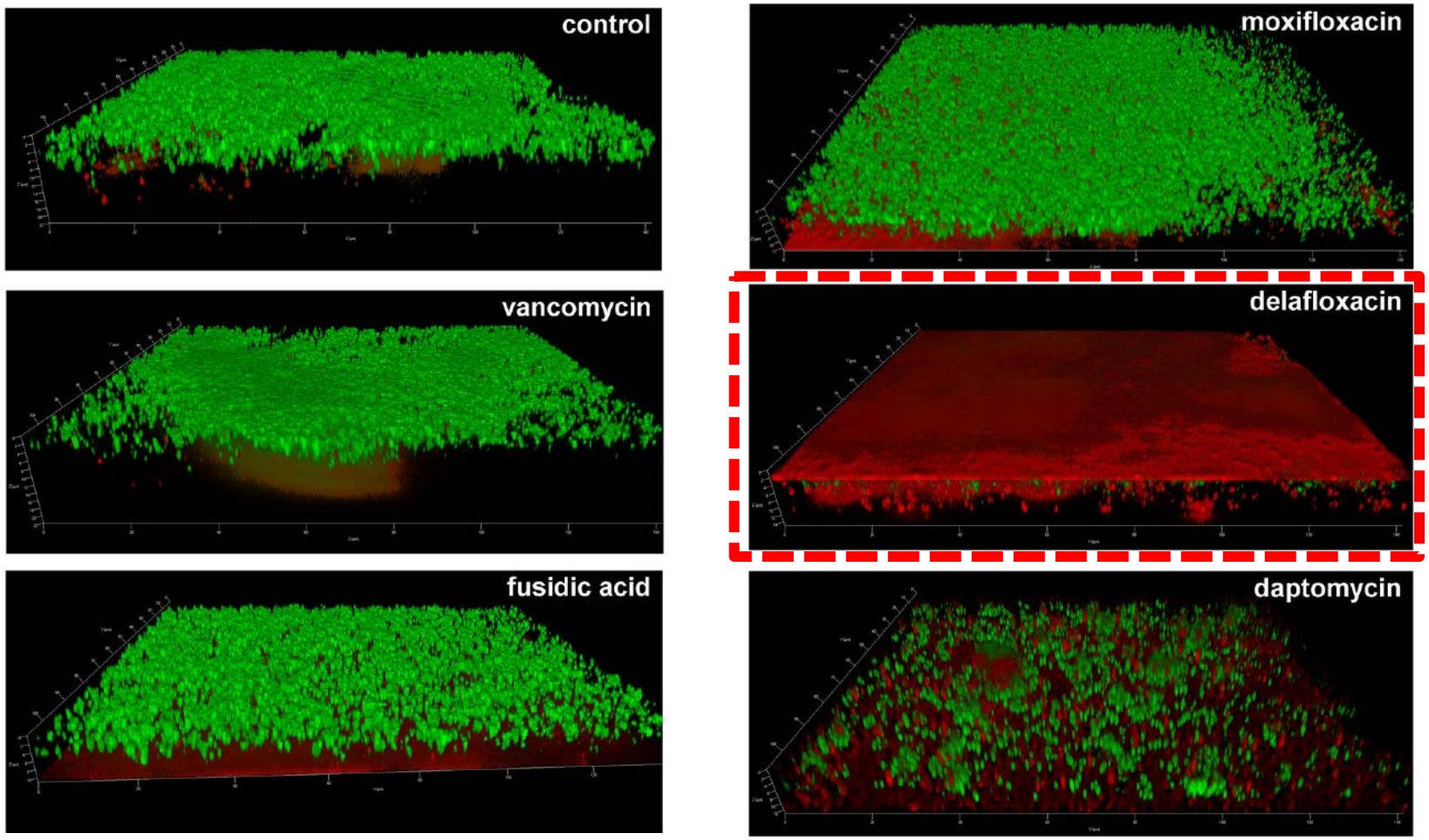


Bauer, Siala *et al*, Antimicrob Ag Chemother. 2013;57:2726-37 – PMID: 23571532

Biofilms: possible strategies

- **select highly bactericidal antibiotics**
- disrupt the matrix
- combine both approaches

Live/dead staining (antibiotics at 32 X MIC) – ATCC MRSA



Bauer, Siala *et al*, Antimicrob Agents Chemother. 2013;57:2726-37 – PMID: 23571532

Biofilms: possible strategies

- select highly bactericidal antibiotics
- **disrupt the matrix**
- combine both approaches

J. Dairy Sci. 100:7864–7873
https://doi.org/10.3168/jds.2017-13012

Disruption of *Staphylococcus aureus* biofilms using rhamnolipid biosurfactants

S. S. e Silva,* J. W. P. Carvalho,† C. P. Aires,‡ and M. Nitschke*[1]
*Department of Physical Chemistry, São Carlos Institute of Chemistry, University of São Paulo, Avenida Trabalhador São Carlense, 400, Caixa Postal 780, CEP 13560-970, São Carlos, SP, Brazil
†Faculty of Architecture and Engineering, State University of Mato Grosso, Rua A, s/n, Cohab São Raimundo, Caixa Postal 92, CEP 78390-0 Barra do Bugres, MT, Brazil
‡Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Avenida do Café s/n, CEP 14040-903, Ribeirão Preto, SP, Brazil

e Silva et al. J Dairy Sci. 2017;100:7864-7873 - PMID: 28822551

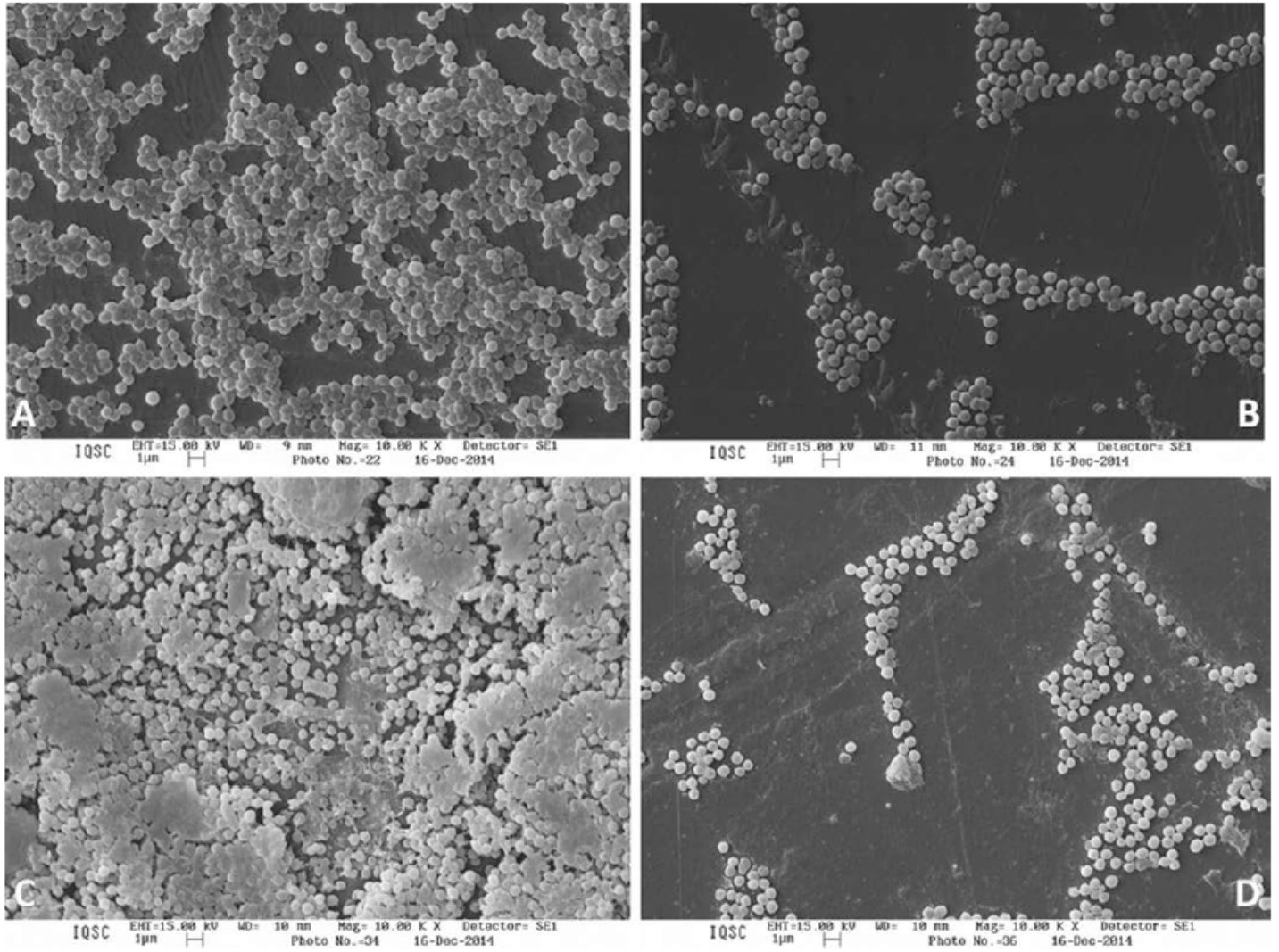


Figure 2. Scanning electron microscopy pictures of *Staphylococcus aureus* biofilms grown in nutrient broth and skim milk before (A and C) and after (B and D) treatment with 0.1% rhamnolipids at 25°C.

