Anti-staphylococcal antibiotics: the new ones and the future ones…

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Université Claude Bernard Lyon1, Lyon

Centre International de Recherche en Infectiologie, CIRI, Inserm U1111, CNRS UMR5308, ENS de Lyon, UCBL1, Lyon, France

CRIOAc Lyon

What's new?

- Several **« New »** antistaphylococcal antibiotics since 10 years
- Chemical modifications of **« Old drugs »** belonging to common antibiotic classes
- **The novelty is not only:**
  - A new drug
  - A new mechanism of action
- **The novelty is also:**
  - New indications, new strategies
  - New routes of delivery

How to develop new antibiotics?

« *Faire du neuf avec du vieux* »
Making new with old

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

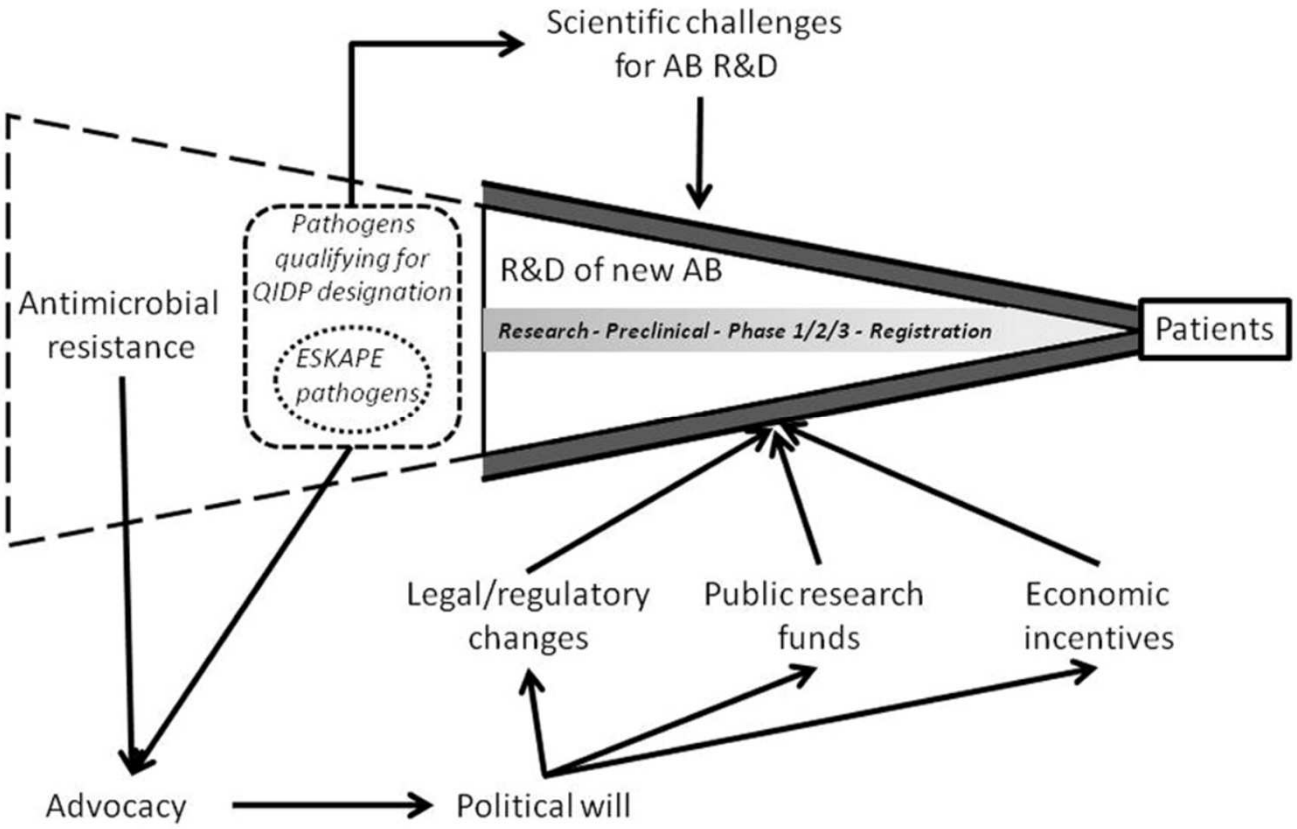
Development of new antibiotics: taking off finally?

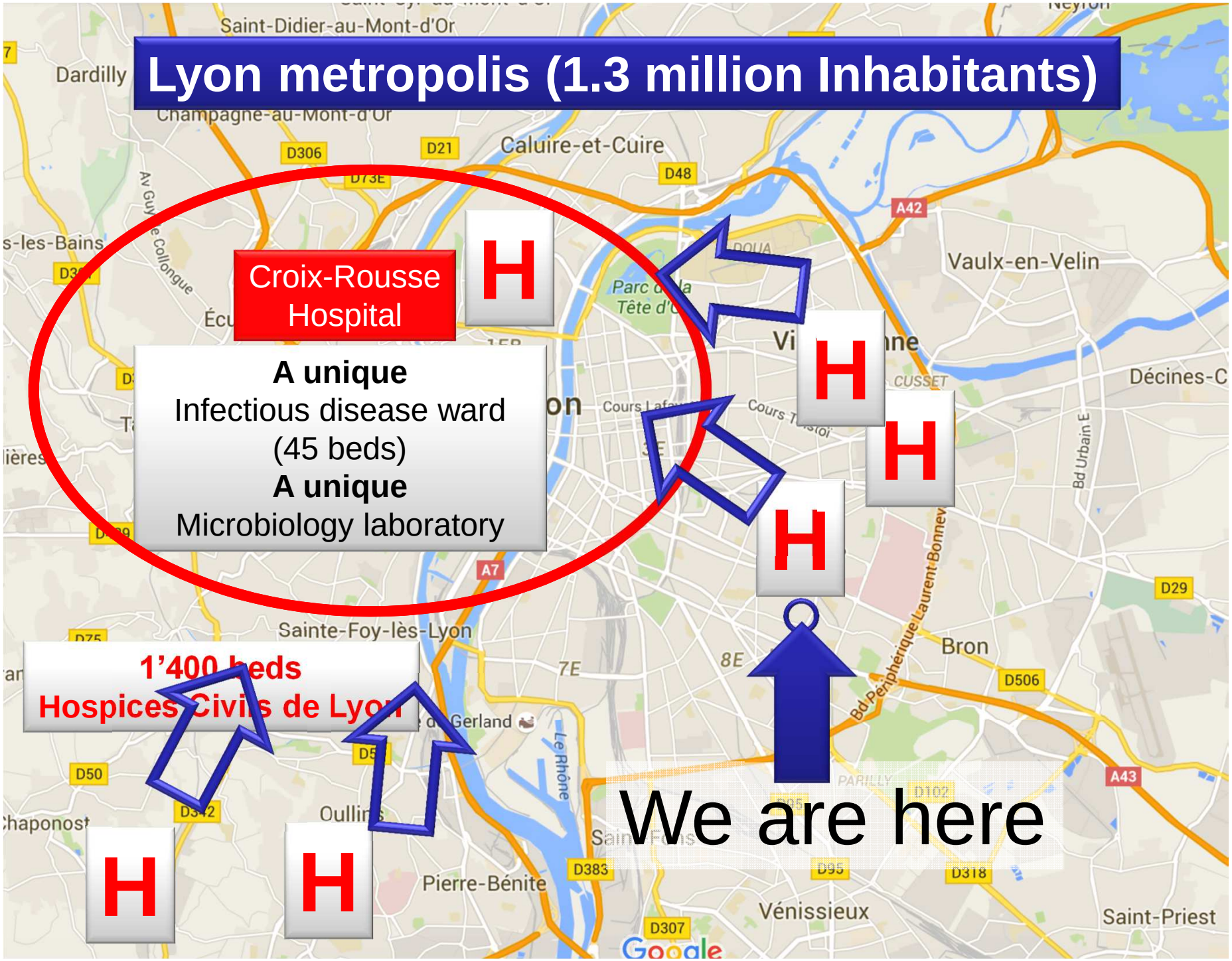
Esther Bettiol[a], *Stephan Harbarth*[a,b]

[a] Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, Switzerland

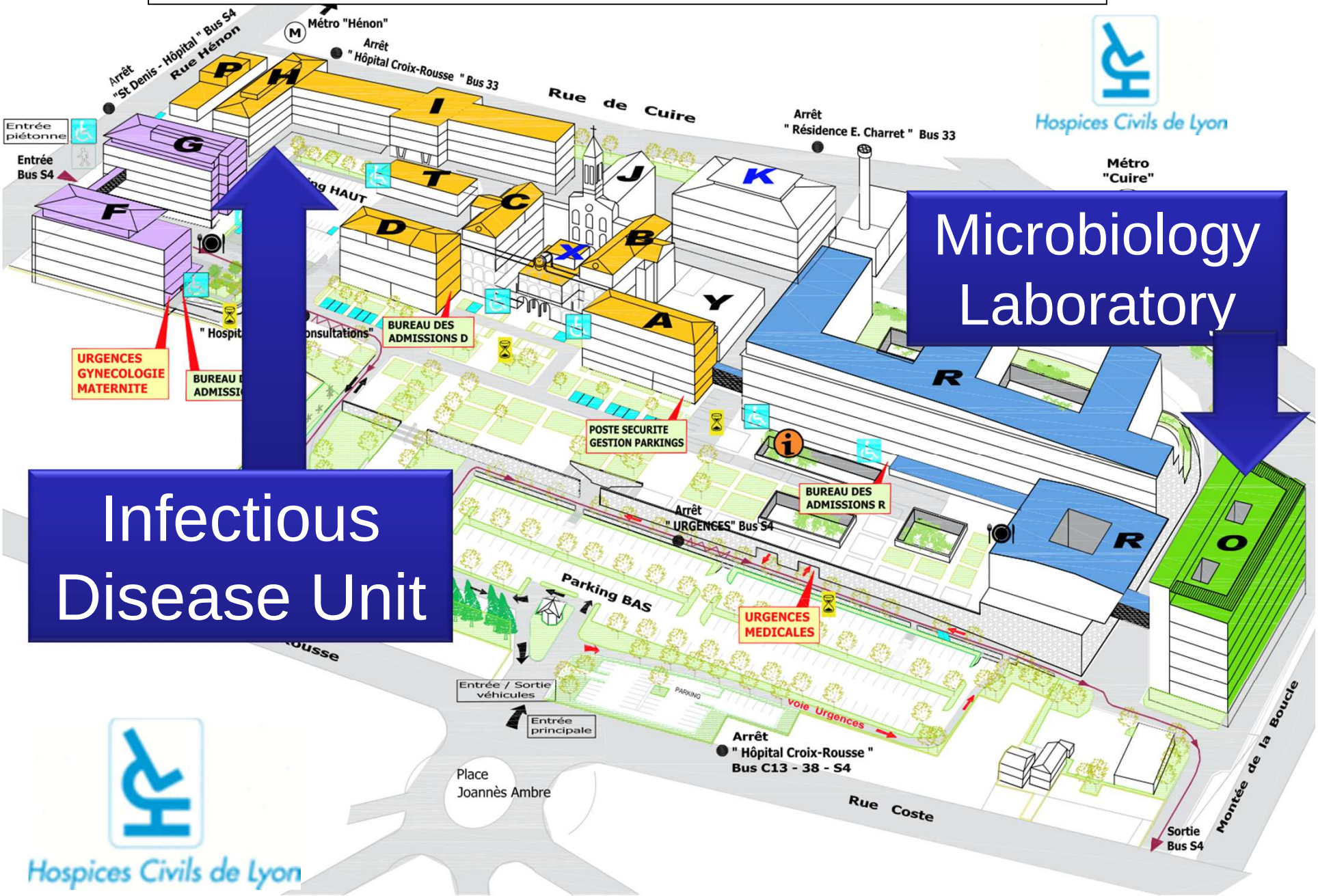
[b] Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Switzerland

In common antibiotic classes




Lyon metropolis (1.3 million Inhabitants)
Croix-Rousse Hospital
A unique
Infectious disease ward
(45 beds)
A unique
Microbiology laboratory
1'400 beds
Hospices Civils de Lyon
We are here
Saint-Didier-au-Mont-d'Or
Dardilly
Champagne-au-Mont-d'Or
Caluire-et-Cuire
Vaulx-en-Velin
Décines-C
Bron
Sainte-Foy-lès-Lyon
Oullins
Pierre-Bénite
Vénissieux
Saint-Priest
Gerland
Le Rhône
Bd Périphérique Laurent Bonnevay
Bd Urbain E
Cours Lafayette
Cours Tolstoï
CUSSET
PARILLY
Google

Croix-Rousse Hospital, Hospices Civils de Lyon



Croix-Rousse Hospital, Hospices Civils de Lyon

Microbiology Laboratory

Infectious Disease Unit

Hospices Civils de Lyon

Hospices Civils de Lyon

New buildings in a old Hospital

The plan

- **« New »** Antistaphylococcal antibiotics based on **« Old drugs »**

- **New routes** of delivery for **« Old drugs »**

- **New drugs** with **new mechanism** of action

Novelty in current antimicrobal classes

- **β-lactams**
- **Lipoglycopeptides**
- **2nd generation (lipo)glycopeptides**
- **Oxazolidinones**
- **Fluoroquinolones**

Ceftaroline
Ceftobiprole

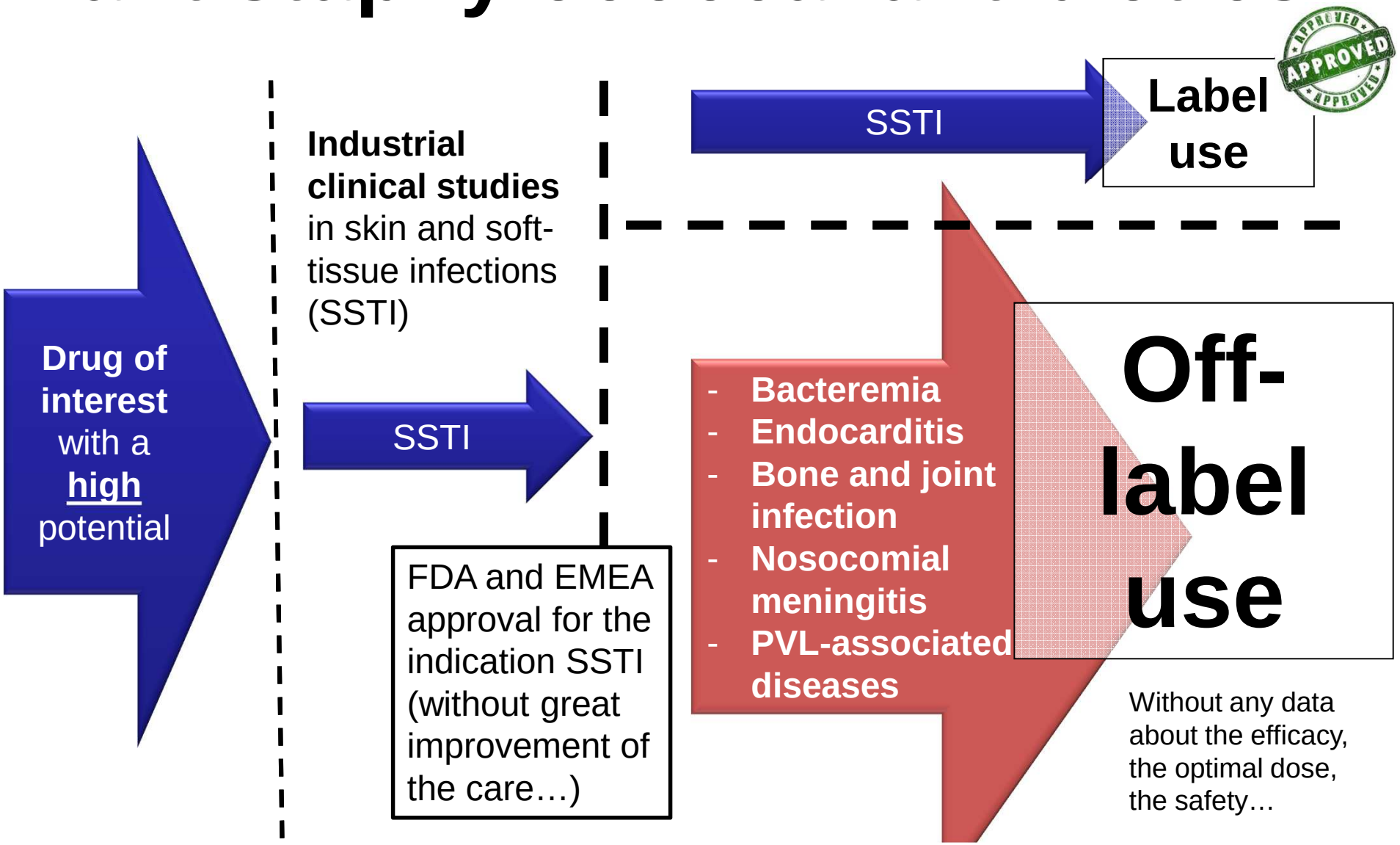
Daptomycin

Telavancin
Dalbavancin
Oritavancin

Tedizolide

Delafloxacine

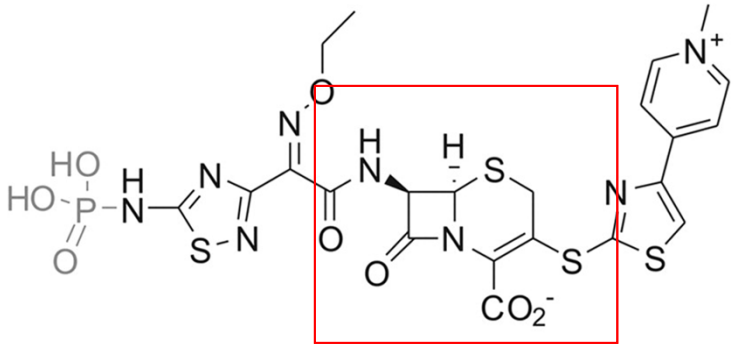
Typical process for antistaphylococcal antibiotics