Biofilms: possible strategies

- select highly bactericidal antibiotics
- disrupt the matrix
- **combine both approaches**

nature COMMUNICATIONS

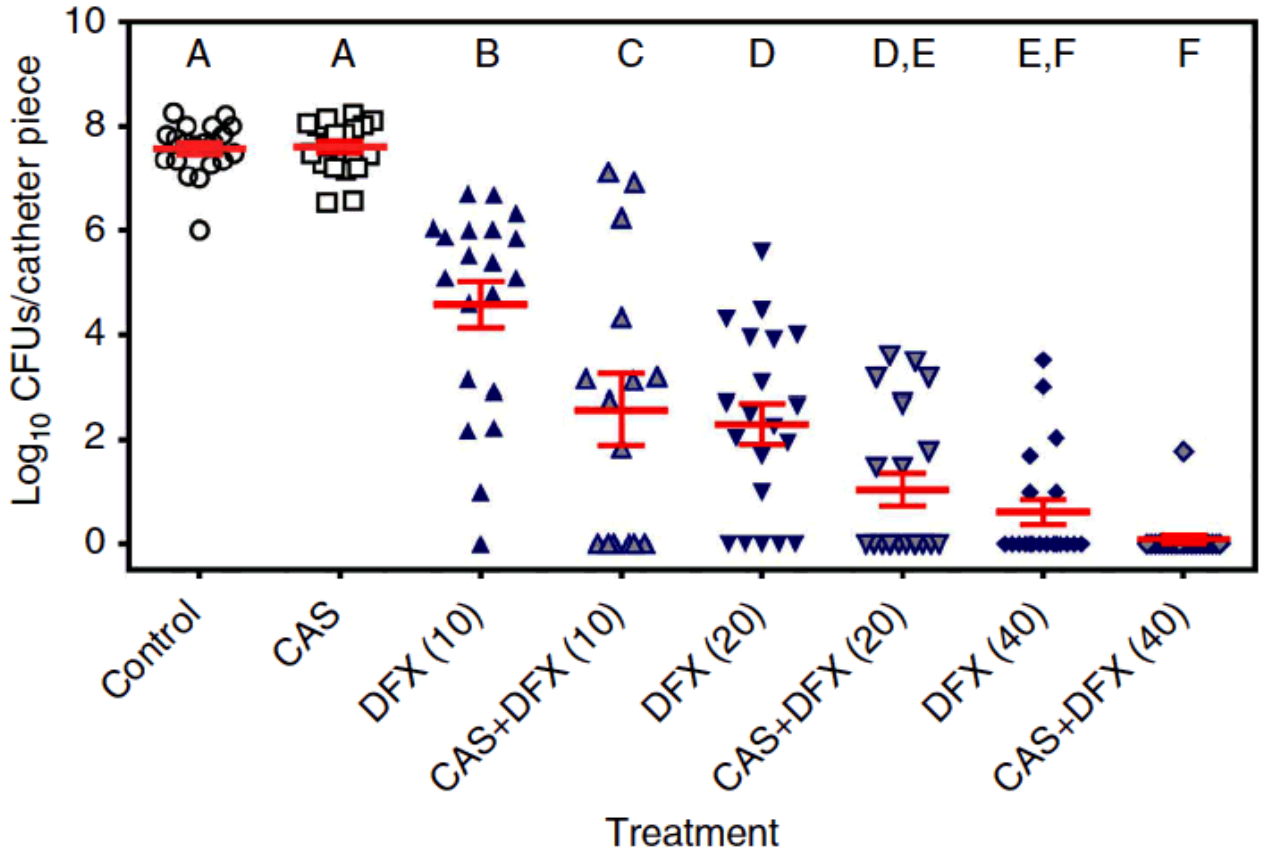
ARTICLE

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]

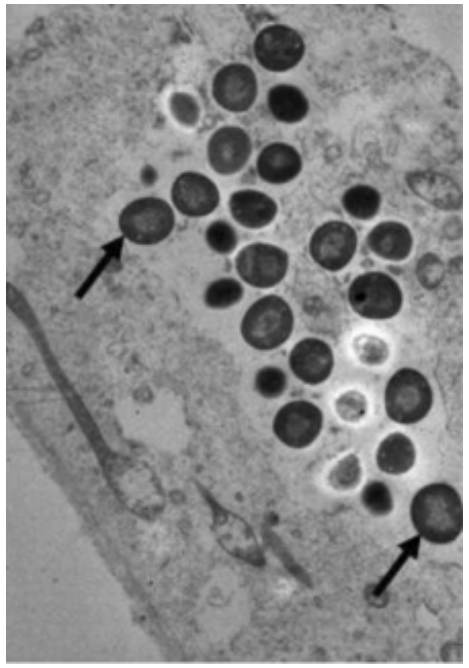
Siala et al. Nat Commun. 2016;7:13286 (15 pages) - PMID: 27808087



Activity (dose response) of delafloxacin 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 (at 10, 20, or 40 mg/kg), 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 ($P<0.05$).

Other challenges: Intracellular forms – Persisters – Small colony Variants

***S. aureus* in human osteoblasts**



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

Recalcitrant to eradication….

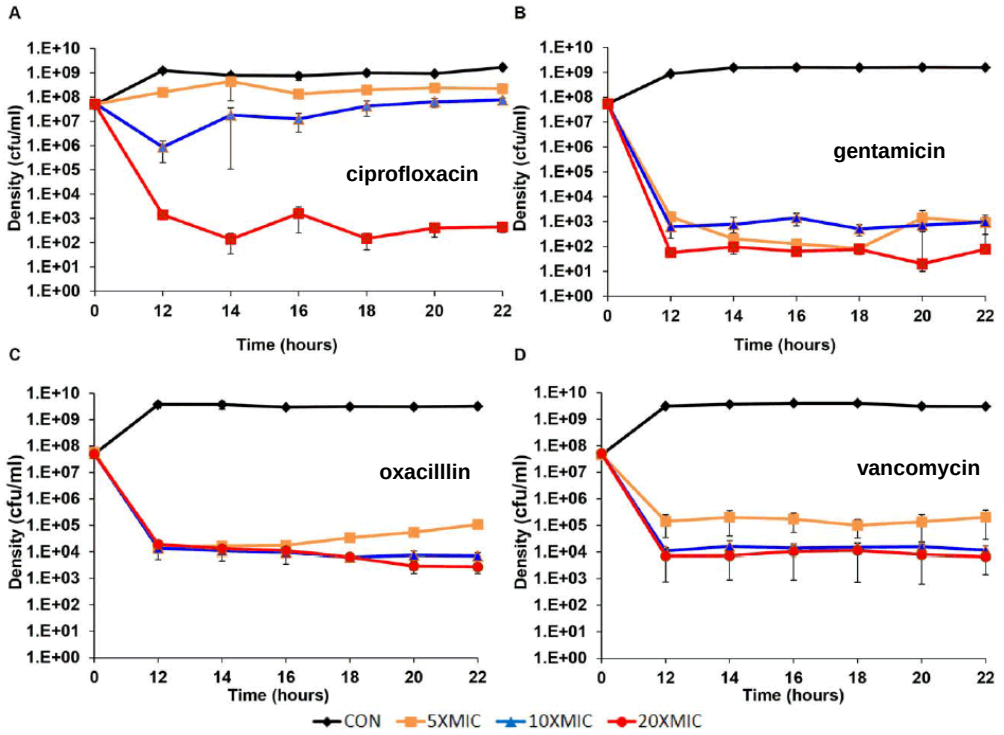


Figure 3. Longer-term time kill experiments. Changes in viable cell density, means and standard errors (bars), for three independent cultures of *S. aureus* each exposed to different concentrations (5× MIC, 10× MIC and 20× MIC) of four antibiotics: (A) Ciprofloxacin, (B) Gentamicin, (C) Oxacillin and (D) Vancomycin.
doi:10.1371/journal.pgen.1003123.g003

Johnson & Levin. PLoS Genet. 2013;9:e1003123. - PMID: 23300474;

Not all bacteria are killed !

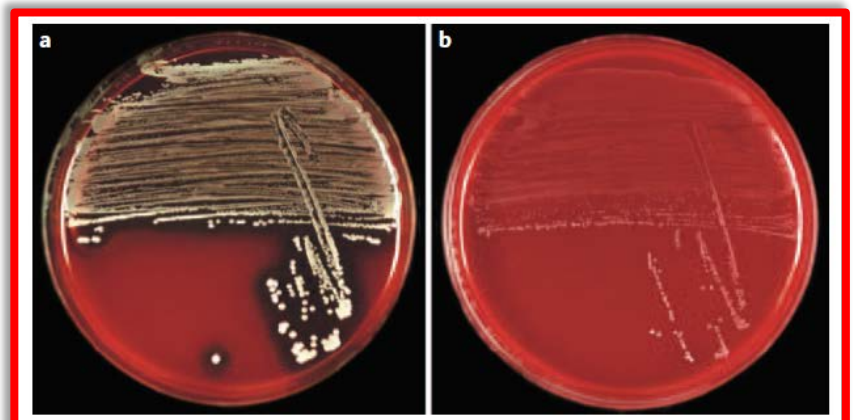


Figure 1 | **Small colony variants.** Columbia blood-agar plates that show the normal (**a**) and the small colony variant (**b**) phenotype of *Staphylococcus aureus* are shown.

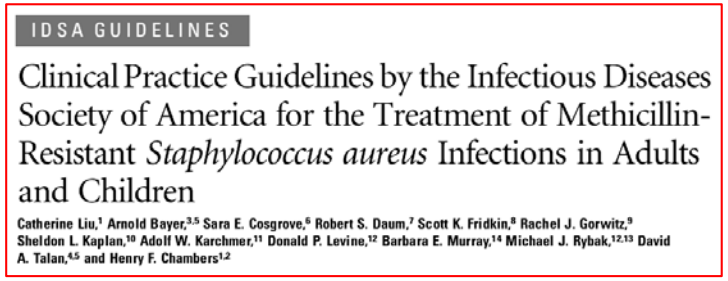
Proctor et al. Nat Rev Microbiol 2006;4:295–305 - PMID: 16541137

Eradication necessitates prolonged antibiotic therapy including drug combinations

Learning objectives

- Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed
- **Current duration of hospitalization: when could the patient go home ?**
- Contribution of new therapeutic option
  - review of some key avialable data
  - my personal views on specific/appropriate
    to both short and long term use and infecti

Treatment duration for MRSA infections: the classical way (IDSA guidelines)



IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

CLI: clindamycin
DAP: daptomycin
LZD: linezolid
RIF: rifampicin
SMX: sulfamethoxazole
TLV: televancin
TMP: trimethprim
VAN: vancomycin

infection	antibiotics	Recommended treatment duration
SSTI	VAN/DAP/LZD/TLV/CLI	7-14 days
uncomplicated bacteremia	VAN/DAP	> 2 weeks
complicated bacteremia	VAN/DAP	4-6 weeks
endocarditis	VAN/DAP	6 weeks
pneumonia	VAN/LZD/CLI	7-21 days
osteomyelitis	VAN/DAP/LZD/CLIN/ SMX-TMP+RIF	> 8 weeks
arthritis	idem	3-4 weeks
meningitis	VAN(+RIF)/LZD/SMX-TMP	2 weeks

→ **Treatment duration not always well defined but depends on infection type**

Liu et al. and Infectious Diseases Society of America. Clin Infect Dis 2011;52:e18-55 - PMID: 21208910

Treatment duration: do we wish shorter treatments ?