Novelty in current antimicrobal classes

- **β-lactams**
  - Ceftaroline
  - Ceftobiprole
- **Lipoglycopeptides**
  - Daptomycin
- **2nd generation (lipo)glycopeptides**
  - Telavancin
  - Dalbavancin
  - Oritavancin
- **Oxazolidinones**
  - Tedizolide
- **Fluoroquinolones**
  - Delafloxacine

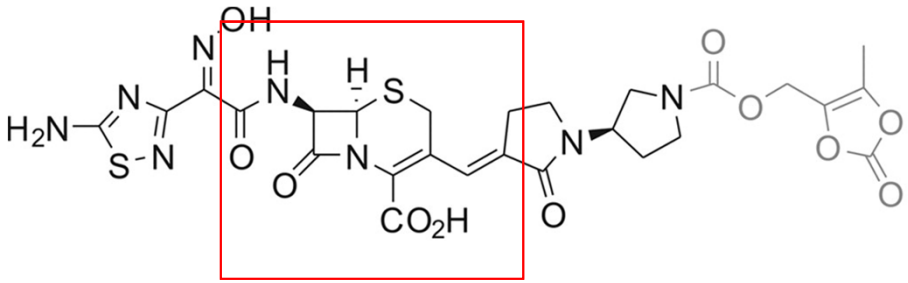
Ceftaroline and ceftobiprole



Ceftaroline fosamil

Spectrum ≈ cefoxitine
i.e. active on *Enterobacteriaceae*
but not on *P. aeruginosa*

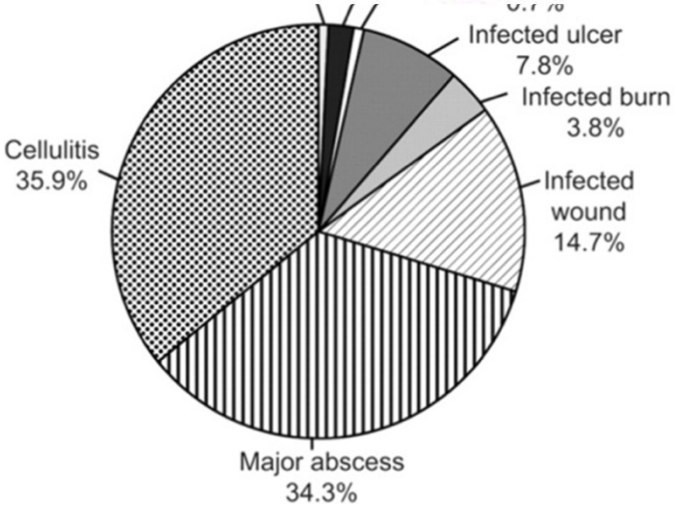
Intravenous cephalosporin
High affinity for PBP2a
Activity against **MRSA**



Ceftobiprole

Spectrum ≈ ceftazidime
i.e. active on *Enterobacteriaceae*
and on *P. aeruginosa*

Ceftaroline and « complicated » skin soft tissue infection



Bacteremia: 4%
Surgery: 14%

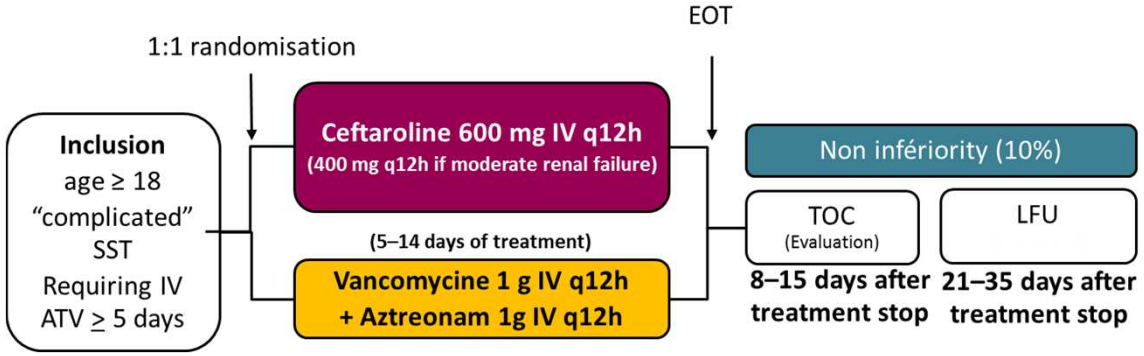
Integrated Analysis of CANVAS 1 and 2: Phase 3, Multicenter, Randomized, Double-Blind Studies to Evaluate the Safety and Efficacy of Ceftaroline versus Vancomycin plus Aztreonam in Complicated Skin and Skin-Structure Infection

G. Ralph Corey,[1] Mark Wilcox,[4] George H. Talbot,[2,a] H. David Friedland,[2] Tanya Baculik,[2] Gary W. Witherell,[2] Ian Critchley,[2] Anita F. Das,[3] and Dirk Thye[2]

[1]Duke Clinical Research Institute, Durham, North Carolina; [2]Cerexa, Inc,[a] Oakland, and [3]AxiStat, Inc, San Francisco, California; [4]Leeds Teaching Hospitals and University of Leeds, Leeds, United Kingdom

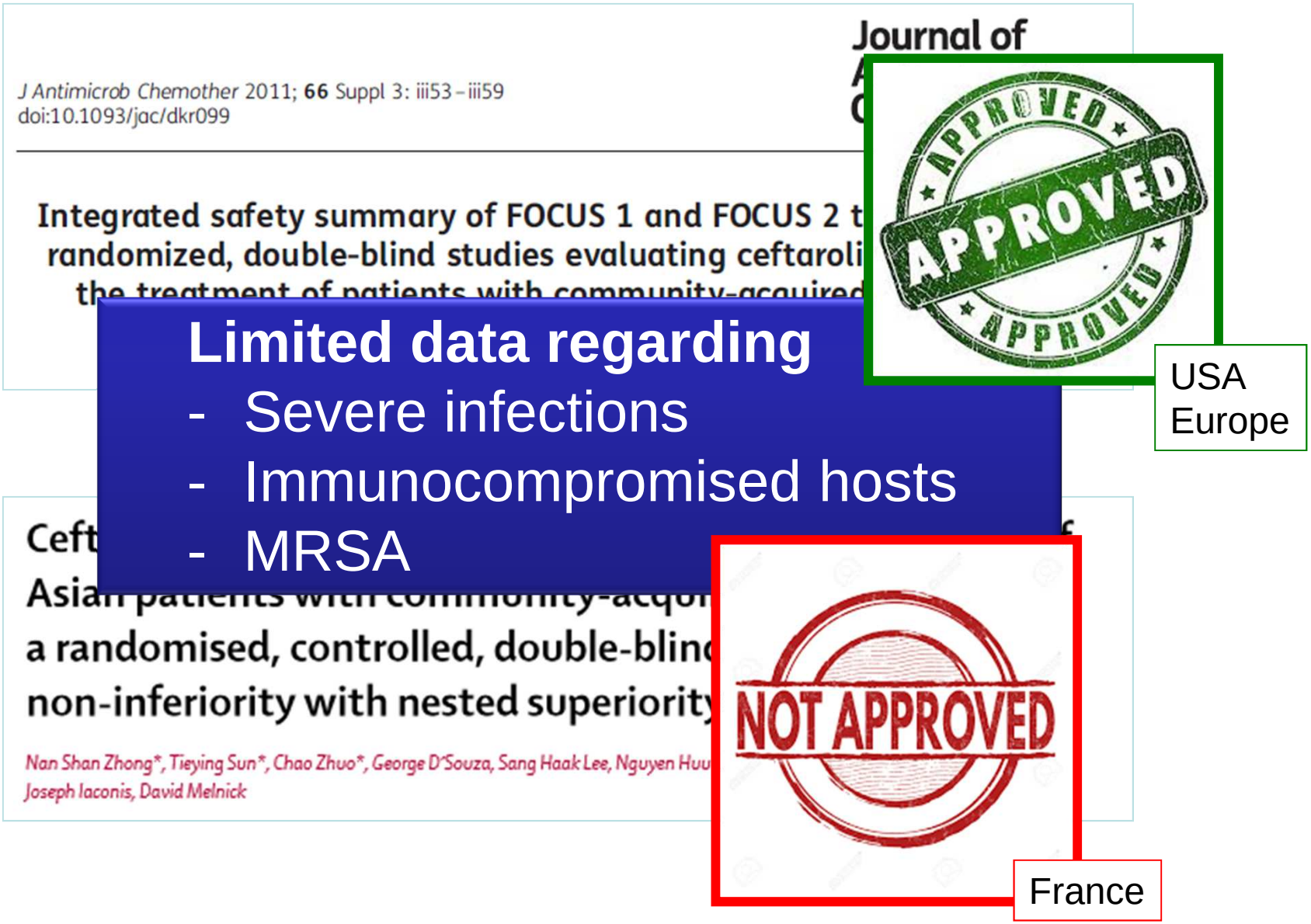
Clinical Infectious Diseases 2010; 51(6):641–650

1378 patients included

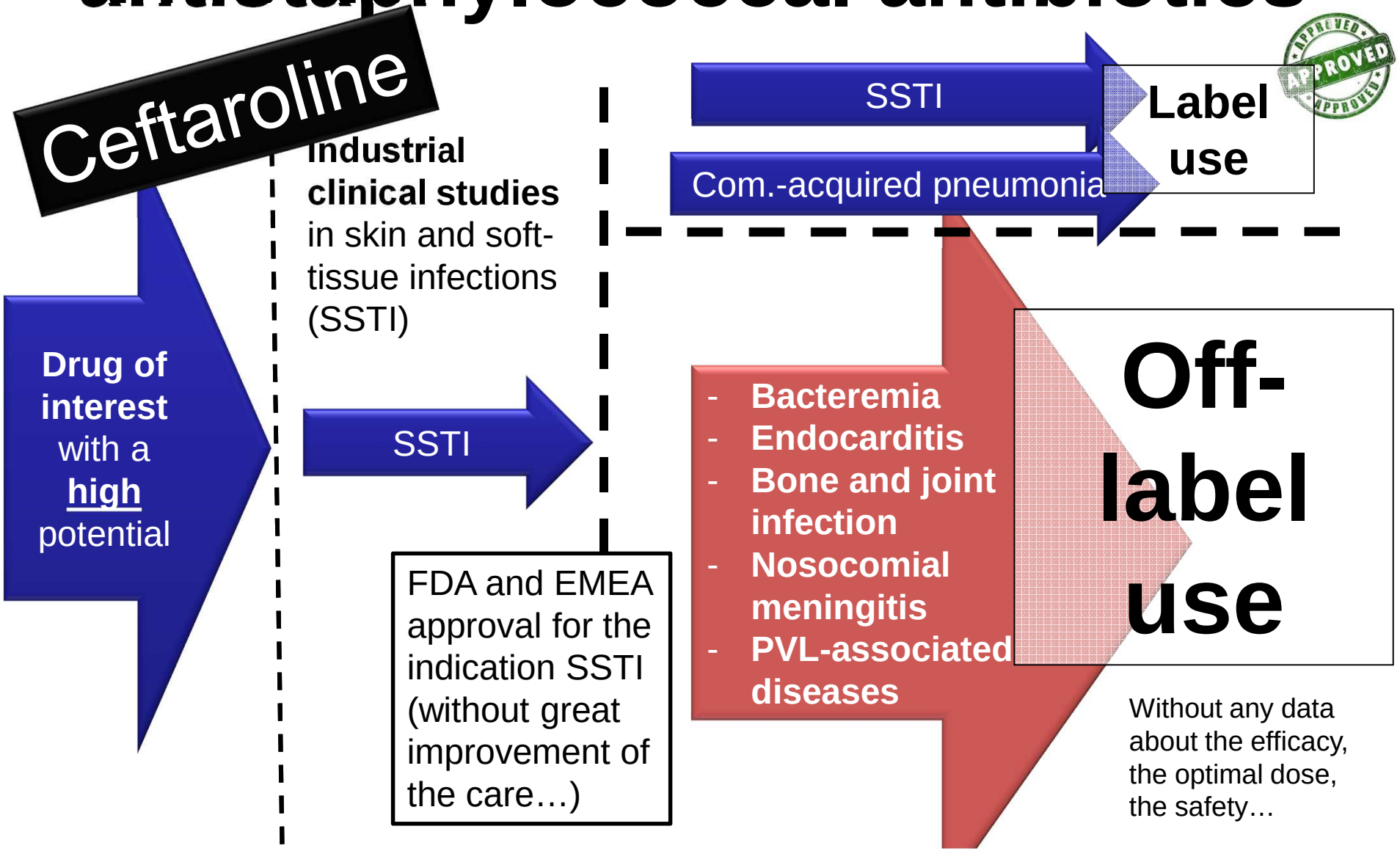


Clinical cure rates
91.6% vs 92.7%
Patients infected with MRSA
93.4% vs 94.3%

Ceftaroline and **community**-acquired pneumonia



Typical process for antistaphylococcal antibiotics



Ceftaroline and off-label **experience**: bacteremia

Ceftaroline Fosamil for the Treatment of *Staphylococcus aureus* Bacteremia Secondary to Acute Bacterial Skin and Skin Structure Infections or Community-Acquired Bacterial Pneumonia

Infect Dis Clin Pract 2015;23

Jose A. Vazquez, MD, FACP, FIDSA, Christy R. Maggiore, PharmD, BCPS,† Phillip Cole, MD,‡ Alexander Smith, MS,‡ Alena Jandourek, MD,‡ and H. David Friedland, MD, MBA‡*

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Short communication

Use of ceftaroline after glycopeptide failure to eradicate meticillin-resistant *Staphylococcus aureus* bacteraemia with elevated vancomycin minimum inhibitory concentrations☆

Joseph A. Paladino[a,b,c,*], David M. Jacobs[a,b], Ryan K. Shields[d], Jerusha Taylor[e], Justin Bader[a], Martin H. Adelman[b], Greg J. Wilton[b], John K. Crane[c,f], Jerome J. Schentag[a,b]

Clinical Therapeutics/Volume 36, Number 10, 2014

Original Research

Antimicrobial Salvage Therapy for Persistent Staphylococcal Bacteremia Using Daptomycin Plus Ceftaroline

George Sakoulas, MD[1]; Pamela A. Moise, PharmD[2]; Anthony M. Casapao, PharmD[3];

Ceftaroline off-label **potential indications**: infective endocarditis

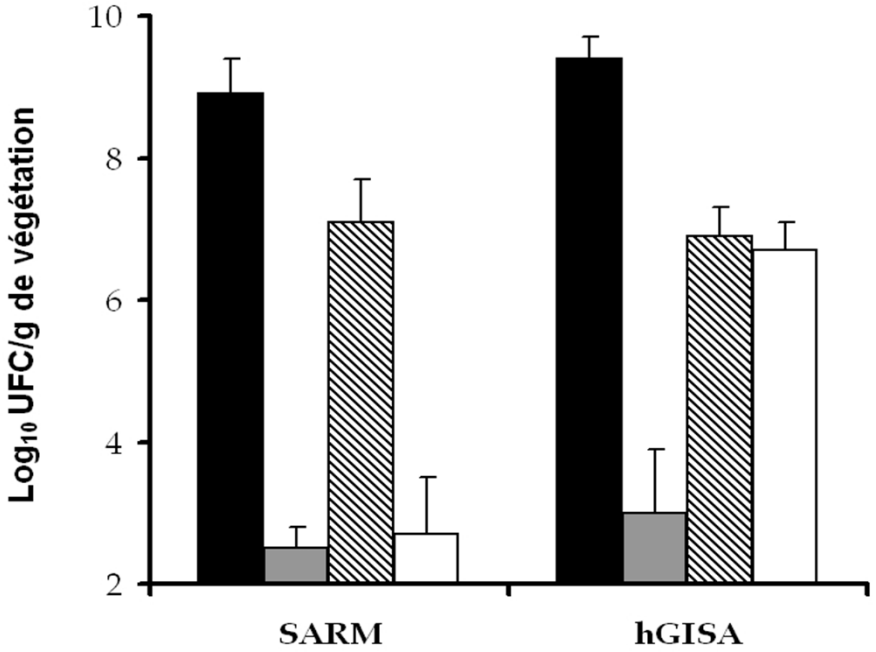
J Antimicrob Chemother 2011; **66**: 863–866
doi:10.1093/jac/dkr019 Advance Access publication 31 January 2011

Comparison of ceftaroline fosamil, daptomycin and tigecycline in an experimental rabbit endocarditis model caused by methicillin-susceptible, methicillin-resistant and glycopeptide-intermediate *Staphylococcus aureus*

Cédric Jacqueline[1]*, Gilles Amador[1], Eric Batard[1], Virginie Le Mabecque[1], Anne-Françoise Miègeville[1], Donald Biek[2], Jocelyne Caillon[1] and Gilles Potel[1]

Animal models: better efficacy than vancomycin, linezolide, tigecycline in MRSA and GISA

Controls (black)
Ceftaroline (grey)
Linezolid
Vancomycine (white)



Ceftaroline off-label **experience**: infective endocarditis

J Antimicrob Chemother 2014
doi:10.1093/jac/dku085
Advance Access publication 28 March 2014

Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study

Pierre Tattevin[1,2*], David Boutoille[2,3], Virginie Vitrat[4], Nicolas Van Grunderbeeck[5], Matthieu Revest[1,2], Mathieu Dupont[6], Serge Alfandari[7] and Jean-Paul Stahl[8]

Very few and heterogenous patients…

8 left-side endocarditis including 4 prosthetic valves

5 MRSA, 3 MRCoNS

400 mg/12h to 800 mg/8h

5 clinical success…

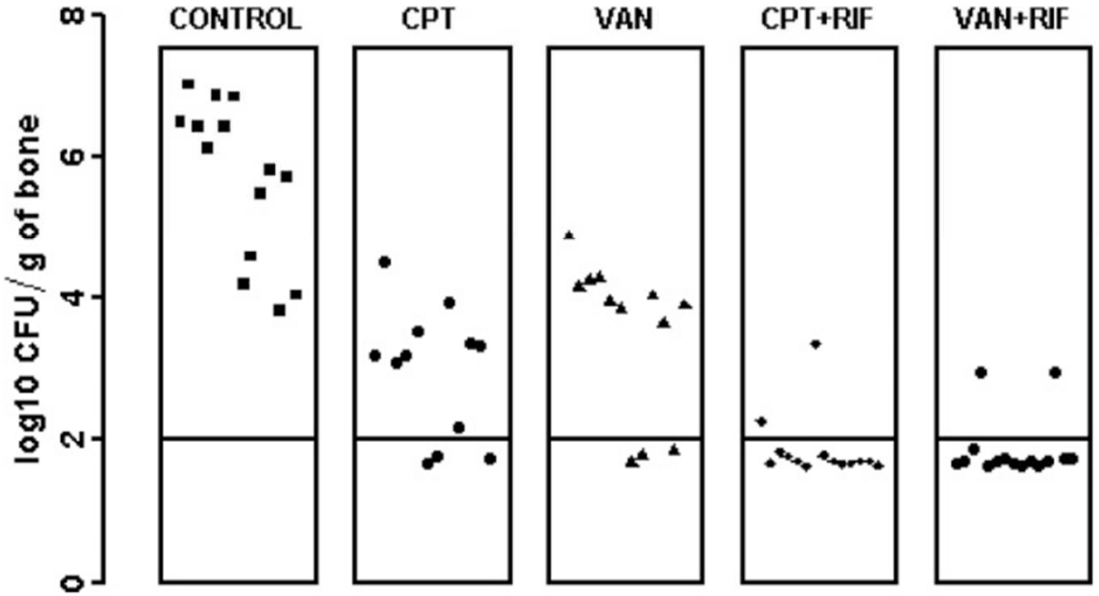
Ceftaroline off-label **potential indications**: Bone and joint infections

Ceftaroline-Fosamil Efficacy against Methicillin-Resistant *Staphylococcus aureus* in a Rabbit Prosthetic Joint Infection Model

Laure Gatin,[a] Azzam Saleh-Mghir,[a] Jason Tasse,[b] Idir Ghout,[c] Frédéric Laurent,[b] Anne-Claude Crémieux[a]

EA 3647, Faculté de Médecine Paris-Île-de-France Ouest, Université Versailles Saint-Quentin en Yvelines, Hôpital Raymond Poincaré, Garches, France[a]; Laboratoire de Bactériologie, Hôpital de la Croix Rousse, Centre National de Référence des Staphylocoques, INSERM Unité 851, Faculté de Médecine Lyon-Est, Lyon, France[b]; URC Paris-Ouest Laboratoire de Biostatistiques, Hôpital Ambroise Pare, Boulogne-Billancourt, France[c]

Antimicrobial Agents and Chemotherapy p. 6496–6500 November 2014 Volume 58 Number 11



Ceftarolin off-label **experience**: Bone and joint infection

High rate of methicillin-resistant staphylococci responsible for BJI
Patients frequently experienced vancomycin-related kidney toxicity

J Infect Chemother (2013) 19:42–49
DOI 10.1007/s10156-012-0449-9

ORIGINAL ARTICLE

The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients

Jennifer C. Lin · Gregory Aung · Amy Thomas · Maximillian Jahng · Scott Johns · Joshua Fierer

4 Bone and Joint infection, including 1 Prosthetic joint infection
4 clinical success…
600 mg/8h à 800 mg/12h

Ceftobiprole and « complicated » skin soft tissue infection

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Ceftazi
Compl

Gary J. Noel, I
Johnson & Johnso

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Refusal of the marketing authorisation for Zeftera (ceftobiprole)
24 June 2010

In November 2008, the CHMP gave a positive opinion on Zeftera, recommending that it be granted marketing authorisation. However, the Committee later received information about an inspection of study sites by the Food and Drug Administration (FDA) in the United States of America that led the Committee to stop the medicine's authorisation process.

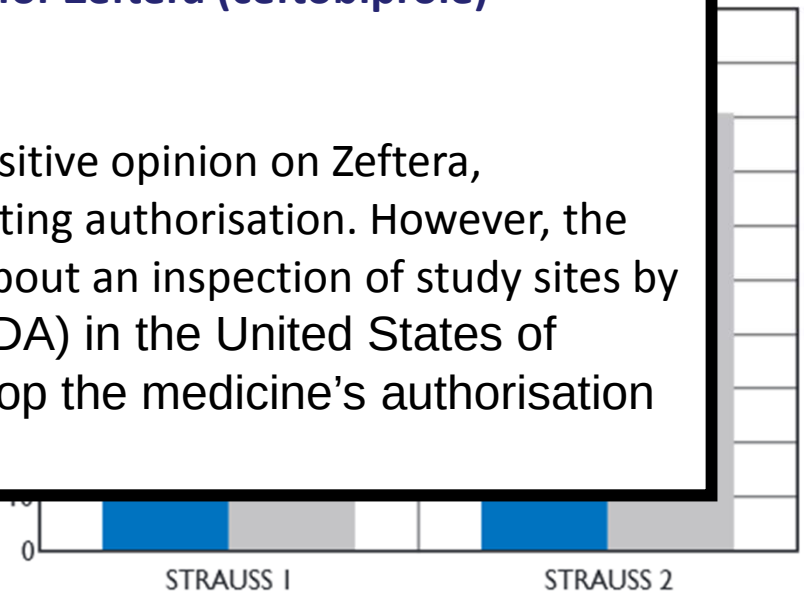


Figure 1 Clinical cure rates for the intent-to-treat population.
(Data from Noel GJ, Straus RS, Amsler K, et al. *Antimicrob Agents Chemother* 2008; 52:37–44;[24] and Noel GJ, Bush K, Bagchi P, et al. *Clin Infect Dis* 2008;46:647–655.[26])

Ceftobiprole and **hospital**-acquired pneumonia

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Samir S. Awad,[1] Alejandro H. Rodriguez,[2] Yin-Ching Chuang,[3] Zsuszanna Marja
Thomas W. L. Scheeren,[7,8] Alejandro S. Sánchez,[9] Xin Zhou,[10] Mikaël Saulay,[11]

Table 2. Primary Endpoint: Clinical Cure at Test of Cure (Intent-to-Treat and Clinically

	Ceftobiprole		Ceftazidime/Linezo			
Analysis Set Group	No.	No.[a] (%)	No.	No.[a] (%		CI)[c]
Intent-to-treat						
All patients	391	195 (49.9)	390	206 (52.8)	−2.9	(−10.0 to 4.1)
HAP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	0.8	(−7.3 to 8.8)
VAP	104					
HAP, mechanically ventilated	69					
Clinically evaluable						
All patients	251					
HAP (excluding VAP)	198					
VAP	53	20 (37.7)	59	33 (55.9)	−18.2	(−36.4 to −.0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	15 (40.5)	14.7	(−7.6 to 37.1)

Ceftobiprole is a safe and effective bactericidal antibiotic for the empiric treatment of HAP (excluding VAP)

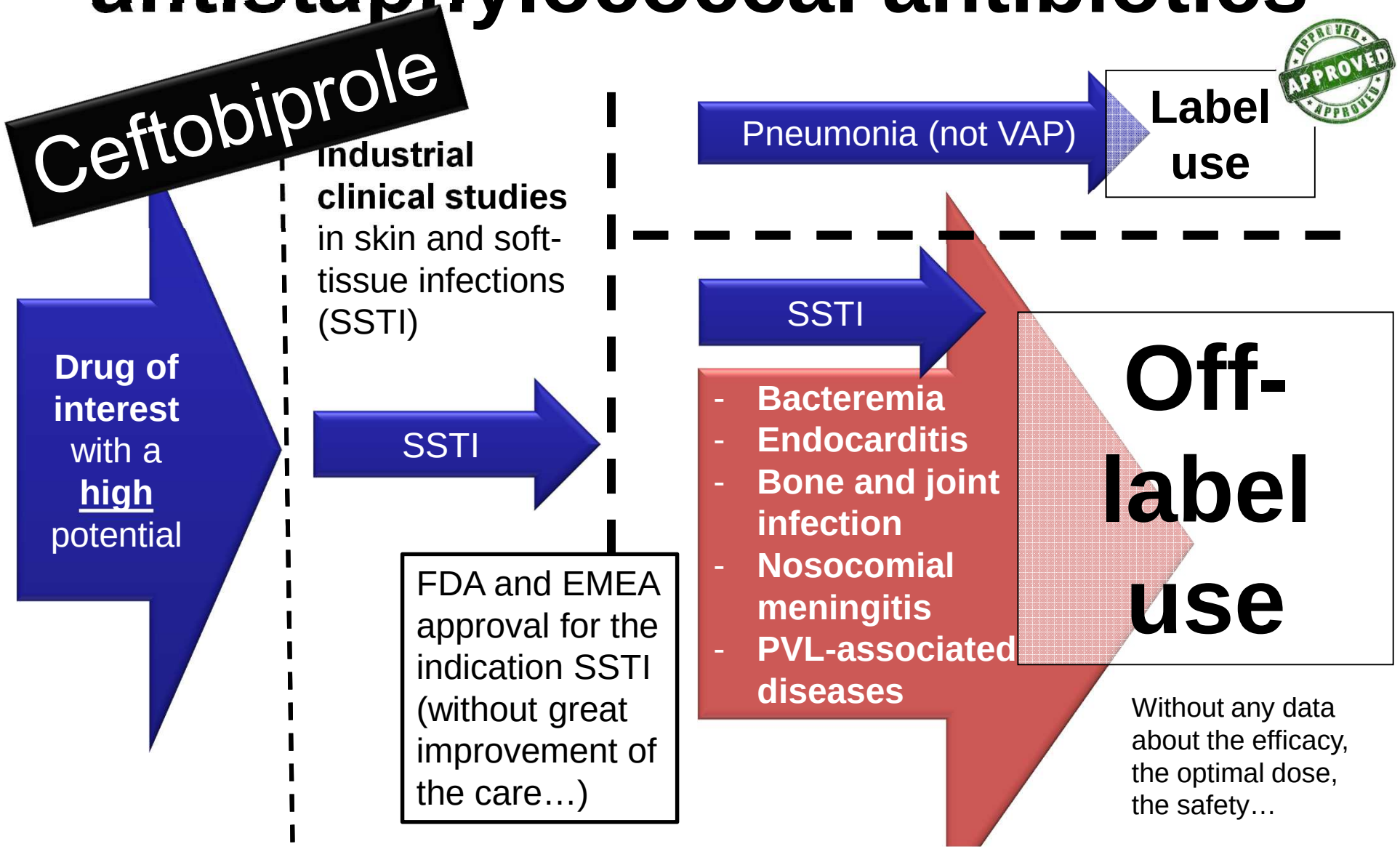
Abbreviations: CI, confidence interval; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

[a] No. of patients with clinical cure at test of cure.

[b] Difference ceftobiprole minus ceftazidime/linezolid.

[c] Two-sided 95% CI is based on the normal approximation to the difference of the 2 proportions.

Typical process for antistaphylococcal antibiotics



Ceftobiprole off-label **potential indications**: Infective endocarditis and bacteremia

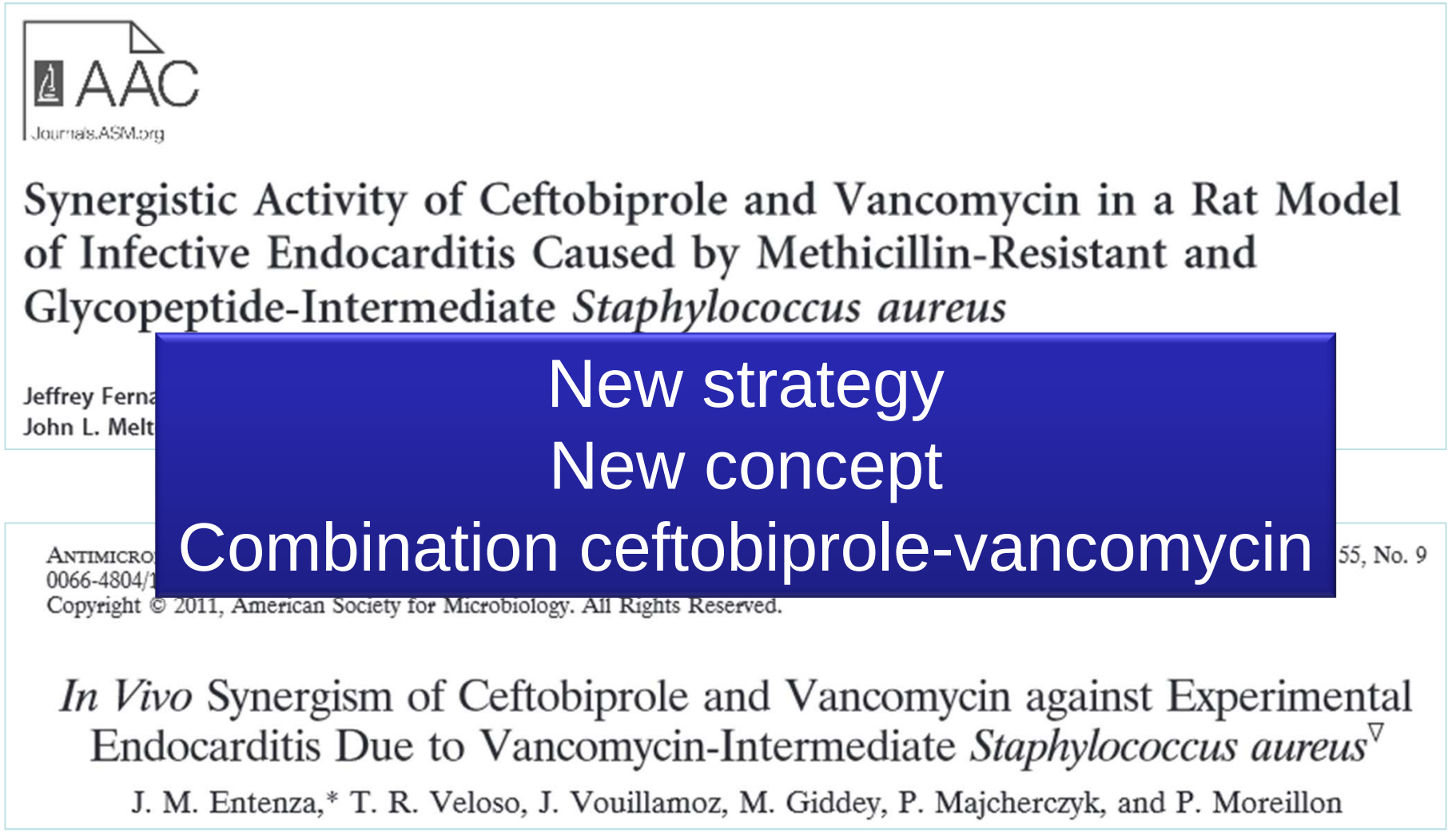
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2010, p. 610–613 Vol. 54, No. 2
0066-4804/10/$12.00 doi:10.1128/AAC.00886-09

Ceftobiprole Is Superior to Vancomycin, Daptomycin, and Linezolid for Treatment of Experimental Endocarditis in Rabbits Caused by Methicillin-Resistant *Staphylococcus aureus*▽

P. Tattevin,* L. Basuino, D. Bauer, B. A. Diep, and H. F. Chambers

Treatment (no. of rabbits)	Mean organism titer (log_{10} CFU/g ± SD) (no. sterile)		
	Vegetation	Spleen	Kidneys
Ceftobiprole (7)	2.1 ± 1.0 (6)	1.8 ± 0.2 (5)	1.7 ± 0 (7)
Control (6)	8.4 ± 0.7 (0)	5.1 ± 0.9 (0)	4.4 ± 1.0 (0)
Daptomycin (7)	3.6 ± 1.4 (1)	2.3 ± 0.7 (2)	2.6 ± 1.1 (3)
Vancomycin (6)	5.9 ± 2.8 (1)	3.3 ± 1.6 (2)	3.1 ± 1.5 (3)
Linezolid (5)	5.9 ± 1.2 (0)	2.9 ± 0.4 (0)	2.5 ± 0.6 (1)

Ceftobiprole off-label **potential indications**: Infective endocarditis and bacteremia



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Journals.ASM.org

Synergistic Activity of Ceftobiprole and Vancomycin in a Rat Model of Infective Endocarditis Caused by Methicillin-Resistant and Glycopeptide-Intermediate *Staphylococcus aureus*

Jeffrey Ferna
John L. Melt

New strategy
New concept
Combination ceftobiprole-vancomycin

ANTIMICRO 55, No. 9
0066-4804/1

In Vivo Synergism of Ceftobiprole and Vancomycin against Experimental Endocarditis Due to Vancomycin-Intermediate *Staphylococcus aureus*[▽]

J. M. Entenza,* T. R. Veloso, J. Vouillamoz, M. Giddey, P. Majcherczyk, and P. Moreillon

Ceftobiprole off-label **experience**: Infective endocarditis and bacteremia

Int J Antimicrob Agents. 2016 Jun;47(6):502-4. doi: 10.1016/j.ijantimicag.2016.04.006. Epub 2016 Apr 25.