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

International Journal of Antimicrobial Agents 45(S1) (2015) S1–S14

Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey

Matthew Dryden [a,*], Arjana Tambic Andrasevic [b], Matteo Bassetti [c], Emilio Bouza [d], Jean Chastre [e,f], Mo Baguneid [g], Silvano Esposito [h], Helen Giamarellou [i], Inge Gys, Andreas Voss [o], Mark Wilcox [p]

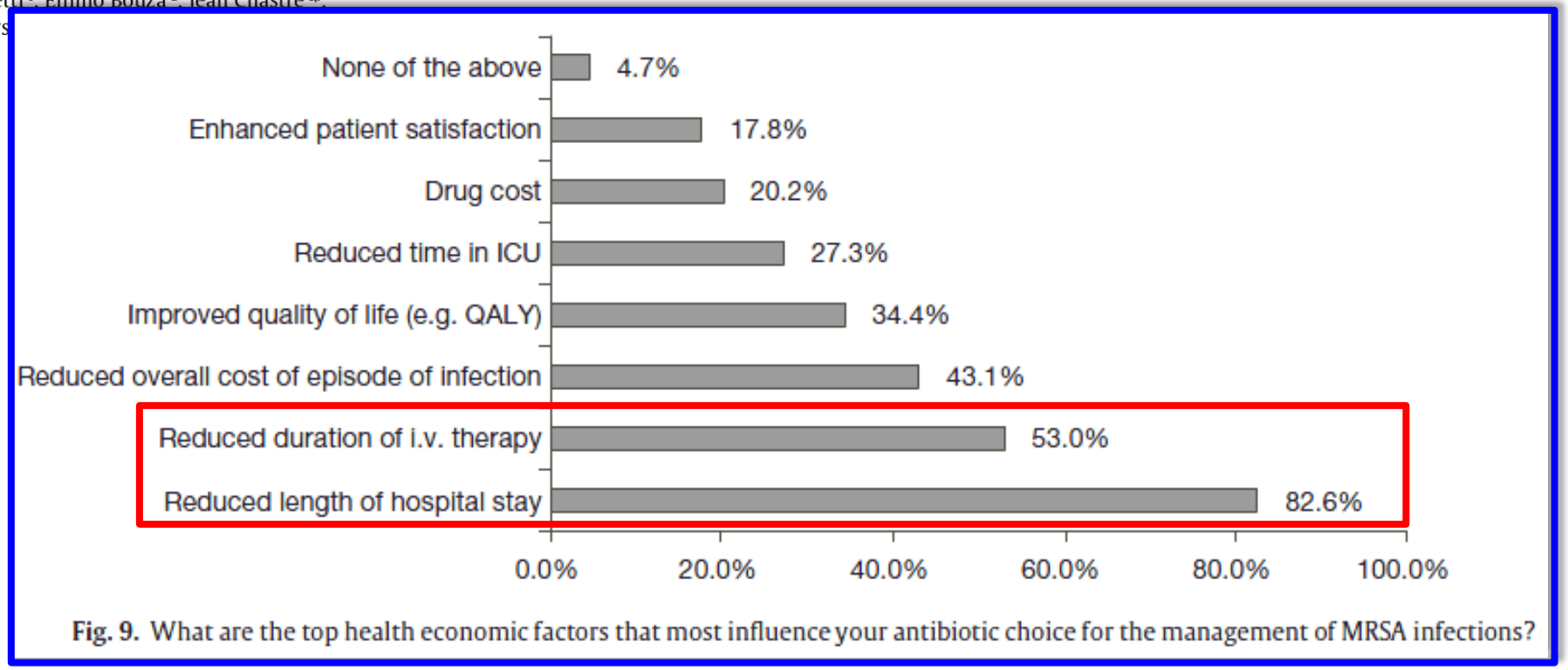
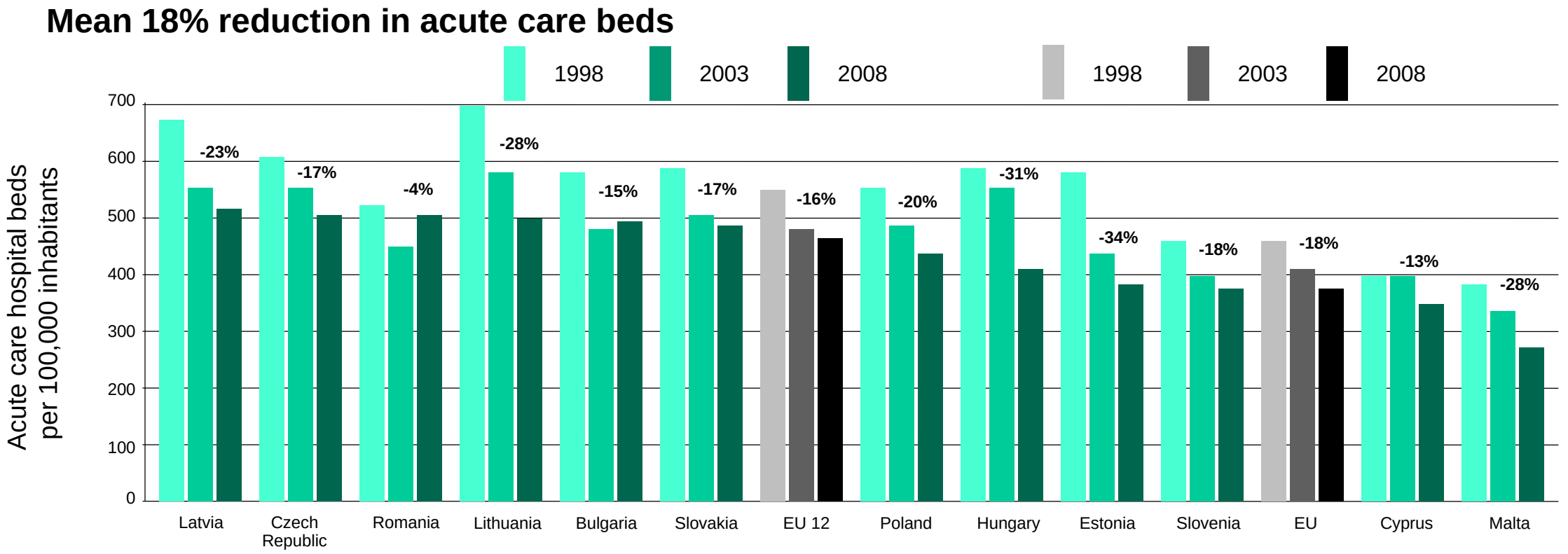


Fig. 9. What are the top health economic factors that most influence your antibiotic choice for the management of MRSA infections?

Dryden et al. Int J Antimicrob Agents. 2015;45 Suppl 1:S1-14 - PMID: 25867210.

Do we need to shorten hospital stay duration?

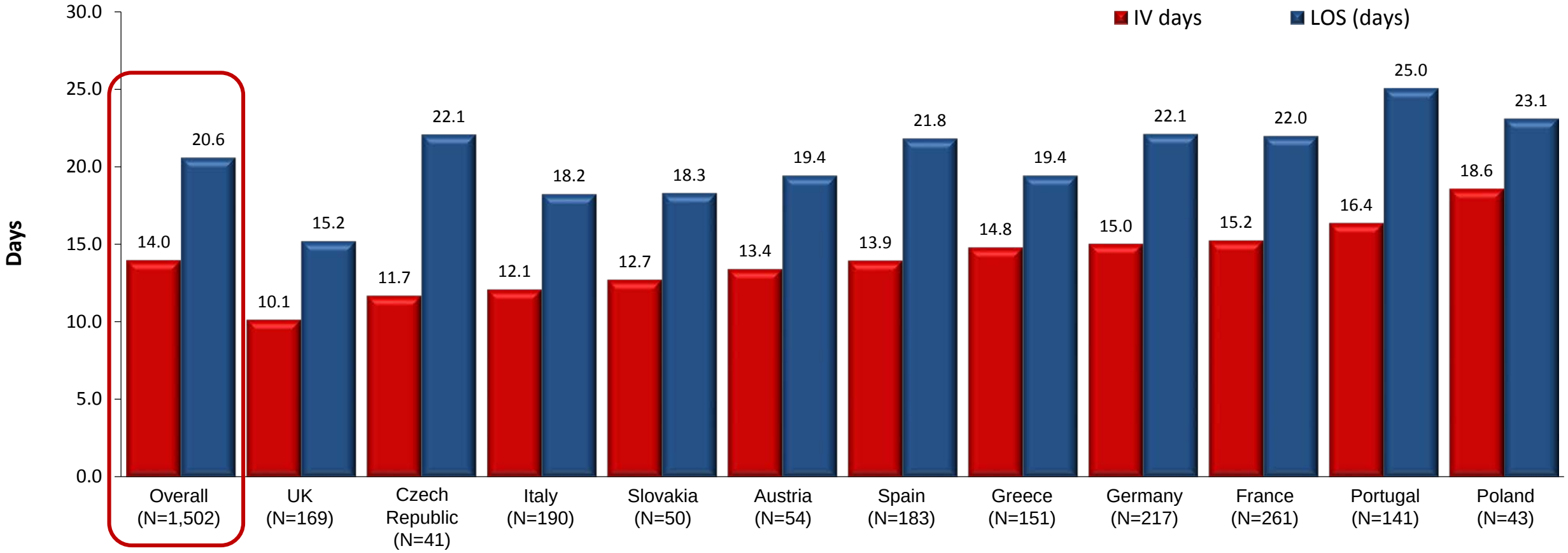
Changes in acute care hospital beds in Europe, 1998–2008



EU, all European Member states plus Switzerland; EU12, countries that joined the EU in 2004 and 2007 (Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Romania, Slovakia and Slovenia).