Meticillin-resistant Staphylococcus aureus endocarditis: first report of daptomycin plus ceftobiprole combination as salvage therapy.

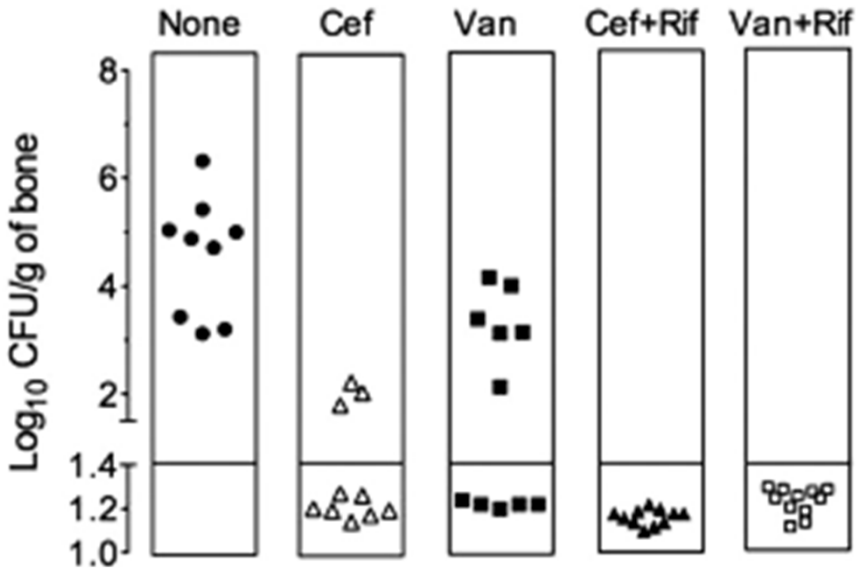
Oltolini C[1], Castiglioni B[2], Tassan Din C[2], Castiglioni A[3], Ossi C[4], La Canna G[5], Pajoro U[6], Scarpellini P[2].

Ceftobiprole off-label **potential indications**: Bone and joint infection

AAC
Journals.ASM.org

Ceftobiprole Efficacy *In Vitro* against Panton-Valentine Leukocidin Production and *In Vivo* against Community-Associated Methicillin-Resistant *Staphylococcus aureus* Osteomyelitis in Rabbits

Azzam Saleh-Mghir,[a,b] Oana Dumitrescu,[c] Aurélien Dinh,[a,b] Yassine Boutrad,[a,b] Laurent Massias,[d] Émilie Martin,[c] François Vandenesch,[c] Jérôme Etienne,[c] Gérard Lina,[c] and Anne Claude Crémieux[a,b]



Ceftobiprole off-label **experience**: Bone and joint infection

CASE REPORT

Ceftobiprole: First reported experience in osteomyelitis

A MacDonald MD[1], G Dow MD[2]

A MacDonald, G Dow. Ceftobiprole: First reported experience in osteomyelitis. Can J Infect Dis Med Microbiol 2010;21(3):138-40.

Le ceftobiprole : Une première expérience déclarée dans le traitement de l'ostéomyélite

Novelty in current antimicrobal classes

- β-lactams
- **Lipoglycopeptides**
- **2nd generation (lipo)glycopeptides**
- **Oxazolidinones**
- **Fluoroquinolones**

Ceftaroline
Ceftobiprole

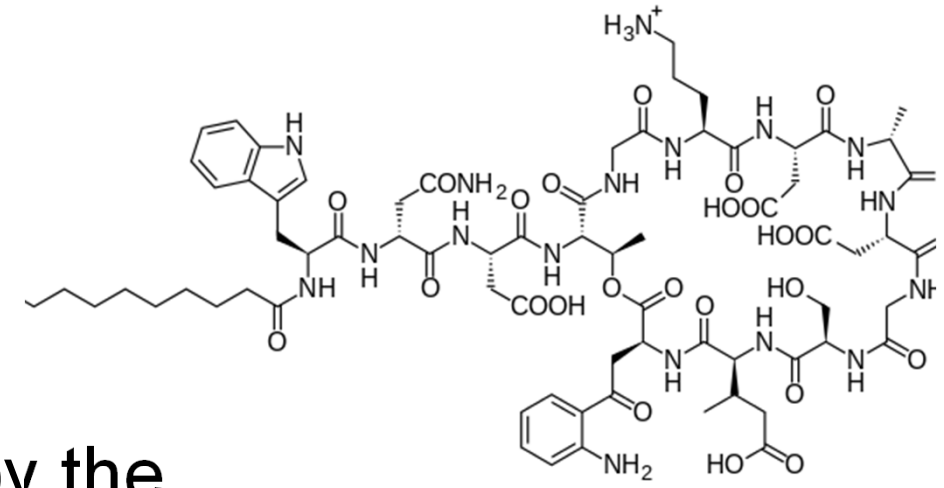
Daptomycin

Telavancin
Dalbavancin
Oritavancin

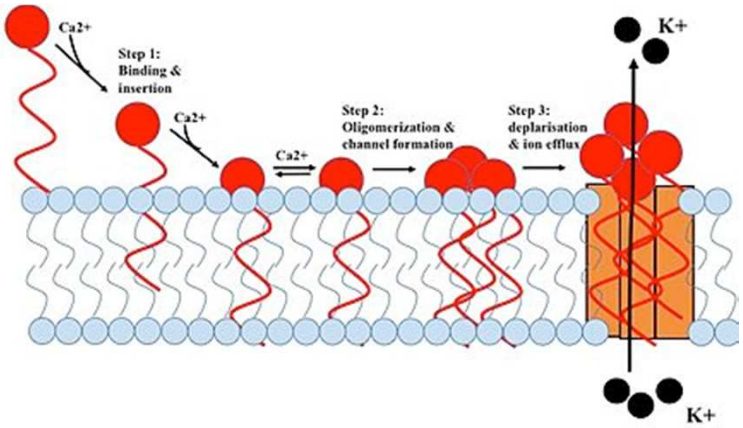
Tedizolid

Delafloxacin

Daptomycin



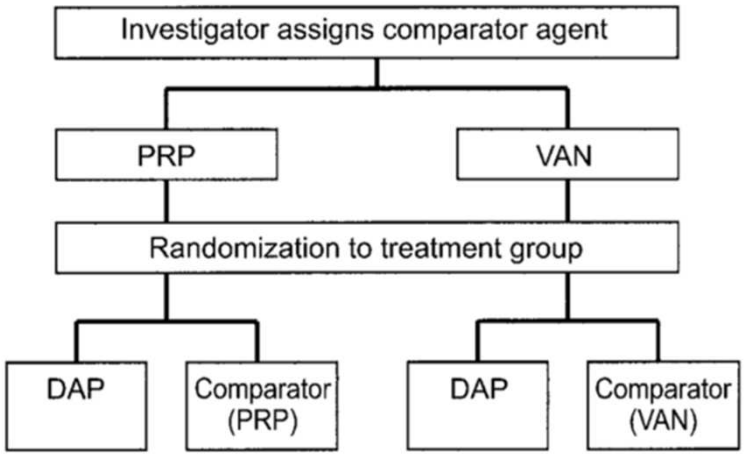
- Naturally produced by the soil saprotroph *Streptomyces roseosporus*
- Membrane depolarisation
- High bactericidal activity
- Inhibited by pulmonary surfactant



Daptomycin and « complicated » skin soft tissue infection

The Safety and Efficacy of Daptomycin for the Treatment of Complicated Skin and Skin-Structure Infections

Robert D. Arbeit,[1,a] Dennis Maki,[2] Francis P. Tally,[1] Edward Campanaro,[1] Barry I. Eisenstein,[1] and the Daptomycin 98-01 and 99-01 Investigators



DAP: daptomycin 4 mg/kg/day

PRP: penicillinase-resistant penicillin

Clinical Infectious Diseases 2004;38:1673–81

Daptomycin and infective endocarditis

The NEW ENGLAN
JOURNAL of MEDIC

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

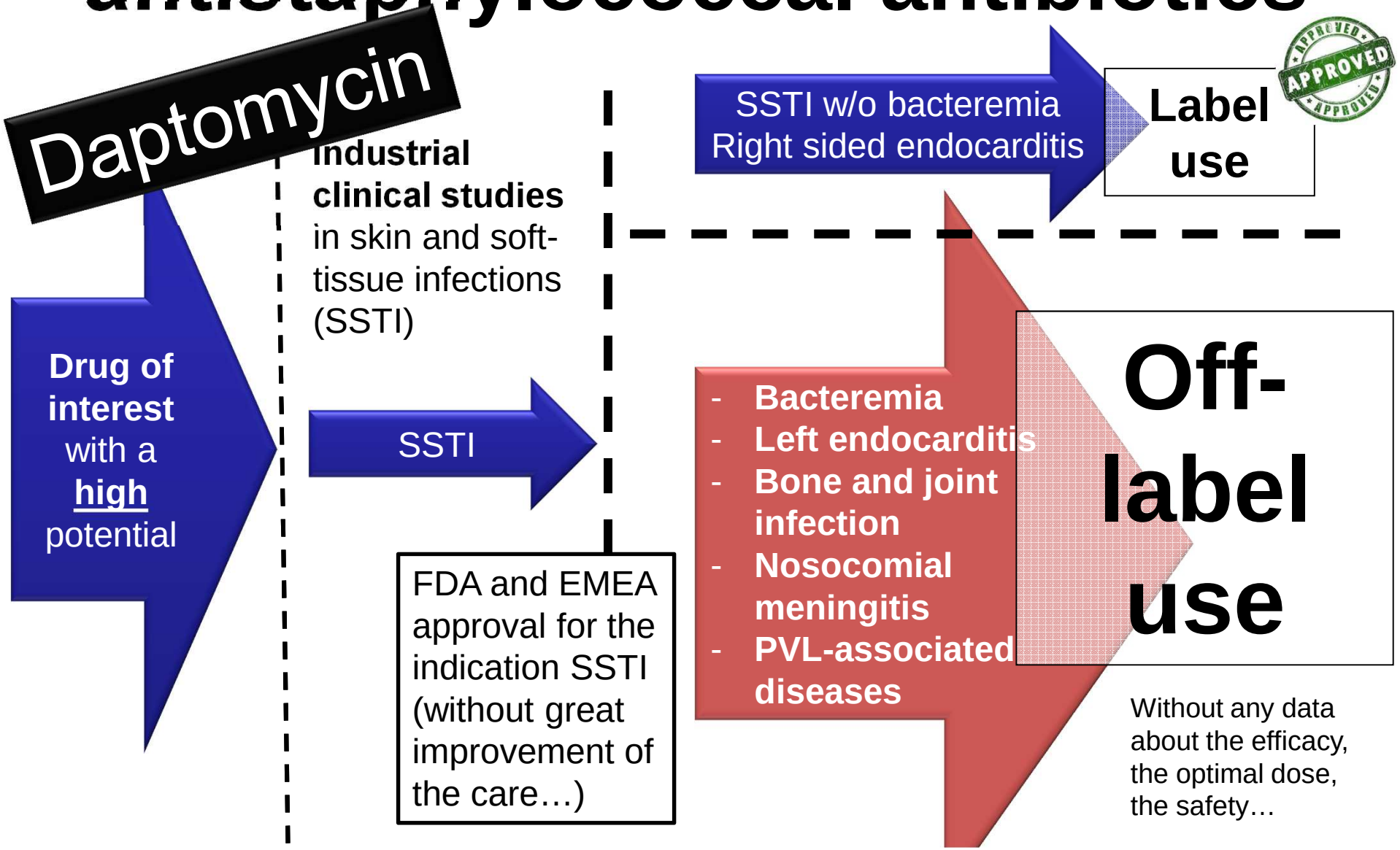
Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D.,

CONCLUSIONS

Daptomycin (6 mg per kilogram daily) is not inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis. (ClinicalTrials.gov number, NCT00093067.)

Typical process for antistaphylococcal antibiotics



Daptomycin off-label **potential indications**: Bone and joint infection

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4589–4593 Vol. 55, No. 10
0066-4804/11/$12.00 doi:10.1128/AAC.00675-11

Adjunctive Rifampin Is Crucial to Optimizing Daptomycin Efficacy against Rabbit Prosthetic Joint Infection Due to Methicillin-Resistant *Staphylococcus aureus*▽†

Azzam Saleh-Mghir,[1,2] Claudette Muller-Serieys,[3] Aurélien Dinh,[1,2] Laurent Massias,[4] and Anne-Claude Crémieux[1,2]*

Treatment[a]	No. of rabbits with sterile bone/total	Log_{10} CFU/g of bone (mean ± SD)	No. of rabbits with daptomycin mutant strain/no. infected
None	0/9	5.93 ± 1.15	2/9
Daptomycin	2/12	4.23 ± 1.44[b]	6/10[c]
Vancomycin	0/12	4.63 ± 1.08[b]	3/12
Daptomycin + rifampin	11/11	1.47 ± 0.04[d,e]	
Vancomycin + rifampin	6/8	1.50 ± 0.12[d]	0/2[d]

Daptomycin off-label **experience**: Bone and joint infection

RESEARCH ARTICLE Open Access

Daptomycin > 6 mg/kg/day as salvage therapy in patients with complex bone and joint infection: cohort study in a regional reference center

Sandrine Roux[1,2], Florent Valour[1,2,3], Judith Karsenty[1,2,4], Marie-Claude Gagnieu[5], Thomas Perpoint[1], Sébastien Lustig[2,6], Florence Ader[1,2,3], Benoit Martha[4], Frédéric Laurent[2,3,7], Christian Chidiac[1,2,3], Tristan Ferry[1,2,3*] and on behalf of the Lyon BJI Study group

Proposed in the IDSA guidelines for the treatment of prosthetic joint infection

Novelty in current antimicrobal classes

- β-lactams
  - Ceftaroline
  - Ceftobiprole
- Lipoglycopeptides
  - Daptomycin
- **2nd generation (lipo)glycopeptides**
  - Telavancin
  - Dalbavancin
  - Oritavancin
- Oxazolidinones
  - Tedizolid
- Fluoroquinolones
  - Delafloxacin

Telavancin, Dalbavancin, Oritavancin

- Belong to the (lipo)glycopeptides family
- Remain active on VISA and daptomycin-resistant *S. aureus*
- Bactericidal effect > vancomycin
- Significant differences with daptomycin
  - Semi-synthetic derivatives of vancomycin
  - Two mechanisms of action
    - Binding to the peptidoglycane D-Ala-D-Ala ter
    - Membrane depolarization
  - Long half-life (>300h for dalba- and orita-

- Approved in Skin and soft tissue injection

Telavancin off-label **potential indications**: Infectious endocarditis

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2005, p. 3163–3165 Vol. 49, No. 8
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.8.3163–3165.2005

Efficacy of Telavancin in a Rabbit Model of Aortic Valve Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus* or Vancomycin-Intermediate *Staphylococcus aureus*

Andres G. Madrigal, Li Basuino, and Henry F. Chambers*

Division of Infectious Diseases, San Francisco General Hospital, Department of Medicine, University of California at San Francisco, 1001 Potrero Avenue, San Francisco, California 94110

Strain	Treatment (mg/kg)	No. of rabbits	Days of therapy	Vegetation titer ($\log_{10}$ CFU/g)	No. of sterile vegetations	No. of deaths
COL	None (control)	7		7.4 ± 0.2	0	
	VAN (30)	10	4	4.0 ± 3.2	3	0
	TLV (30)	11	4	2.7 ± 3.1[a]	6	1
	TLV (30)	6	2	3.2 ± 3.5[b]	3	0
	TLV (50)	6	2	4.1 ± 3.2[b]	2	0
HIP 5836	None (control)	5		6.7 ± 0.5	0	
	VAN (30)	6	4	6.8 ± 0.45	0	4
	TLV (30)	6	4	1.2 ± 2.6[c]	4[d]	1

Telavancin off-label **potential indications**: Bone and joint infection

Journal of Antimicrobial Chemotherapy (2009) **63**, 357–360
doi:10.1093/jac/dkn490
Advance Access publication 5 December 2008

JAC

Efficacy of telavancin in the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis: studies with a rabbit model

Li-Yan Yin[1], Jason H. Calhoun[1]*, Theodore S. Thomas[1] and Eric D. Wirtz[2]

Treatment group	MRSA-positive tibial cultures at day 56, *n/N* (%)
Untreated controls	9/15 (60.0)
Vancomycin 30 mg/kg, sc, twice daily	3/15 (20.0)*
Linezolid 60 mg/kg, oral, three times daily	4/14 (28.6)
Telavancin 30 mg/kg, sc, twice daily	3/15 (20.0)*