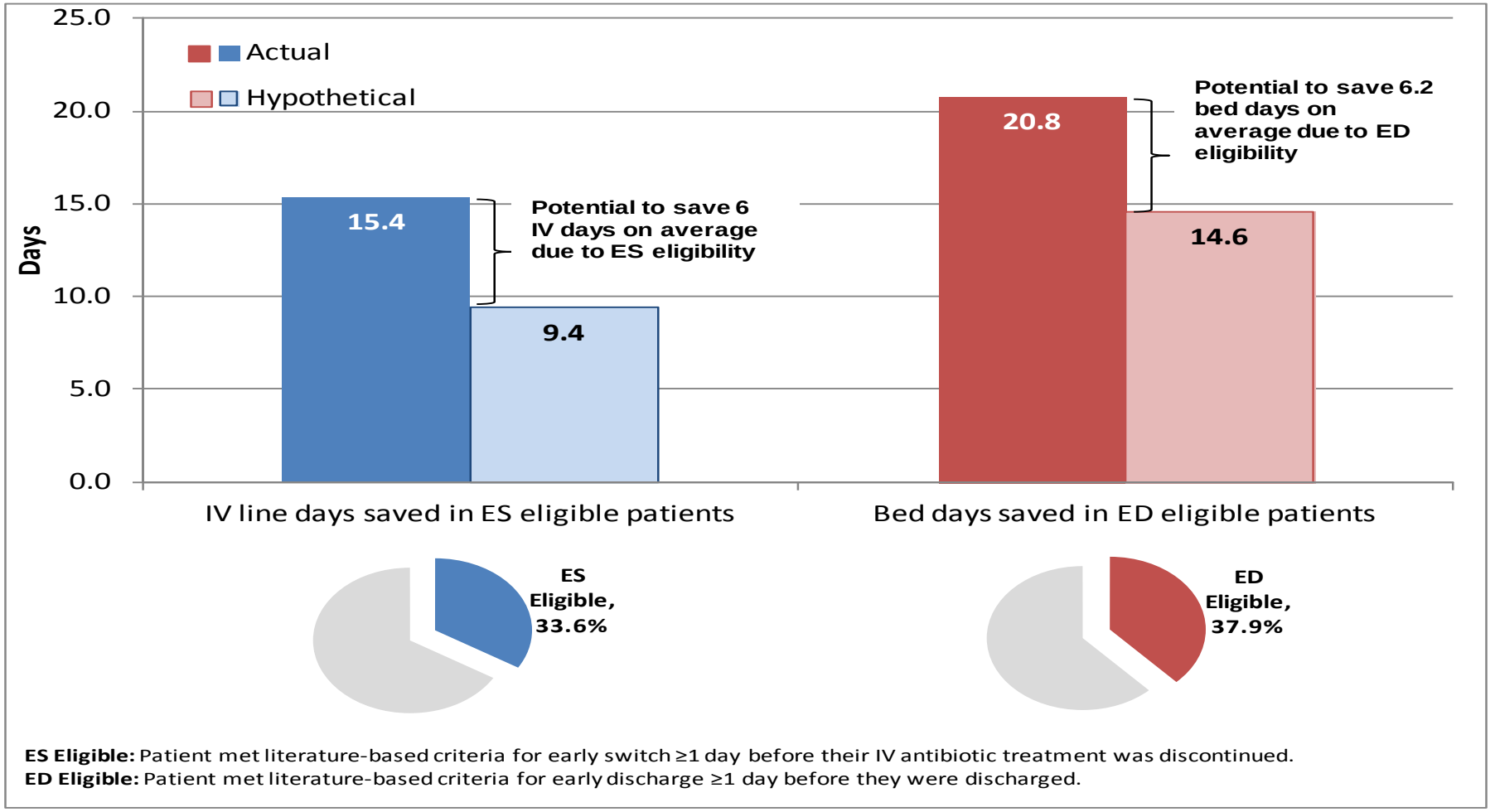
HOPE. Hospitals in Europe Healthcare Data 2011. Available at: www.hope.be/03activities/quality_eu-hospitals/eu_country_profiles/00-hospitals_in_europe-synthesis_vs2011-06.pdf [Accessed Jun 2014].

Key results: country-specific patterns



Eckmann *et al*. Int J Antimicrob Agents 2014;44:56-64 - PMID: 24928311

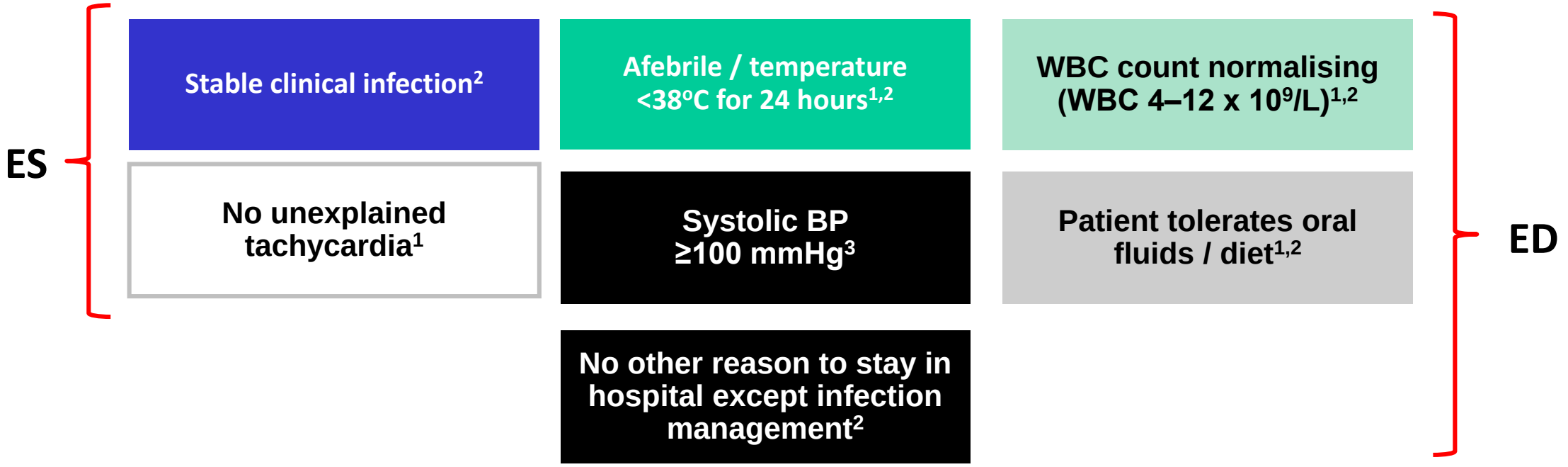
Early switch and early discharge – potential days saved



Nathwani *et al.* Clin Microbiol Infect. 2014;20:993-1000 – PMID: 24673973
Eckmann *et al*. Int J Antimicrob Agents 2014;44:56-64 - PMID: 24928311 .

Short(er) treatments (early switch [ES] / early discharge [ED]): we have simple criteria !

- Literature review with expert validation formed the basis for a list of 14 criteria tested in the study, inclusive of Desai[1] and Parodi[2] criteria
- The key (essential) criteria were selected by key opinion leaders and were used to estimate ES/ED hypothetical opportunities



1. Desai *et al.* BMC Infect Dis. 2006;6:94 – PMID: 16762061
2. Parodi *et al.* J Manag Care Pharm. 2003;9:317–326. – PMID: 14613450
3. Nathwani *et al.* Clin Microbiol Infect. 2014;20:993-1000 – PMID: 24673973
4. Eckmann *et al.* Int J Antimicrob Agents 2014;44:56-64 - PMID: 24928311.

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New Anti Gram-positive approved drugs

Company in Europe	Drug	Pharmacol. class	Approved indications [1]	Useful activity against		
				MRSA	MDRSP	VRE
Theravance	telavancin	lipoglycopeptides	cSSSI (US only) HABP/VABP	✓	✓	VanB only
Allergan	dalbavancin		ABSSSI	✓	✓	VanB only
The MedCo [2]	oritavancin		ABSSSI	✓	✓	✓
MSD / Bayer	tedizolid	oxazolidinone	ABSSSI	✓	✓	✓
Pfizer	ceftaroline	β-lactams	ABSSSI / CABP	✓	✓	✓
Basilea [3]	ceftobiprole[4]		CAP / HAP	✓	✓	✓
Menarini [5]	delafloxacin[5]	fluoroquinolone[6]	ABSSSI (US only / EMA submitted)	✓	✓	E. *faecalis* only

[1] FDA (US Food and Drug Administration) and/or EMA (European Medicines Agency) unless indicated otherwise
[2] antibiotic portfolio acquired by Melinta in 2018
[3] distributed by Cardiome (end of 2017)
[4] approved in 13 EU countries: AT, BE, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK
[5] licensee of Melinta; delafloxacin is presently approved only in the US (FDA) and not in EU
[6] activity also demonstrated against several Gram-negative organisms but with documentation

cSSSi: complicated skin and skin structures infections
ABSSSI: acute bacterial skin and skin structures infections
CABP: community-acquired bacterial pneumonia
HAP: hospital-acquired pneumonia (nosocomial)

MRSA: Methicillin-resistant *Staphylococcus aureus*
MSRSP: multidrug resistant *Streptococcus pneumoniae*
VRE: vancomycin resistant *Enterococci*

Susceptibility breakpoints

Breakpoints *vs*. susceptibility of current MRSA isolates

	antibiotic	breakpoint		susceptibility		
		S	R	MIC $_{50}$	MIC $_{90}$	range
EUCAST	telavancin	≤ 0.125	> 0.125	0.03	0.06	≤ 0.015 - 0.25
	dalbavancin	≤ 0.125	> 0.125	0.06	0.06	≤ 0.008 - 0.25
	oritavancin	≤ 0.125	> 0.125	0.03	0.03	≤ 0.008 - 0.25
	ceftobiprole	≤ 2	> 2	1	1	0.25 - 2
	ceftaroline	≤ 1	> 1	0.5	1	0.06 - 4
	tedizolid	≤ 0.5	> 0.5	0.25	0.25	0.03 - 0.5
FDA	delafloxacin*	≤ 0.25	≥ 1	0.06	0.5	≤ 0.004 - 4