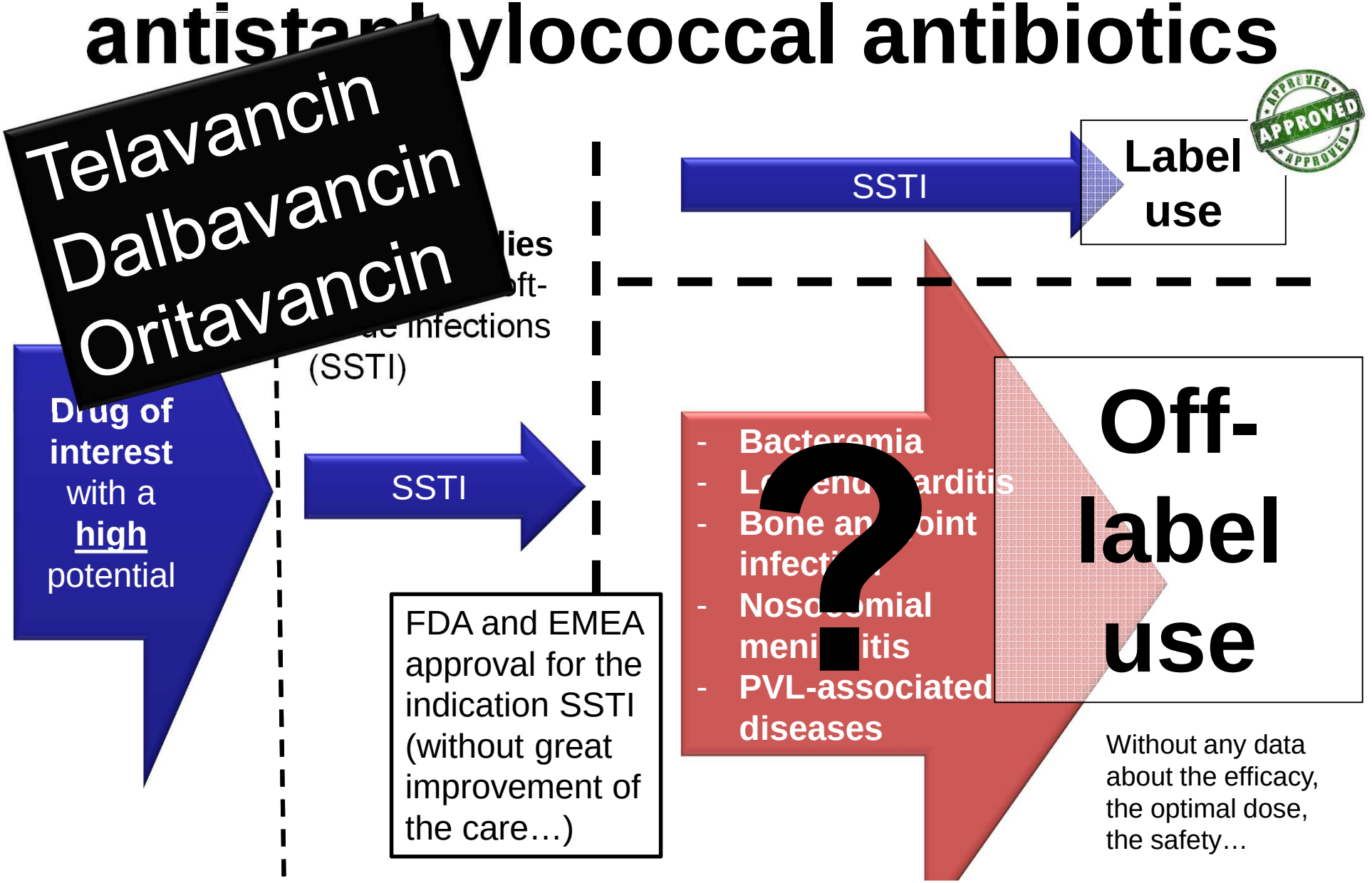
New (lipo)glycopeptides off-label **experience**

J Antimicrob Chemother. 2011 Nov;66(11):2675-7. doi: 10.1093/jac/dkr329. Epub 2011 Aug 10.

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

Twilla JD, Gelfand MS, Cleveland KO, Usery JB.

Typical process for antistaphylococcal antibiotics



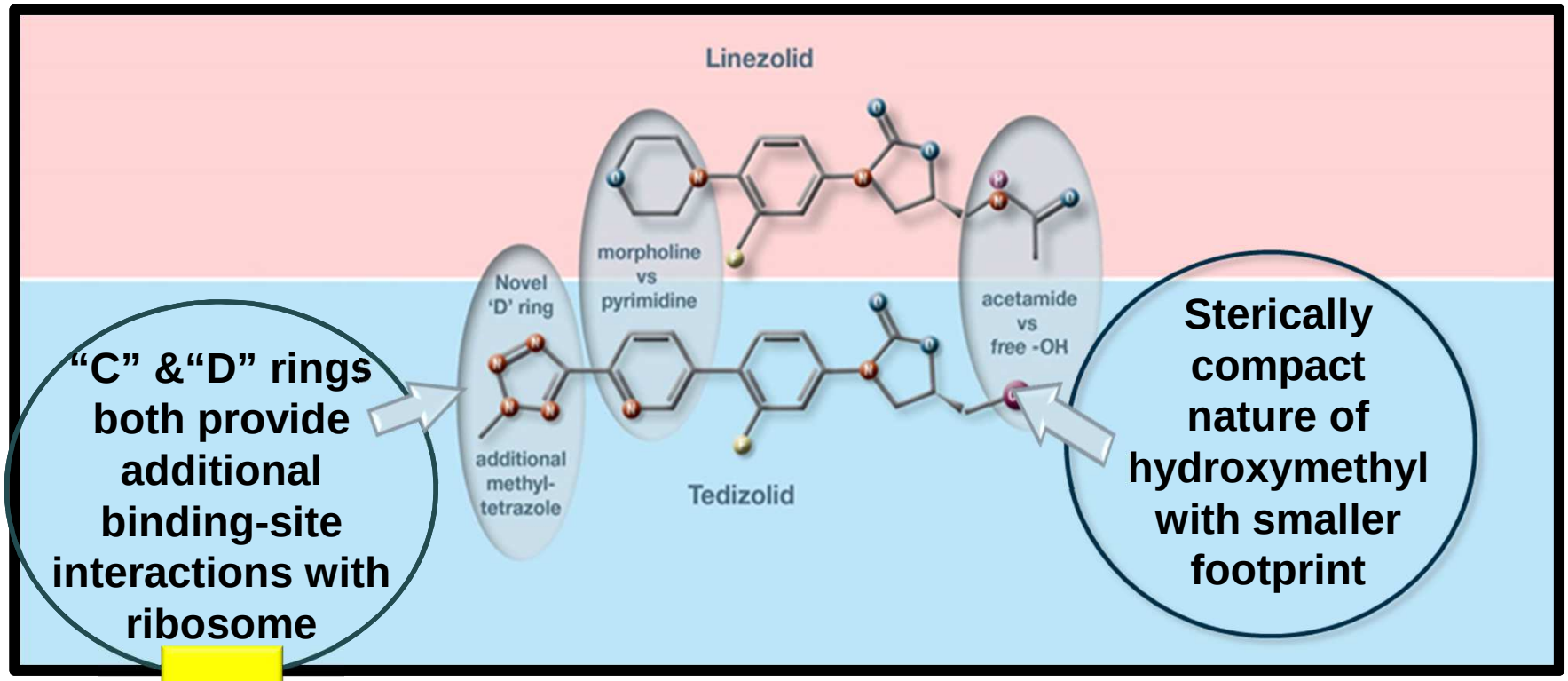
Novelty in current antimicrobal classes

- β-lactams
  - Ceftaroline
  - Ceftobiprole
- Lipoglycopeptides
  - Daptomycin
- 2nd generation (lipo)glycopeptides
  - Telavancin
  - Dalbavancin
  - Oritavancin
- **Oxazolidinones**
  - Tedizolid
- Fluoroquinolones
  - Delafloxacin

Tedizolide

- Belong to the Oxazolidinone family
- Linezolid was the 1st marketed molecule
  - Advantages
    - Oral bioavailability of 100%
    - Clinical efficacy in skin and soft tissue infections hospital pneumonia
    - « anti-toxinic » activity
  - Disavantages
    - Safety of prolonged administration
    - Drug-drug interactions
    - Acquisition of resistance by mutations

Tedizolide



- Additional fixation on the ribosomal 50s subunit
- Enhanced potency
- Improved antibacterial activity

Shaw KJ, et al. *Antimicrob Agents Chemother*. 2008;52:4442-4447.

Low MICs with tedizolid

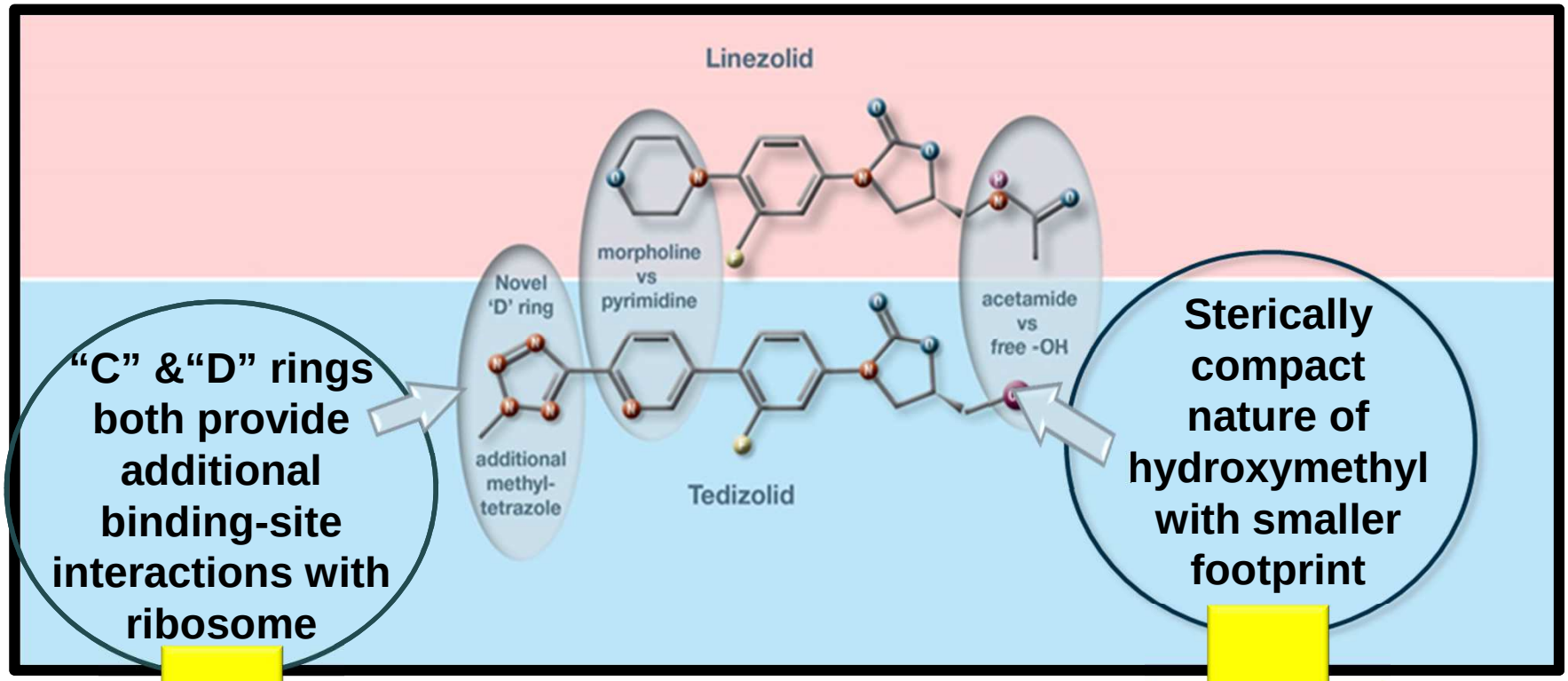
Table 1 In vitro activity (MIC mg/L) of tedizolid and comparators against aerobic Gram-positive organisms

Bacteria	Tedizolid			Linezolid			Vancomycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Staphylococcus aureus (MS)	0.25	0.5	≤0.015–8	2	2	≤0.25 to >8	1	1	0.25–2
Staphylococcus aureus (MR)	0.25	0.5	≤0.015–16	2	2	≤0.25 to >8	1	2	0.25–2
CoNS (MS)	0.25	0.5	0.06–1	1	2	≤0.25–4	2	2	1–2
CoNS (MR)	0.25	0.5	≤0.03–4	1	2	≤0.25–8	2	4	1–4
Enterococcus faecalis (VS)	0.5	0.5	0.12–1	2	2	0.5–4	1	2	0.5–4
Enterococcus faecalis (VR)	0.5	0.5	0.25–1	2	2	0.5–4	512	512	8 to >512
Enterococcus faecium (VS)	0.5	0.5	0.06–2	2	4	0.5–4	0.5	1	0.5–2
Enterococcus faecium (VR)	0.5	0.5	0.06–2	2	4	0.5 to >8	512	512	8 to >512
Streptococcus pyogenes (group A)	0.25	0.25	0.06–0.5	1	1	0.06–2	0.5	1	0.5–1
Streptococcus agalactiae (group B)	0.25	0.25	0.06–1	2	2	1–2	0.25	0.5	0.25–0.5
Streptococcus pneumoniae (PS)	0.25	0.25	0.03–0.5	1	2	0.12–2	0.25	0.5	0.06–1
Streptococcus pneumoniae (PI)	0.25	0.25	0.06–0.5	1	2	0.5–4	0.5	1	0.25–1
Streptococcus pneumoniae (PR)	0.25	0.25	0.06–0.5	1	2	0.25–2	0.25	0.5	0.06–2
Listeria monocytogenes	0.25	0.25	0.25–0.5	2	2	2	0.5	1	0.06–2

MR methicillin-resistant, *MS* methicillin-susceptible, *CoNS* coagulase-negative staphylococci, *PS* penicillin-susceptible (MIC ≤0.06 mg/L), *PI* penicillin-intermediate (MIC: 0.12–1 mg/L), *PR* penicillin-resistant (MIC ≥2 mg/L), *VS* vancomycin-susceptible (MIC ≤4 mg/L), *VR* vancomycin resistant (MIC ≥32 mg/L). Adapted from references [26–46]

Zhanel et al, Drugs 2015;75:253-270

Tedizolide



- Additional fixation on the ribosomal 50s subunit
- Enhanced potency
- Improved antibacterial activity

- Not impacted by Cfr methyltransferase (linezolide resistance)

Shaw KJ, et al. *Antimicrob Agents Chemother*. 2008;52:4442-4447. **Locke JB, et al. *Antimicrob Agents Chemother.* 2010;54:5337-5343.**

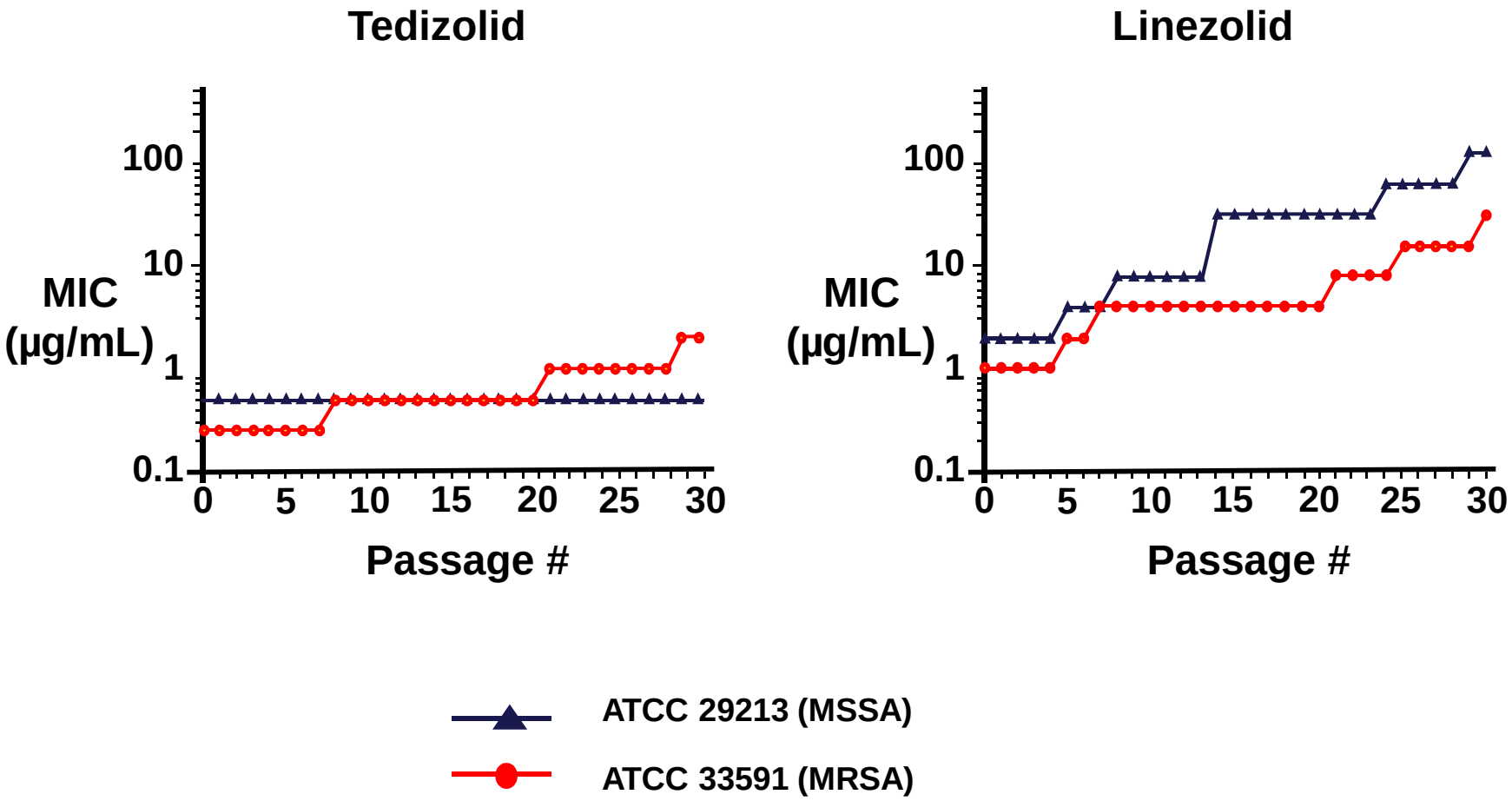
Tedizolid demonstrates low frequency of spontaneous resistance