* not currently approved in Europe

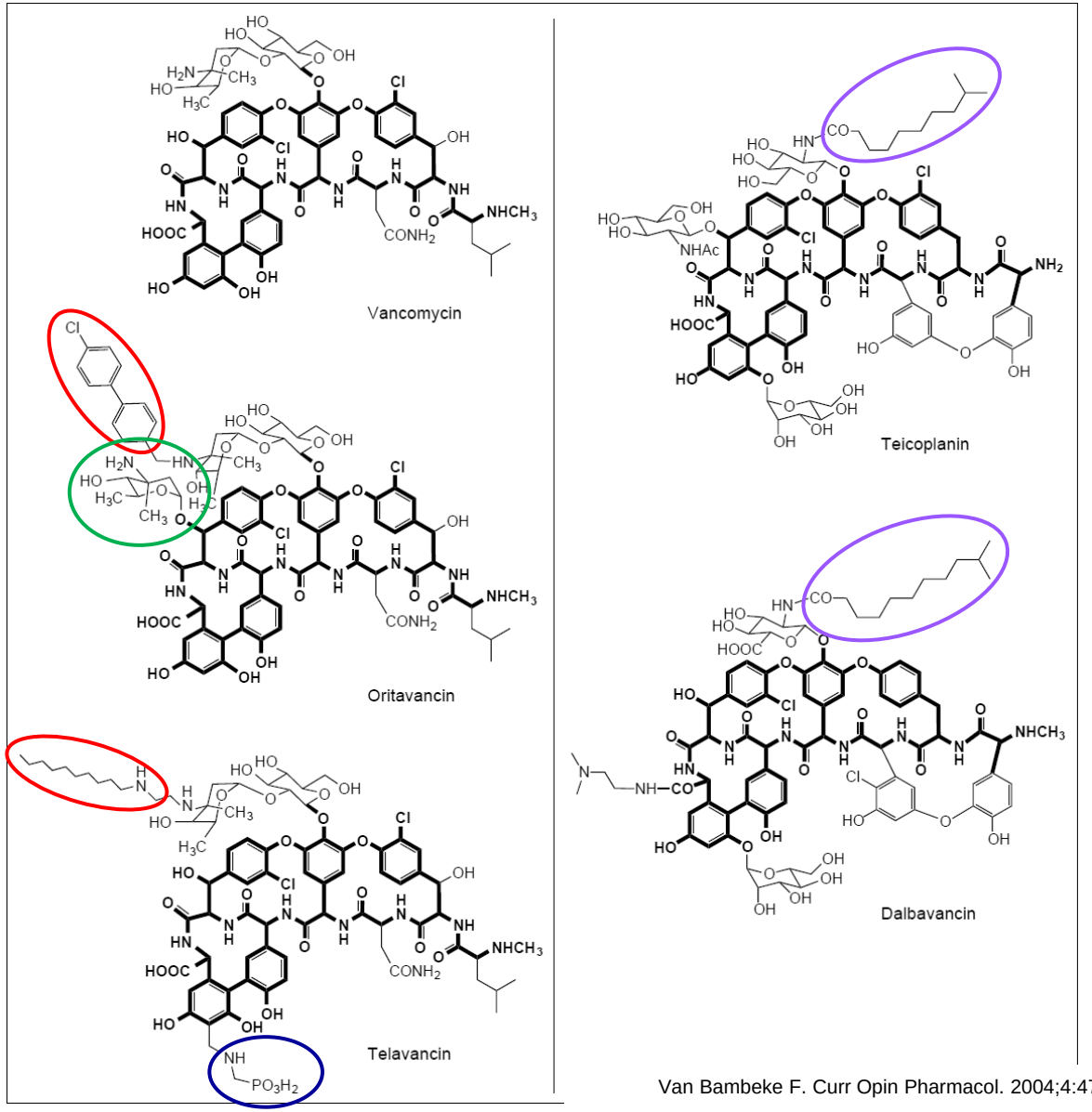
Most current isolates are susceptible BUT surveillance is essential !

Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

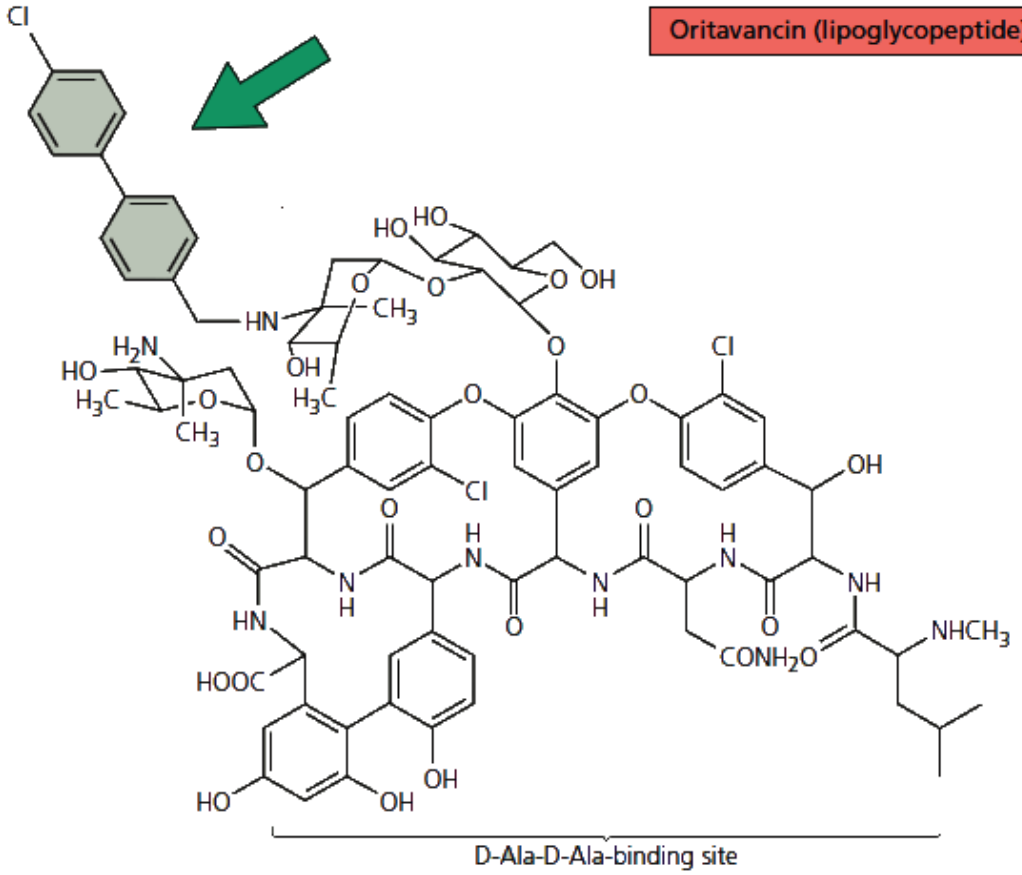
decreased half-life

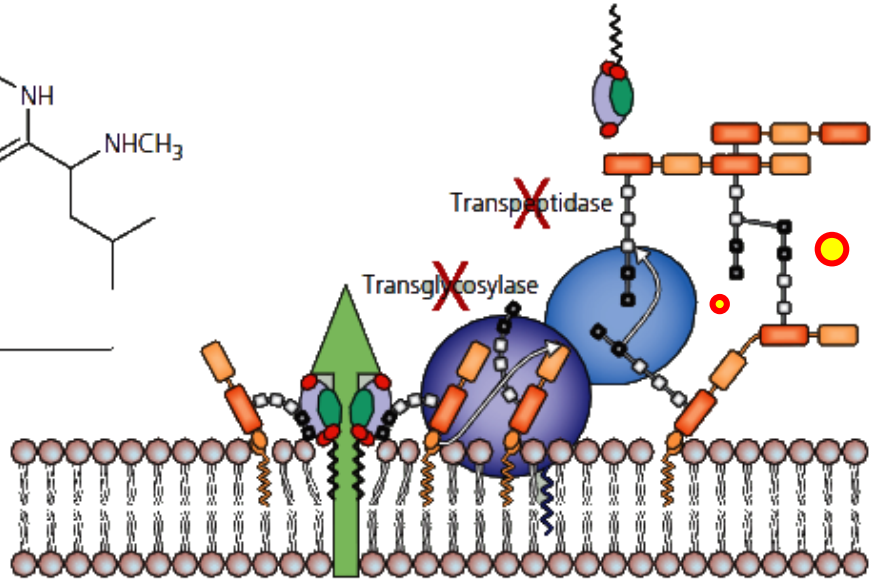


prolonged half-life

Van Bambeke F. Curr Opin Pharmacol. 2004;4:471-8 - PMID 15351351.

Lipoglycopeptides: dual mode of action





Oritavancin has a dual mode of action !

Van Bambeke et al. Infectious Diseases, 3d Ed. Chap. 130; Elsevier/Mosby, 2010; Available on line at http://www.expertconsultbook.com/

Lipoglycopeptides: the key is their pharmacokinetics

parameter	vancomycin	telavancin	oritavancin	dalbavancin
Dosage	15 mg/kg	10 mg/kg	1200 mg	1000 mg
C_{max} (mg/L)	20-50	93	138	287
AUC (mg.h/L)	260	668	1110 (24h) 2800 (tot)	3185 (24h) 23443 (tot)
(%) prot. binding	55	95	85	99
$t_{½}$ (h)	1 (β) 3-9 (γ)	8	14 (β) **245 (γ)**	**346 (γ)**

common approved dosage / schedule for ABSSSI
(FDA/EMA)

1 g q12h
7-14 days

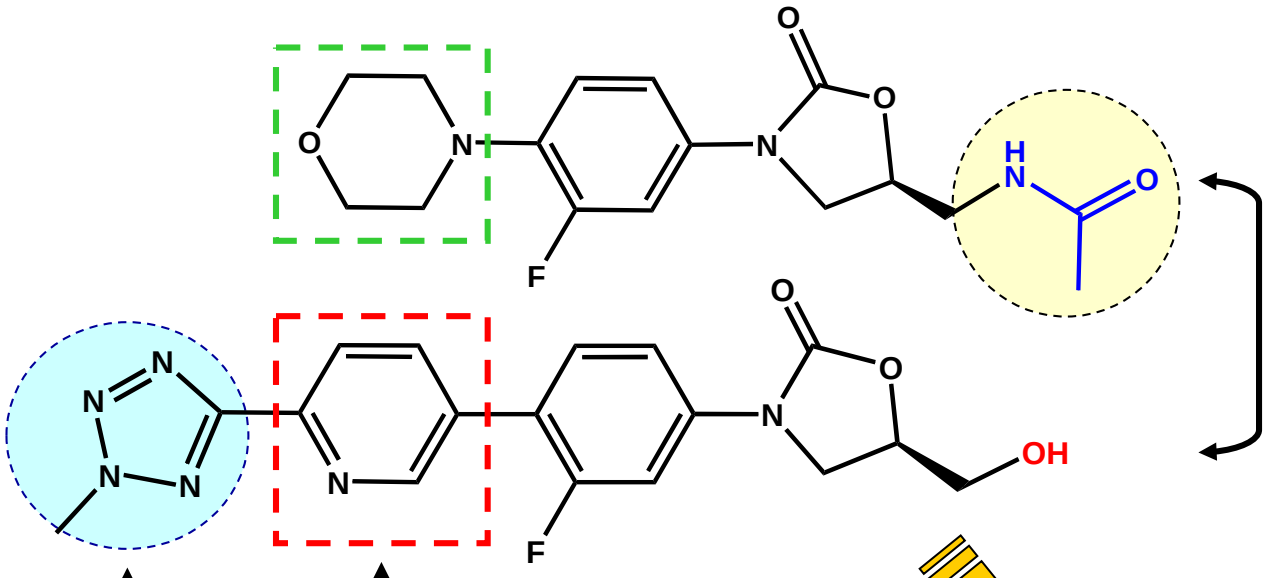
10 mg/kg **qD**
7-14 days

1.2 g
single dose

1.5 g
single dose
or 1000 mg + 500 mg at day 7

Tedizolid: structure changes vs. linezolid and implications …

Linezolid



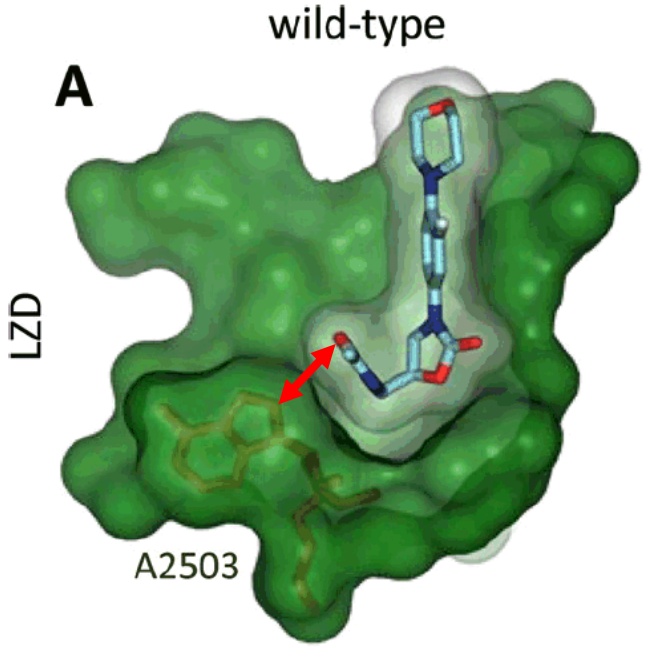
Tedizolid (TR-700)

Substantial differences that DO impact on

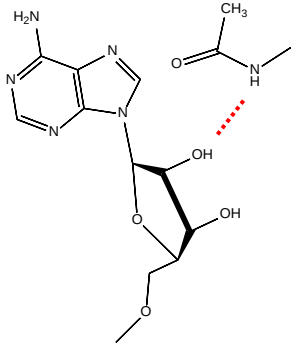
- **intrinsic activity** *(4-8 x more potent)*
- **activity against *cfr*$^{+}$ LZD^{R} strains**
- **half-life** *(~2 x longer)*

Oxazolidinones: the *cfr*+ mechanism of resistance

- both chromosome and **plasmid**-mediated [1]
- First identified in animals and then in clinical isolates [2,3]
- acting through **C-8 methylation** of the a ribosomal adenine (A2503) [4,5]
- causes **cross-resistance** to linezolid and **5 drug classes** (phenicols, lincosamides, pleuromutilins, streptogramins and 16-membered macrolides) [6,7]
- present now in **Europe** [8,9] and in **China** [10]



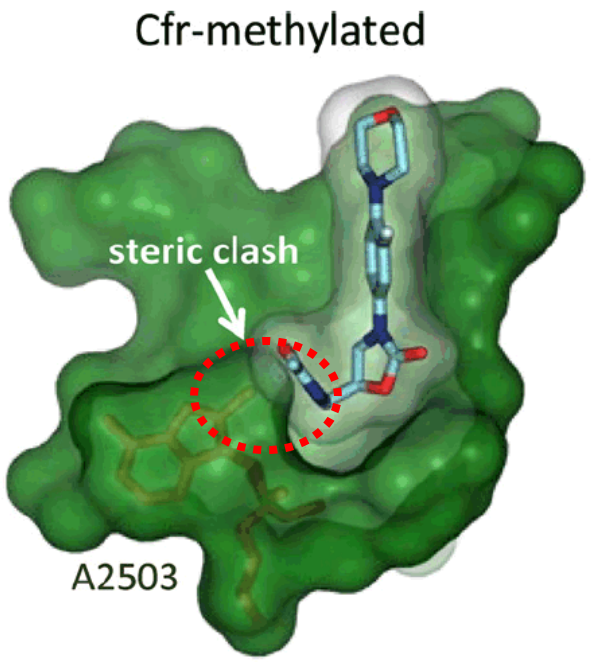
Locke *et al*.
Antimicrob Agents Chemother.
2010;54:5337-43
PMID: 20837751



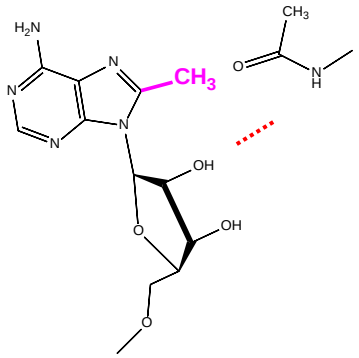
1 Toh *et al.* Mol Microbiol 2007;64:1506-14 - PMID 17555436
2 Schwarz *et al.* Antimicrob Agents Chemother 2000;44:2530-3 - PMID 10952608
3 Kehrenberg & Schwarz. Antimicrob Agents Chemother 2006;50:1156-63 - PMID 16569824
4 Kehrenberg *et al*. Mol Microbiol. 2005;57:1064-73 - PMID 16091044
5 Giessing *et al*. RNA 2009;15:327-36 - PMID 19144912
6 Long *et al.* Antimicrob Agents Chemother 2006;50:2500-5 - PMID 16801432
7 Smith & Mankin. Antimicrob Agents Chemother 2008;52:1703-12 - PMID 18299405
8 Inkster *et al*. J Hosp Infect. 2017;97:397-402. - PMID 28698020
9 Dortet *et al*. J Antimicrob Chemother 2018;73:41-51 - PMID 29092052.
10 Bi *et al.* J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

Oxazolidinones: the *cfr*+ mechanism of resistance

- both chromosome and **plasmid**-mediated [1]
- First identified in animals and then in clinical isolates [2,3]
- acting through **C-8 methylation** of the a ribosomal adenine (A2503) [4,5]
- causes **cross-resistance** to linezolid and **5 drug classes** (phenicols, lincosamides, pleuromutilins, streptogramins and 16-membered macrolides) [6,7]
- present now in **Europe** [8,9] and in **China** [10]



Locke *et al*.
Antimicrob Agents Chemother.
2010;54:5337-43
PMID: 20837751



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10 Bi *et al.* J Glob Antimicrob Resist 2017;pii:S2213-7165(17)30205-9 - PMID 29101082

Tedizolid: key PK/PD parameters and breakpoints

- **long half-life (~ 12 h)**
  (with concentrations > 0.5 mg/L for ~18 h)
- **activity dependent from the AUC_{24h} (total daily dose/clearance) irrespective of the dosing scheme (Q8, Q12, Q24)**

✓ **ONCE daily dosing (oral or IV) @ 200 mg**

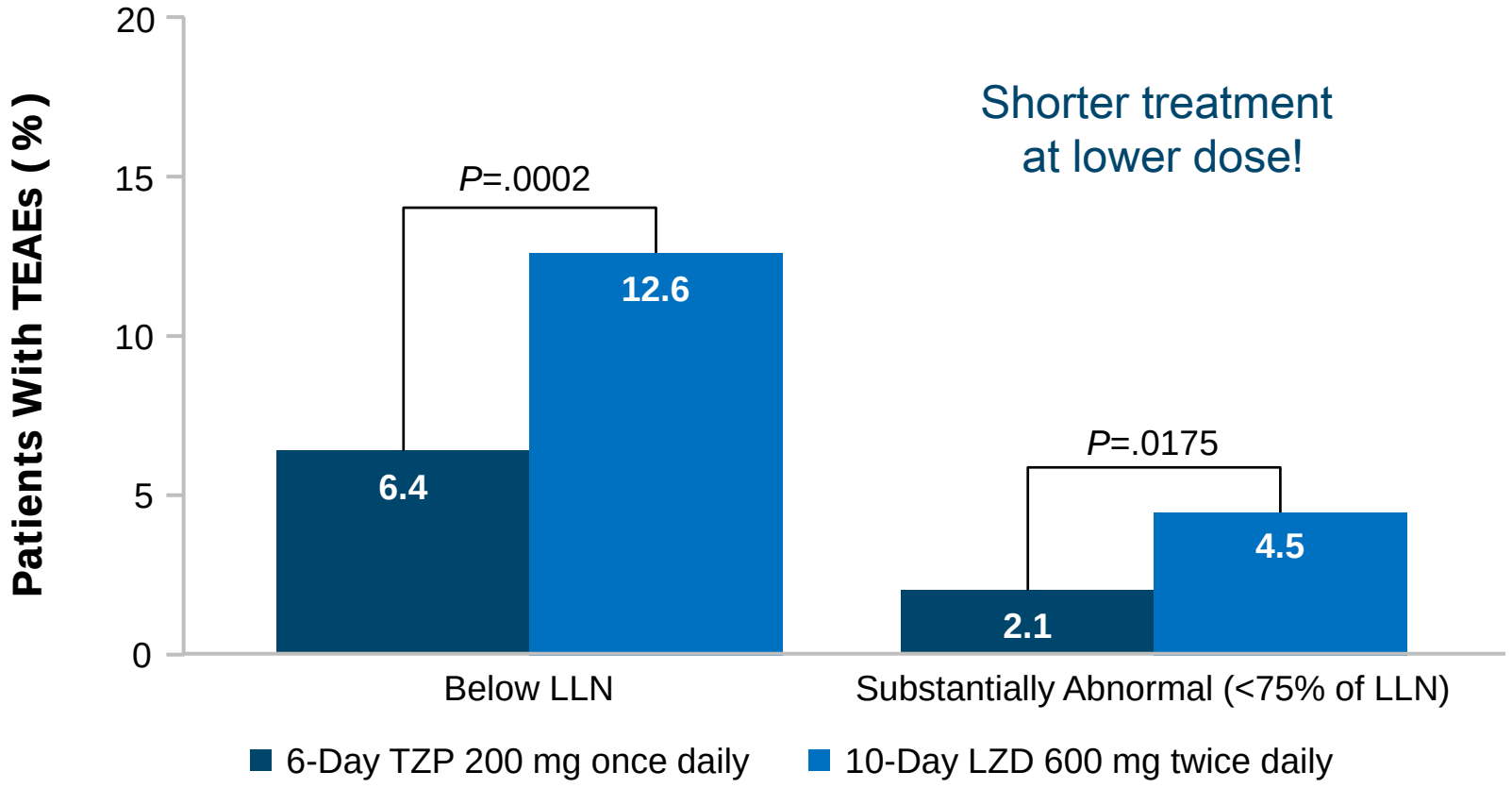
✓ **breakpoint: S ≤ 0.5 mg/L – R > 0.5 (EUCAST) or ≥ 2 (FDA)**