Isolate	Antibiotic Selection	Mutation Frequency
S. aureus **ATCC 29213 (MSSA)**	**2× MIC**	**1.1×10^{-10}**
	4× MIC	**$<4.5\times10^{-10}$***
S. aureus **ATCC 33591 (MRSA)**	**2× MIC**	**1.9×10^{-10}**
S. aureus **USA300-0114 (MRSA)**	**4× MIC**	**$<4.5\times10^{-10}$***
E. faecalis **ATCC 29212 (VanS)**	**4× MIC**	**$<5.7\times10^{-11}$***
E. faecalis **ATCC 700802 (VanR)**	**4× MIC**	**$<6.1\times10^{-11}$***
S. pyogenes **ATCC 49399**	**4× MIC**	**$<1.0\times10^{-10}$***
S. agalactiae **ATCC 13813**	**4× MIC**	**$<3.1\times10^{-10}$***

No growth; mutation frequency calculated as <1/inoculum

Locke et al, AAC 2009;53:5265-74

Serial passage confirms low rate of resistance development



Locke et al, AAC 2009;53:5265-74

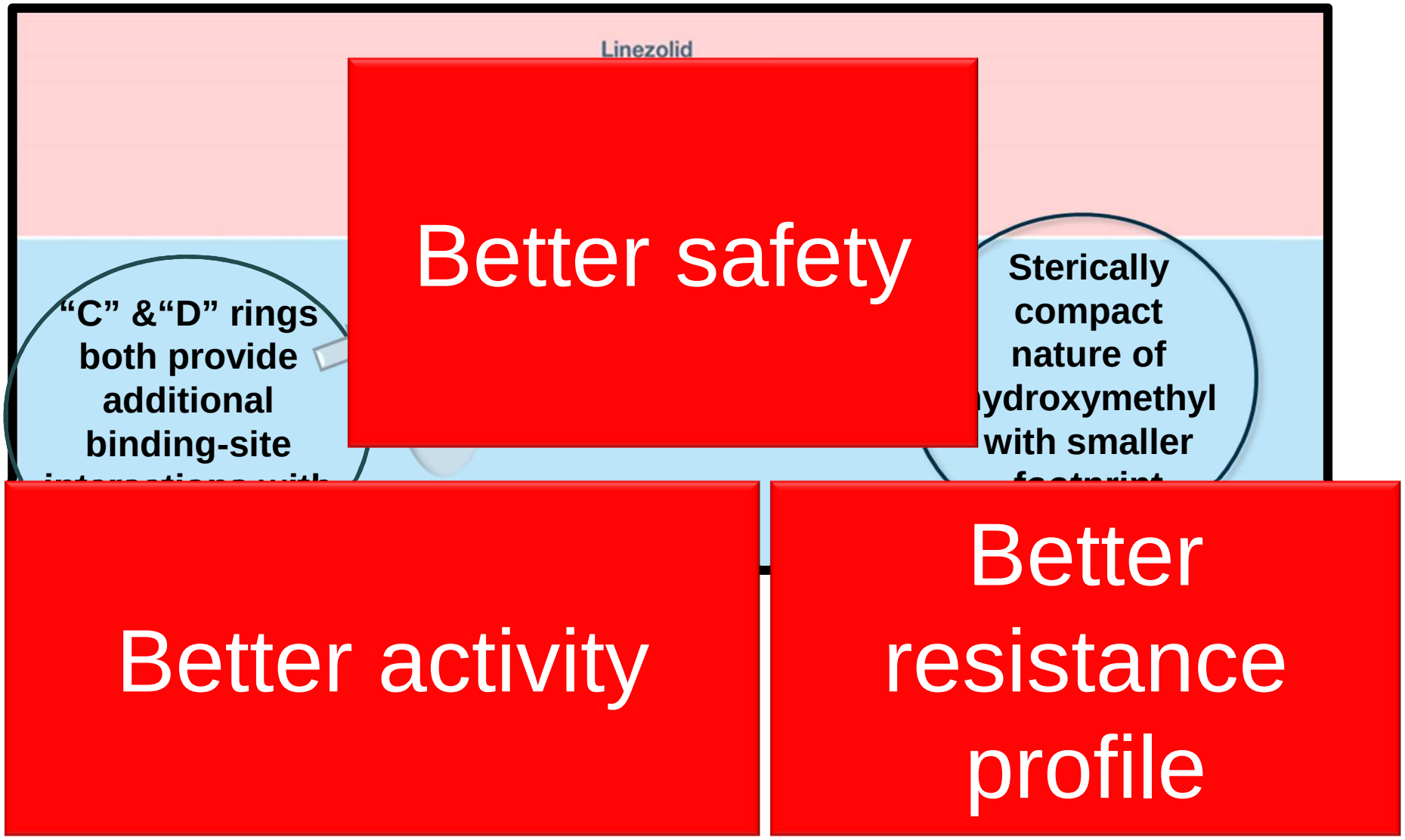
Tedizolid is active on most of *S. aureus* strains with decreased susceptibility to vancomycin, daptomycin and linezolid

Strain	TZD—number (cumulative percentage) inhibited at MIC (mg/L)							TZD MIC_{90} (mg/L)	TZD MIC range (mg/L)	LZD MIC_{90} (mg/L)	LZD MIC range (mg/L)
	≤0.063	0.125	0.25	0.5	1	2	4				
MRSA											
hVISA (n=120)	7 (5.8)	18 (20.8)	55 (66.7)	38 (98.3)	2[a] (100)	— (100)	— (100)	0.5	0.03–1	4	0.25–8
VISA (n=100)	7 (7)	52 (59)	25 (84)	16 (100)	— (100)	— (100)	— (100)	0.5	0.03–0.5	4	0.125–4
DNS (n=75)	— (0)	23 (30.7)	38 (81.3)	14 (100)	— (100)	— (100)	— (100)	0.5	0.125–0.5	2	1–4
LR[b] (n=7)	1 (14.3)	1 (28.6)	2 (57.1)	— (57.1)	3 (100)	— (100)	— (100)	NA	0.063–1	NA	8–16
VRE											
E. faecium (n=120)	— (0)	6 (5)	51 (47.5)	32 (74.2)	25 (95)	3 (97.5)	3 (100)	1	0.125–4	4	1–32
E. faecalis (n=100)	1 (1)	29 (30)	69 (99)	1 (100)	— (100)	— (100)	— (100)	0.25	0.063–0.5	2	0.25–2
LR *E. faecium* (n=10)	— (0)	— (0)	— (0)	— (0)	4 (40)	3 (70)	3 (100)	NA	1–4	NA	8–32
DNS *E. faecium* (n=25)	— (0)	— (0)	11 (44)	3 (56)	8 (88)	2 (96)	1 (100)	NA	0.25–4	NA	1–32

TZD, tedizolid; LZD, linezolid; NA, not applicable.
[a]These two hVISA isolates were LR, with linezolid MIC values of 8 mg/L.
[b]The three isolates with tedizolid MICs of 1 mg/L did not possess the *cfr* gene.

J Antimicrob Chemother 2016; 71: 152–155

Tedizolide



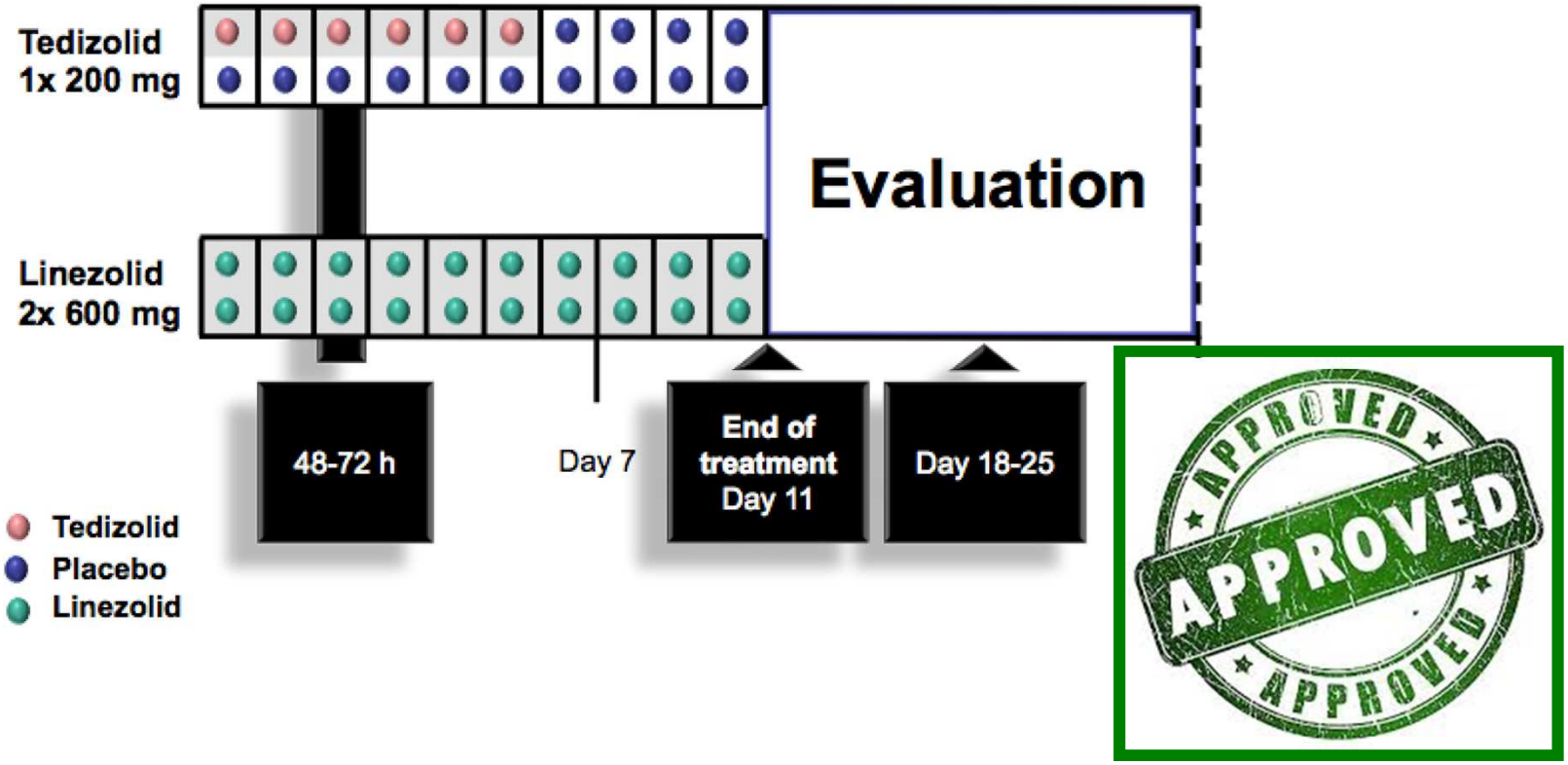
Shaw KJ, et al. *Antimicrob Agents Chemother*. 2008;52:4442-4447. Locke JB, et al. *Antimicrob Agents Chemother.* 2010;54:5337-5343.

Tedizolid and skin soft tissue infection

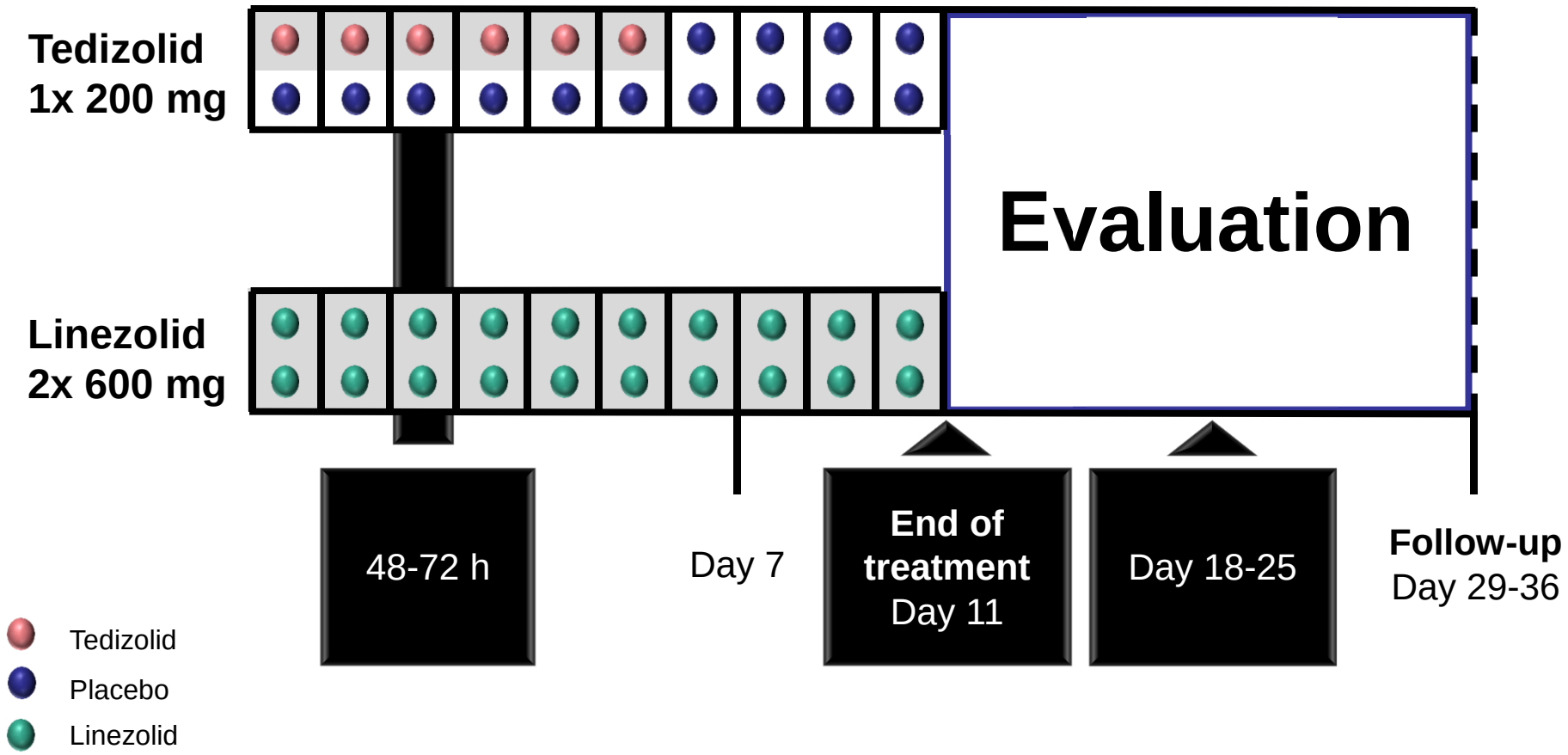
Analysis of the Phase 3 ESTABLISH Trials of Tedizolid versus Linezolid in Acute Bacterial Skin and Skin Structure Infections

Andrew F. Shorr,[a] Thomas P. Lodise,[b] G. Ralph Corey,[c] Carisa De Anda,[d] Edward Fang,[d] Anita F. Das,[e] Philippe Prokocimer[d]

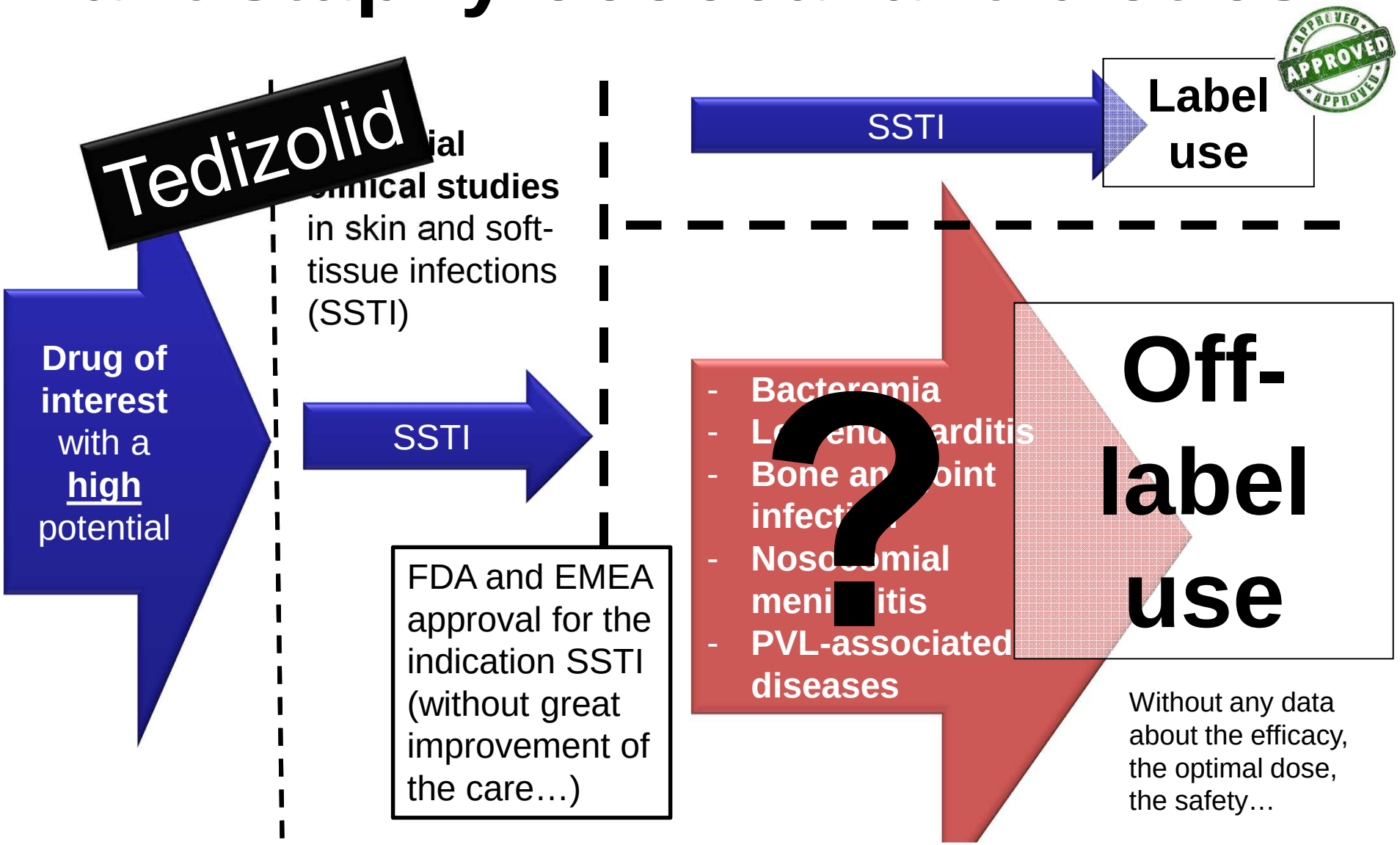
Pulmonary and Critical Care Medicine, Washington Hospital Center, Washington, DC, USA[a]; Albany College of Pharmacy and Health Sciences, Albany, New York, USA[b]; Duke University Health System, Durham, North Carolina, USA[c]; Cubist Pharmaceuticals, San Diego, California, USA[d]; InClin, Inc., San Mateo, California, USA[e]



Tedizolid and « complicated » skin soft tissue infection



Typical process for antistaphylococcal antibiotics



Novelty in current antimicrobal classes

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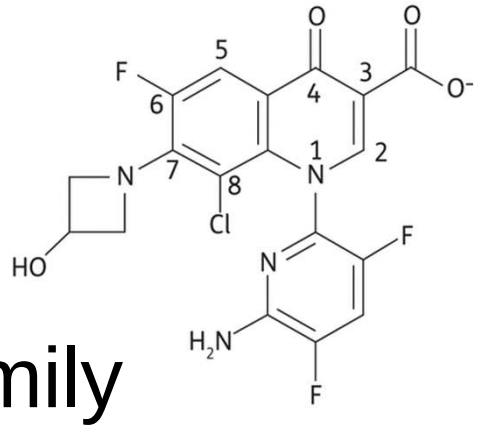
  - Oritavancin
- Oxazolidinines
  - Tedizolid
- Fluoroquinolones
  - Delafloxacin

Delafloxacin



- Belong to the Fluoroquinolone family
- Ofloxacin, levofloxacin, ciprofloxacin, moxifloxacin are marketed molecules
  - Advantages
    - Oral bioavailability of 100%
    - Large tissular diffusion (bone and joint)
  - Disavantages
    - Large dissemination of fluoroquinolone resistance by mutations/clonal diffusion
      - MRSA
      - Methicillin-resistant staphylococci

Delafloxacin is active on levofloxacin-resistant staphylococci

Table 1. Susceptibility of relevant Gram-positive pathogens to delafloxacin and other commercially available fluoroquinolones.

Species	Phenotype	Number of strains	Antibiotic	MIC_{50} (mg/l)	MIC_{90} (mg/l)	MIC range (mg/l)	Ref.†
S. aureus	All	681	Levofloxacin	0.12	>32	0.03–>32	[41]
		681	Delafloxacin	0.12	0.5	≤0.004–16	[41]
	FQ-S	70	Levofloxacin	0.25	0.5	0.06–0.5	[23]
		88		0.12	0.25	0.06–1	[42]
		70	Moxifloxacin	0.06	0.1	0.015–0.5	[23]
		70	Delafloxacin	0.004	0.008	0.002–0.008	[23]
		88		0.002	0.008	≤0.001–0.06	[42]
	FQ-R	71	Levofloxacin	16	32	4–64	[23]
		100		4	8	2–32	[42]
		71	Moxifloxacin	4	8	0.25–16	[23]
		71	Delafloxacin	0.25	1	0.015–1	[23]
		100		0.006	0.12	0.015–2	[42]
S. epidermidis	FQ-S	9	Levofloxacin		0.25	0.12–0.5	[23]
		9	Moxifloxacin		0.12	0.03–0.12	[23]
		9	Delafloxacin		0.008	0.002–0.08	[23]
	FQ-R	10	Levofloxacin	16	16	4–128	[23]
		10	Moxifloxacin	2	2	1–>128	[23]
		10	Delafloxacin	0.5	0.5	0.12–1	[23]
Coagulase-negative staphylococci	All	19	Levofloxacin	0.12	>32	0.06–>32	[42]
		19	Delafloxacin	0.004	1	0.001–2	[42]
	FQ-R	10	Levofloxacin	8	64	4–128	[18]
		10	Delafloxacin	0.25	0.5	0.03–0.5	[18]

Delafloxacin and skin soft tissue infection

J Antimicrob Chemother 2016; **71**: 821–829
doi:10.1093/jac/dkv411 Advance Access publication 17 December 2015

Journal of Antimicrobial Chemotherapy

A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin

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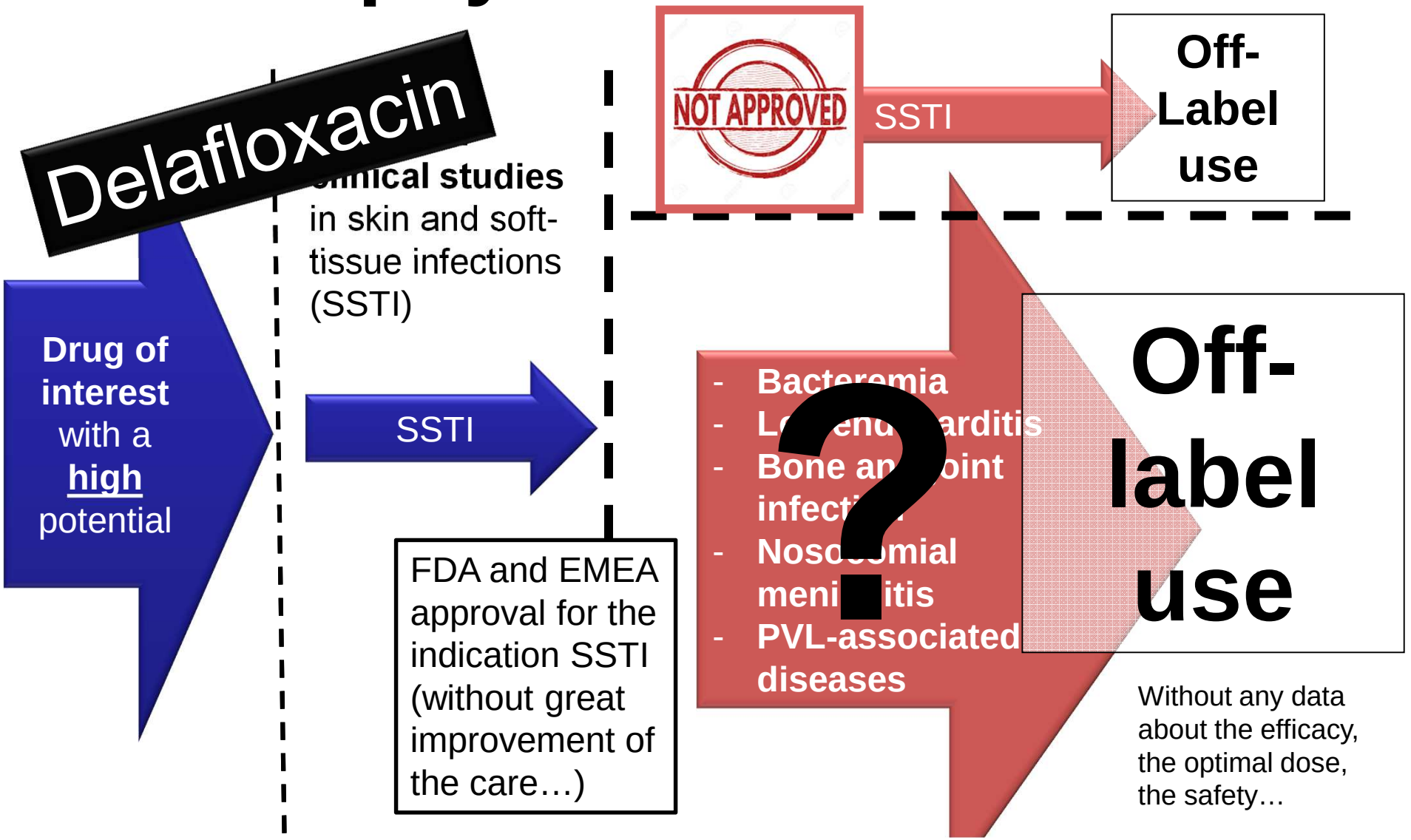
Table 2. Subjective clinical efficacy: investigator assessment of outcome at follow-up (ITT population)

	Response, *n* (%)	
	delafloxacin (*n*=81)	linezolid (*n*=77)
Cure[a]	57 (70.4)	50 (64.9)
Improved	11 (13.6)	13 (16.9)
Failure	5 (6.2)	3 (3.9)
Indeterminate	8 (9.9)	11 (14.3)

[a]Clinical success is defined as investigator assessm
improved, failure and indeterminate equate to failure.
[b]$P < 0.05$ versus delafloxacin, Cochran–Mantel–Haenszel test.

Typical process for antistaphylococcal antibiotics



Delafloxacin off-label **potential indications**: Bone and joint infection

Comparison of the Antibiotic Activities of Daptomycin, Vancomycin, and the Investigational Fluoroquinolone Delafloxacin against Biofilms from *Staphylococcus aureus* Clinical Isolates

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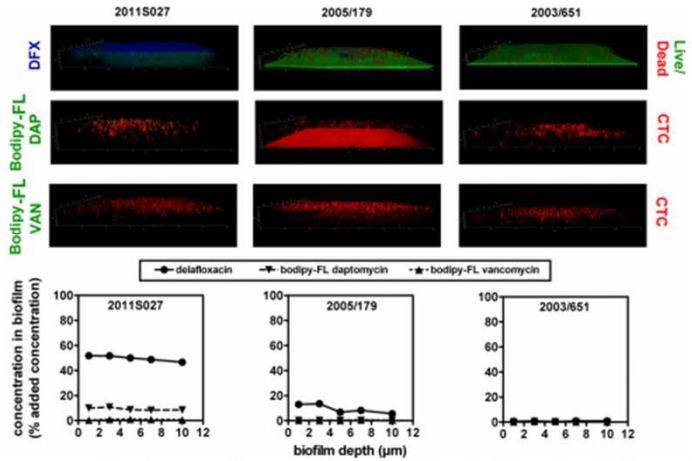
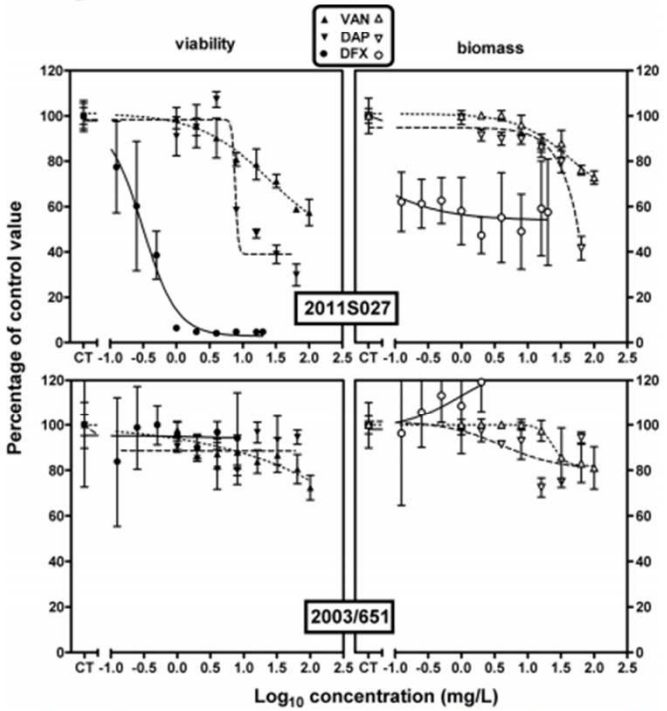


FIG 4 Penetration of antibiotics within biofilms. Confocal images of biofilms incubated for 1 h with 50 mg/liter delafloxacin (top [blue]), 20 mg/liter Bodipy-FL-daptomycin (middle [green]), or 20 mg/liter Bodipy-FL-vancomycin (bottom [green]) and labeled with LIVE/DEAD stain (top: red, dead; green, live) or CTC (middle and bottom: red). The graphs below each column compare the relative penetration of the drugs within the depth of the corresponding biofilm, expressed as the percentage of the added concentration (DFX, delafloxacin; DAP, daptomycin; VAN, vancomycin).



against biofilms. Concentration-response activities of antibiotics against 24-h biofilms of strain 2011S027 (top) or 2003/651 (bottom). Twenty-four-hour biofilms were incubated with increasing concentrations of antibiotics for 48 h (DFX, delafloxacin; DAP, daptomycin; VAN, vancomycin). The ordinate shows the change in viability (assessed by resorufin fluorescence; left) or in biomass (assessed by crystal violet absorbance; right) as the percentage of the control (CT) value (no antibiotic present). All values are the means ± standard deviations (SD) of 8 wells (when not visible, the SD bars are smaller than the size of the symbols).

« New » routes of delivery

Local antibiotherapy

- **Aerosolized antibiotics**
  - Severe pneumonia
- **Vacuum Assisted Closure (VAC system) with antibiotic instillation**
  - Severe skin and soft/tissue or bone and joint infection with bone exposition
- **Antibiotic-based cement in orthopaedic surgery**
  - Prosthetic joint infection and septic pseudarthrosis

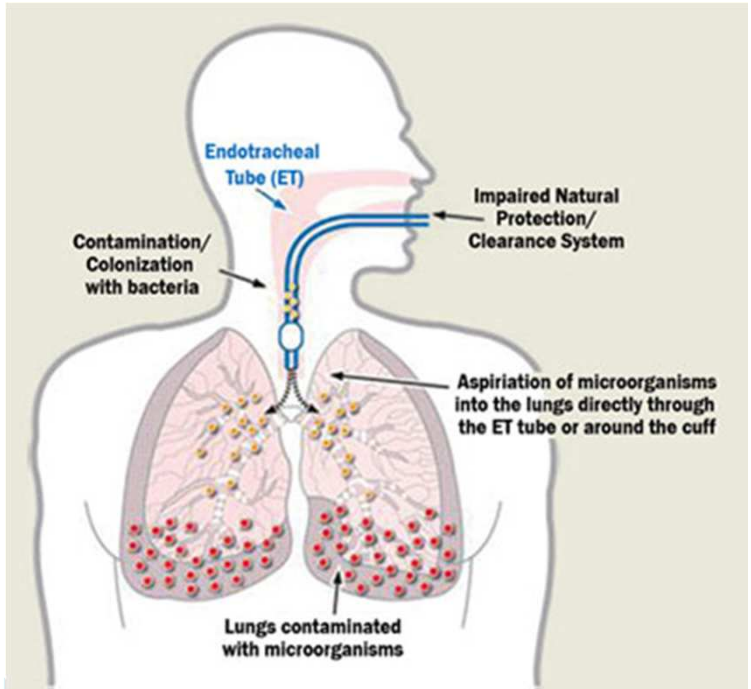
Aerosolized Antibiotics

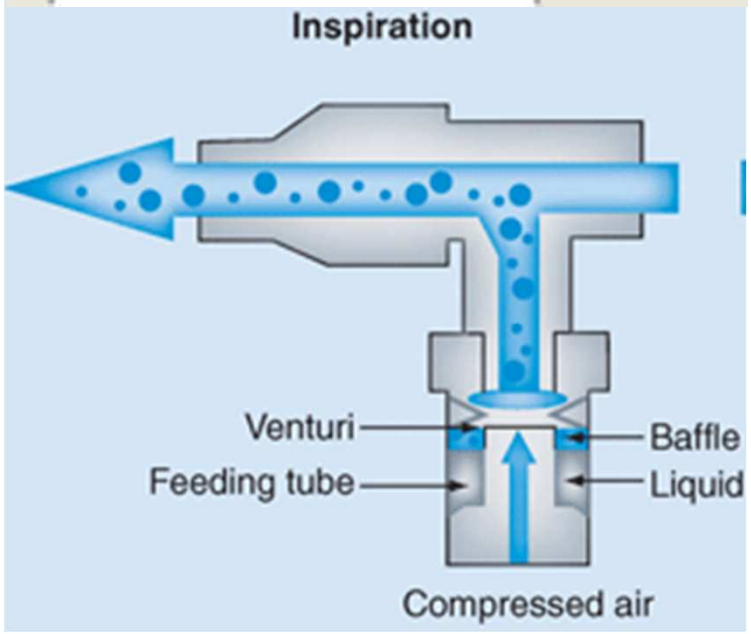
Table 1. List of the Available and Tested Aerosolized Antibiotics Reported in the Literature for Treatment of Infections Associated With Specific Clinical Conditions