- **almost complete bioavailability of the oral form (por-drug)**

✓ **early oral switch possible**

Tedizolid safety: Platelet counts – Pooled Phase 3 Studies

At any post-baseline assessment through last dose of study drug [a]



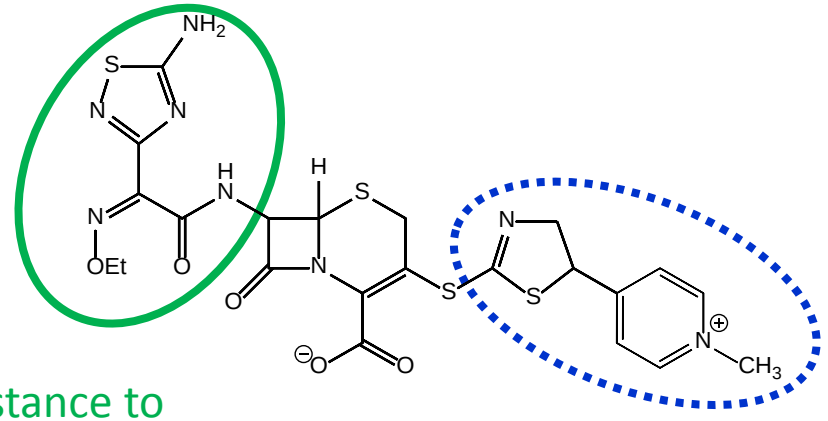
TEAE=treatment-emergent adverse events; LLN=lower limit of normal; TZP=tedizolid; LZD=linezolid.

[a] Platelet counts were collected on Study Day 7-9, Study Day 11-13, and after the last dose of study drug.

DeAnda *et al*. Integrated results from 2 phase 3 studies comparing tedizolid phosphate 6 days vs. linezolid 10 days in patients with ABSSSI. Poster presented at: 53rd Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC); September 10-13, 2013; Denver, CO. (L-203).

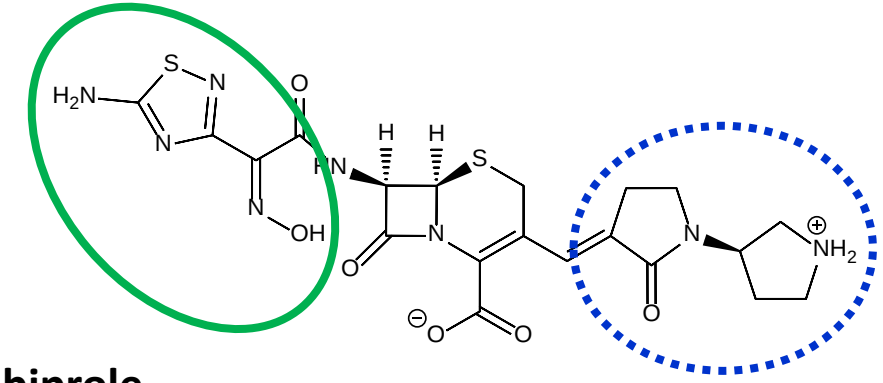
Anti-MRSA cephalosporins

ceftaroline



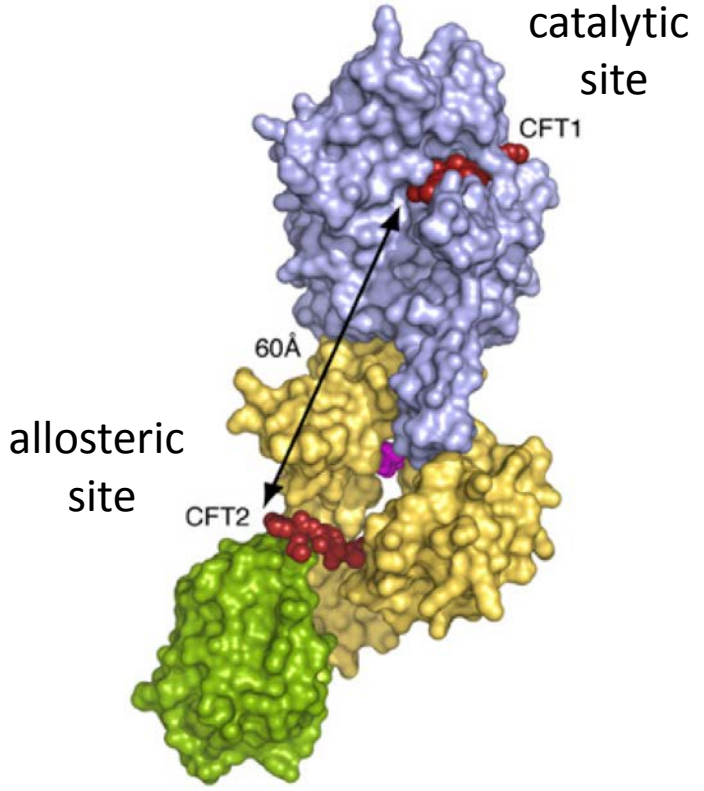
Resistance to β-lactamases

Binding to PBP2a



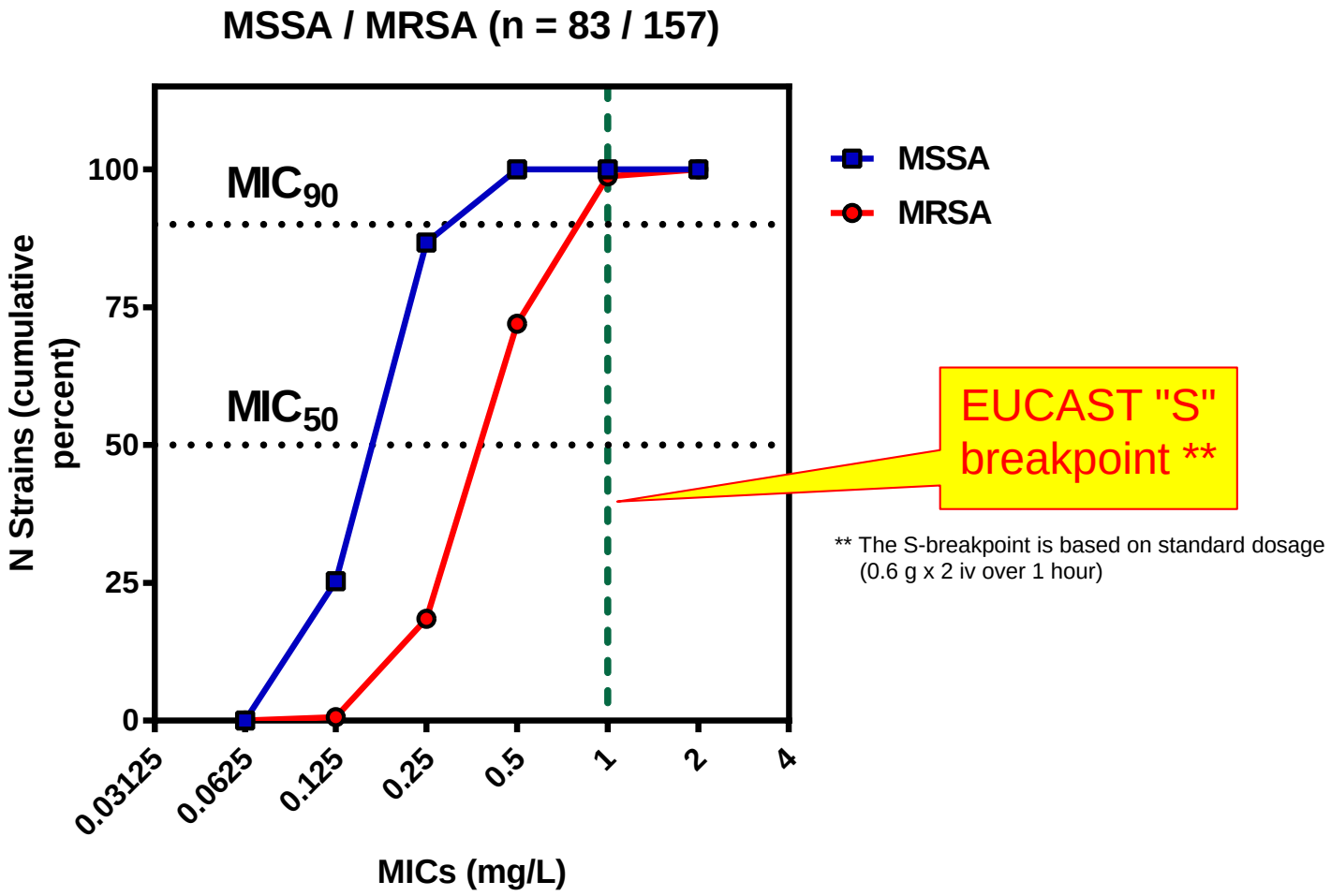
ceftobiprole

ceftaroline & PBP2a



Otero et al, PNAS 2013; 110:16808–13

Ceftaroline *vs* MSSA and MRSA *



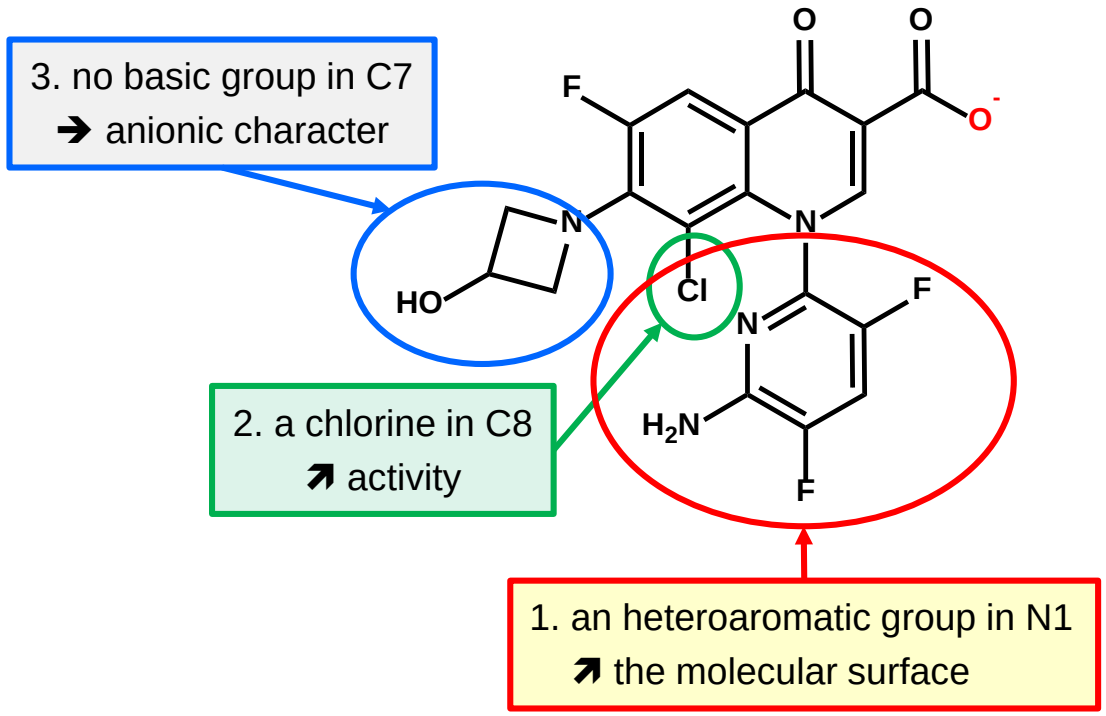
** The S-breakpoint is based on standard dosage (0.6 g x 2 iv over 1 hour)

* isolates collected between 2011 and 2012 from patients suffering of wound infections in 3 hospitals (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013 and unpublished

Delafloxacin: pharmacochemistry…

In a nutshell



Akira et al. PCT Int. Appl. (1997), WO 9711068 A1 19970327 (and other patents)
Mealy & Castaner. Drugs of the Future 2002;27:1033-1038 (doi: 10.1358/dof.2002.027.11.707859)
Hanselmann et al. PCT Int. Appl. (2010), WO 2010036329 A2 20100401 (and other patents)
Duffy et al. 50th ICAAC 2010: Abstract E183
Kocsis et al. Ann Clin Microbiol Antimicrob 2016;15:34 (8 pages) - PMID: 27215369
Candel & Peñuelas. Drug Des Devel Ther. 2017;11:881-891 - PMID: 28356714
Mogle *et al.* J Antimicrob Chemother. 2018 - Epub ahead of print - PMID: 29425340

Delafloxacin: recent MICs…

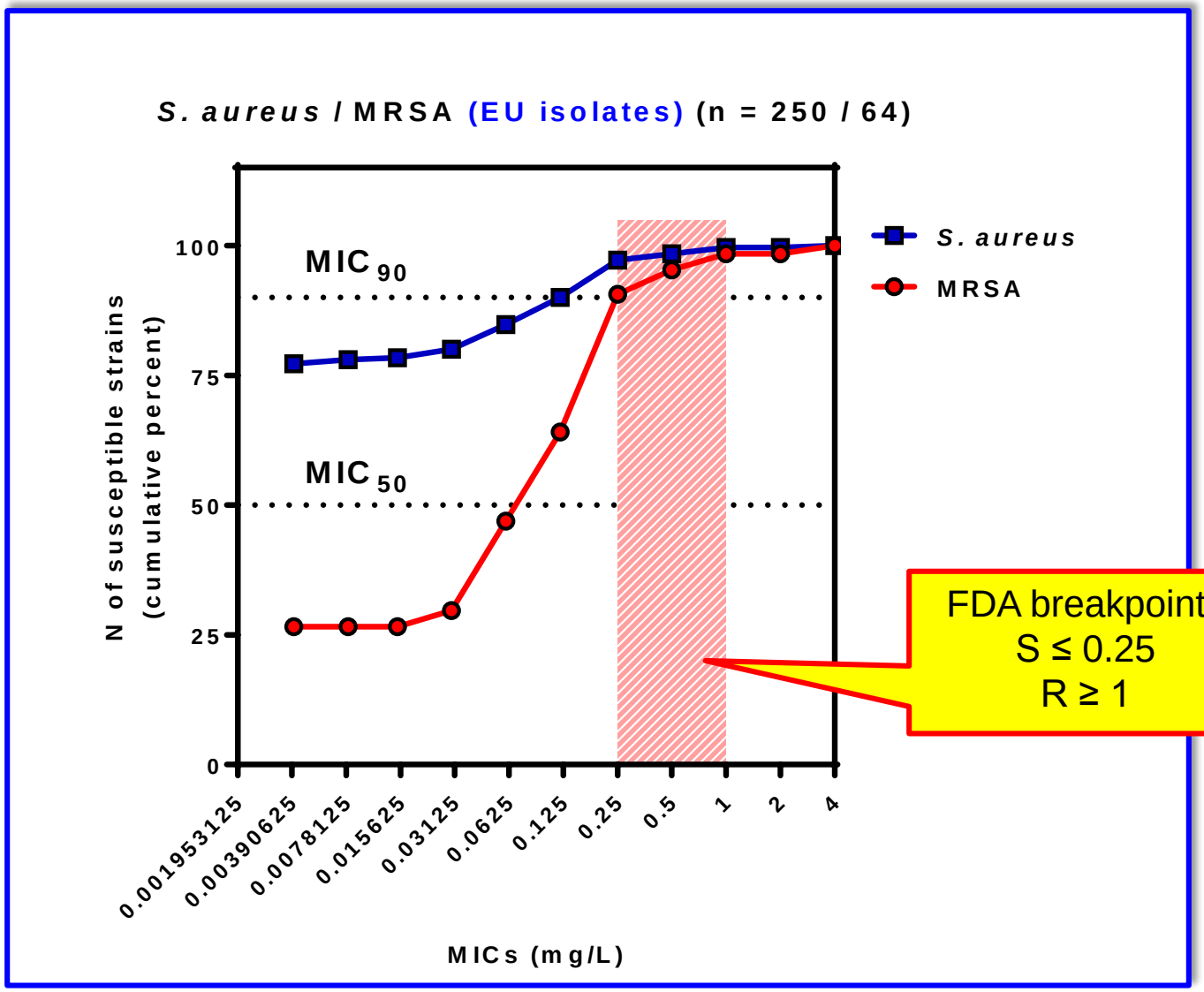
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

In Vitro Activity of Delafloxacin against Contemporary Bacterial Pathogens from the United States and Europe, 2014

M. A. Pfaller,[a,b] H. S. Sader,[a] P. R. Rhomberg,[a] R. K. Flamm[a]

JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa, Iowa City, Iowa, USA[b]

Pfaller et al. Antimicrob Agents Chemother 2017;61:pii: e02609-16 - PMID: 28167542



Pfaller et al. Antimicrob Agents Chemother 2017;61:pii: e02609-16 - PMID: 28167542

* see original paper for data from the US and additional data in Mogle *et al.* J Antimicrob Chemother. 2018 – Epub ahead of print - PMID: 29425340

Learning objectives

- Describe common challenges with managing Gram positive infections in the hospital & how they are currently managed
- Current duration of hospitalization: when could the patient go home ?
- Contribution of new therapeutic options:
  - review of some key available data
  - **my personal views on specific/appropriate contribution of the new therapeutic options to both short and long term use and infection management**

What do new drugs bring to our arsenal ?

Empirical therapy ? Short treatment ? Switch to oral ? Safety concerns ?

antibiotic	spectrum	treatment (duration /doses)	oral bioavailability	main risk
telavancin [a]	G+	7-14 days (q24h) *	No	nephrotoxicity
dalbavancin	G+	**2 doses** (at days 1 & 7)	No but 2 doses only	drug retention
oritavancin	G+	**1 dose** (a day 1)	No but 1 dose only	drug retention / interactions
ceftobiprole	G+ G- [b]	not specified	No	hypersensitivity
ceftaroline	G+ G- [b]	5-14 days (BID/TID)*	No	hypersensitivity
tedizolid	G+	**6 days** q24h*	**almost full (90%)**	linezolid-like *
delafloxacin [c]	G+ G- [d]	5-14 days q12h*	**partial (~ 60%)**	quinolones-like **

[a] not approved in EU for skin and skin structures infections
[b] but NOT ESBL producers
[c] not currently approved in EU
[d] documentation needed

* q24h: every 24h
q12h: every 12h
q8h: every 8h

* milder in clinical trials and in case reports
** as per the US (FDA) label

Based on analysis of the corresponding Summary of Product Characteristics (SmPC [EMA; MHRA for ceftobiprole]) or of US (FDA) label for delafloxacin, and recent literature data

What will be our future ?

Like Spain did it, we need to explore the new continent …

While it became generally accepted after Vespucci that Columbus's discoveries were not Asia but a "New World", the geographic relationship between the two continents was still unclear…

- https://en.wikipedia.org/wiki/New_World
- J.H. Parry, *The Discovery of the Sea* (1974: p. 227)