Antibiotic	CF	NCFB	VAP
Aminoglycosides			
Gentamicin	Yes	Yes	Yes
Colomycin	Yes	Yes	
Amikacin	Yes	Yes	Yes
Liposomal amik			
Neomycin			
Sisomycin			Yes
Tobramycin			Yes
Polymyxins			
Colistin/polymy			Yes
Glycopeptides			
Vancomycin			Yes
Monobactams			
Aztreonam lysi			
β-Lactams			
Ceftazidim			Yes
Ticarcillin			
Fluoroquinolones			
Ciprofloxacin	Yes		

CF = cystic fibrosis
NCFB = non-CF bronchiectasis
VAP = ventilator-associated pneumonia

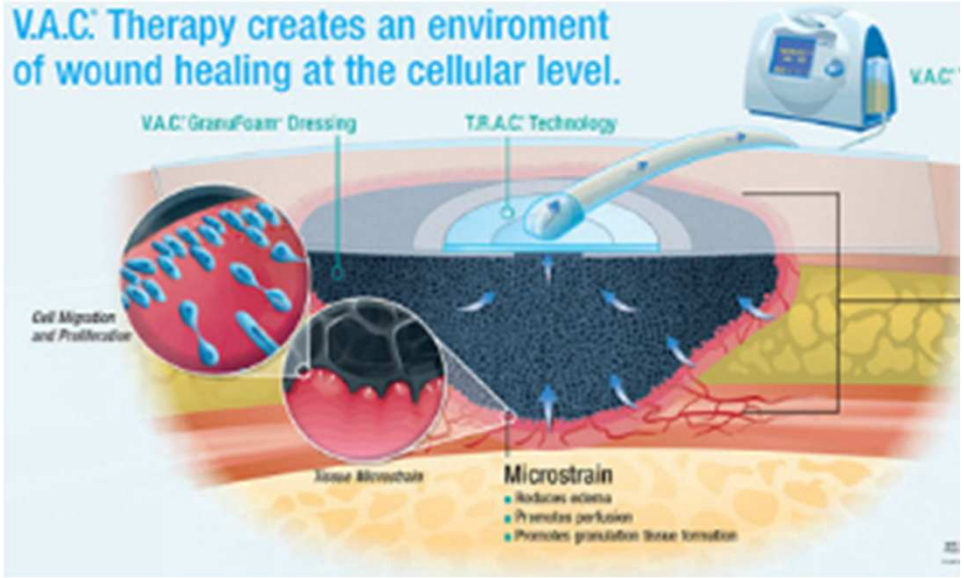
High performance aerosol drug delivery nebulizers

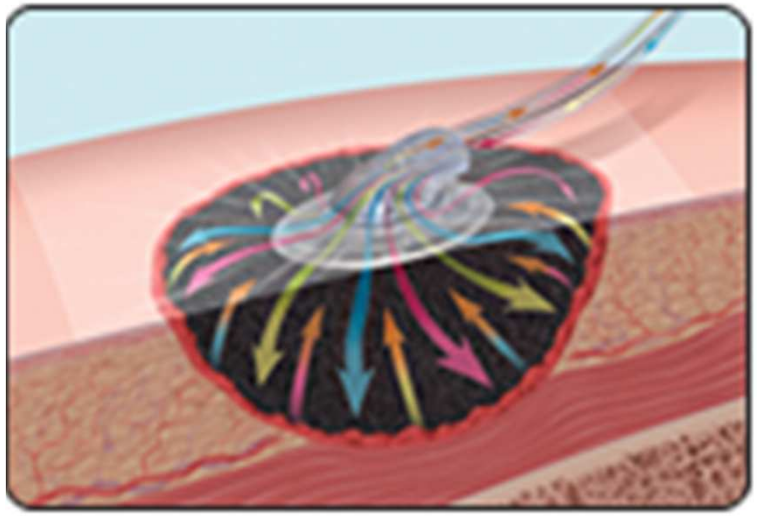


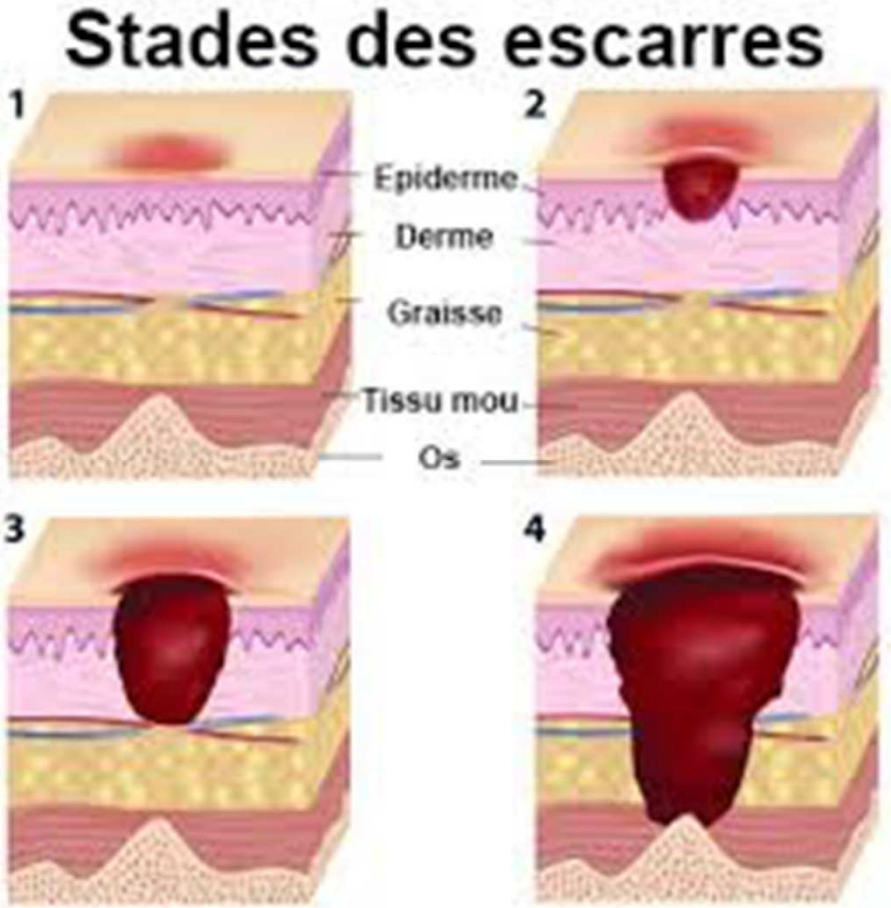


Respir Care. 2015;60(6):762-1

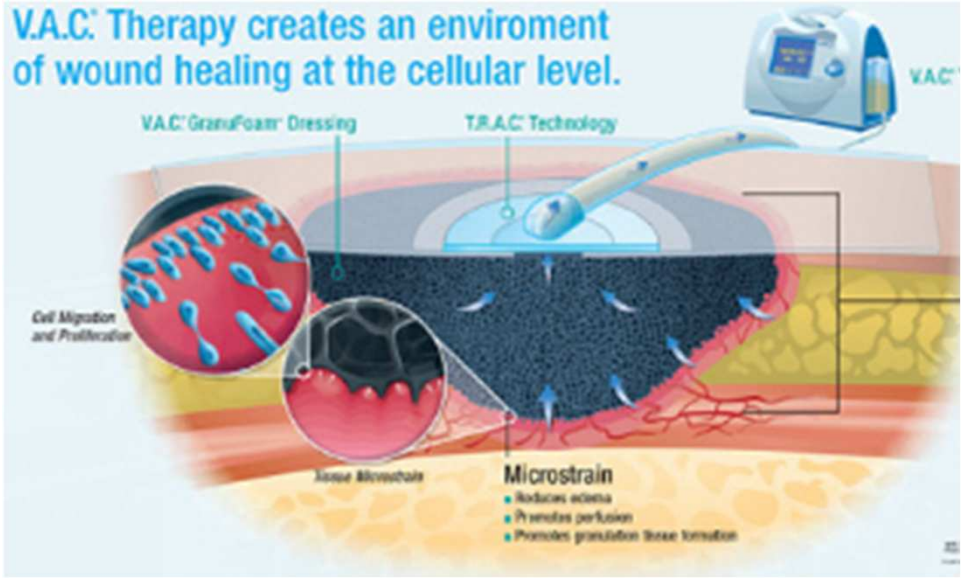
Vacuum Assisted Closure (VAC system)
with antibiotic instillation





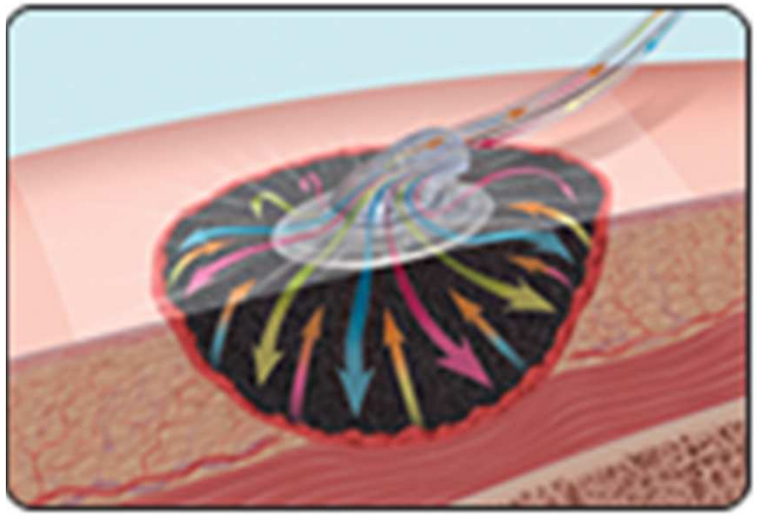


Vacuum Assisted Closure (VAC system)
with antibiotic instillation



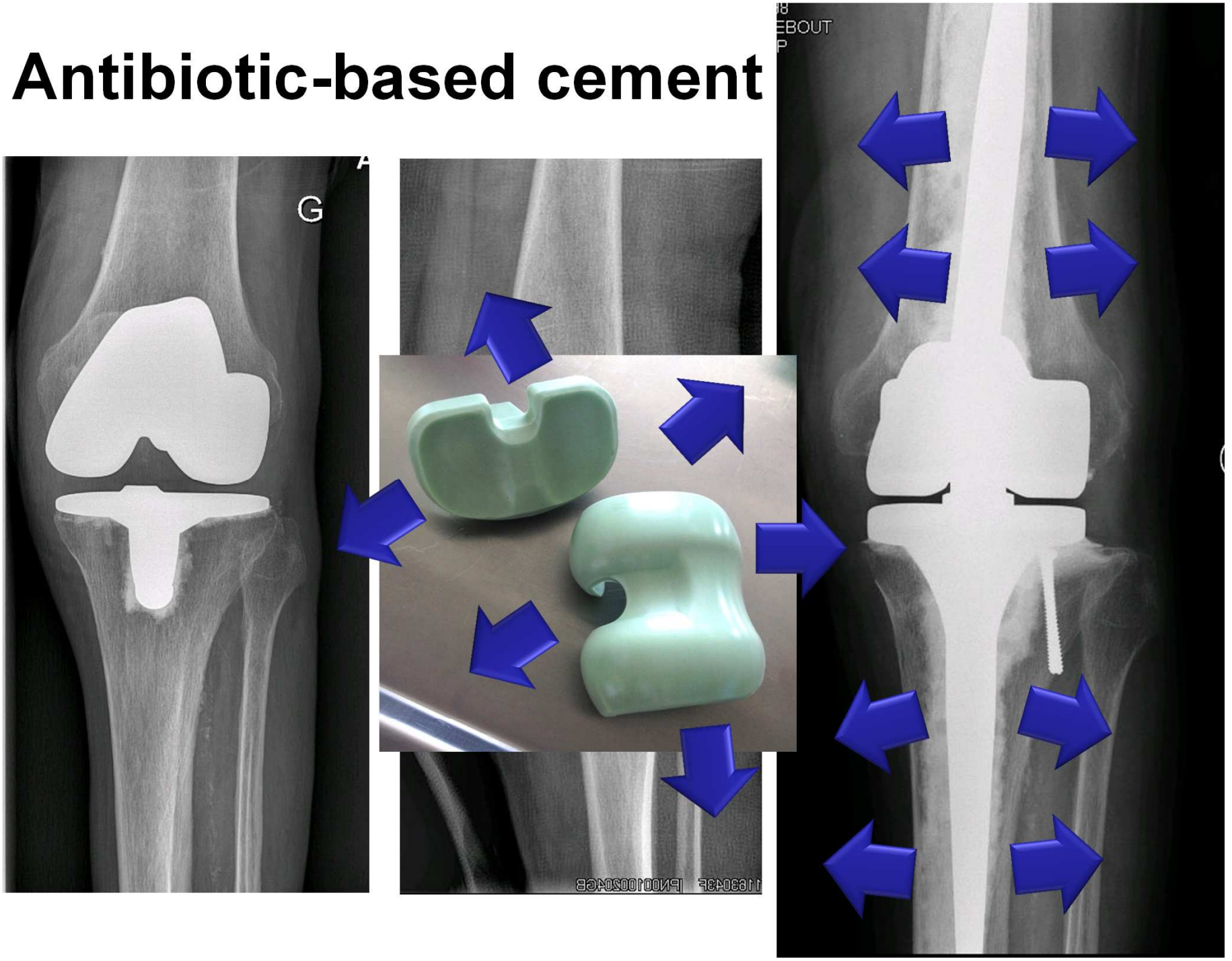
Applying topical antibiotics may be that high concentrations are achieved at the site of infection

But…

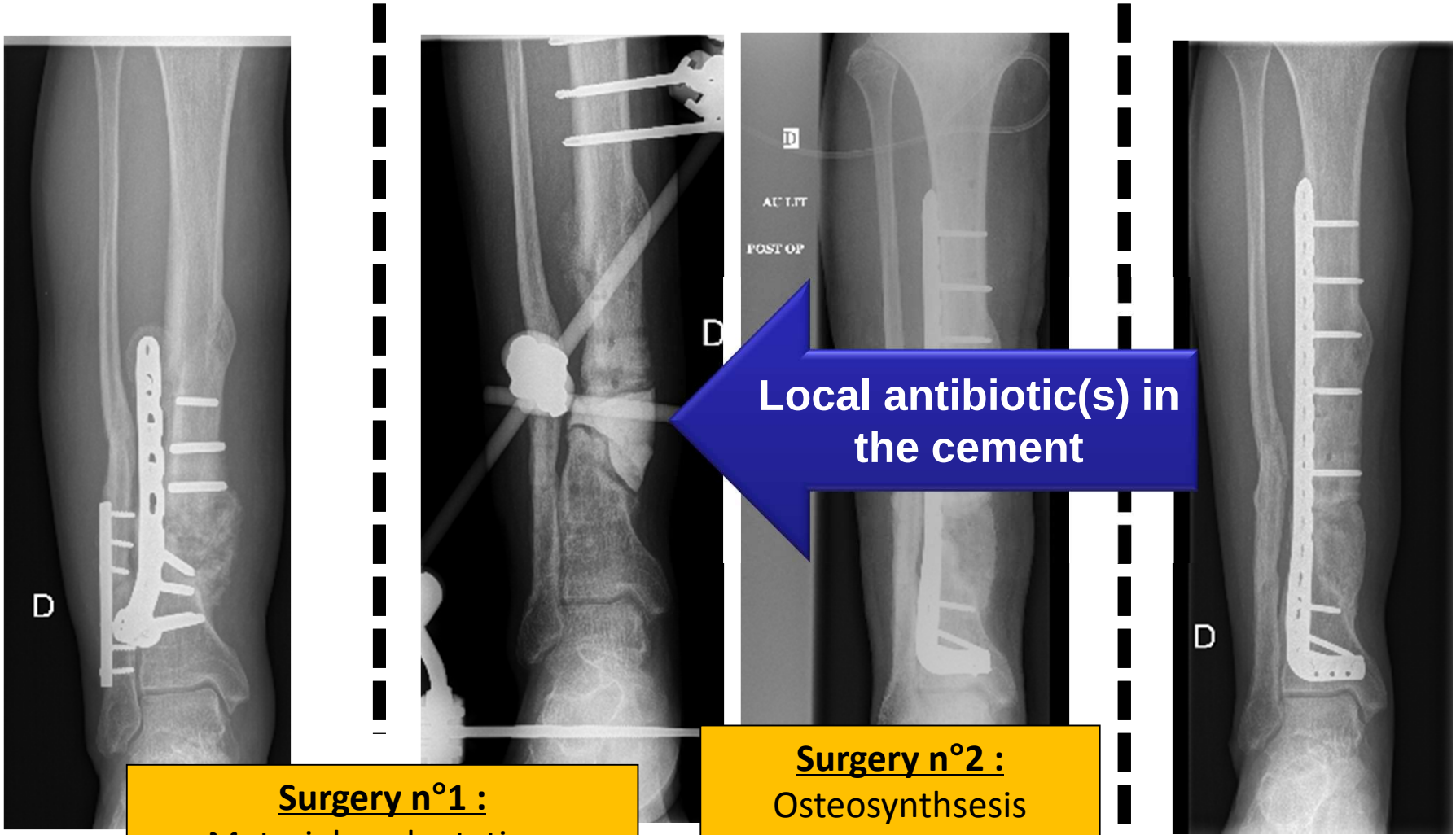


The use of topical antibiotics is considered highly controversial among physicians

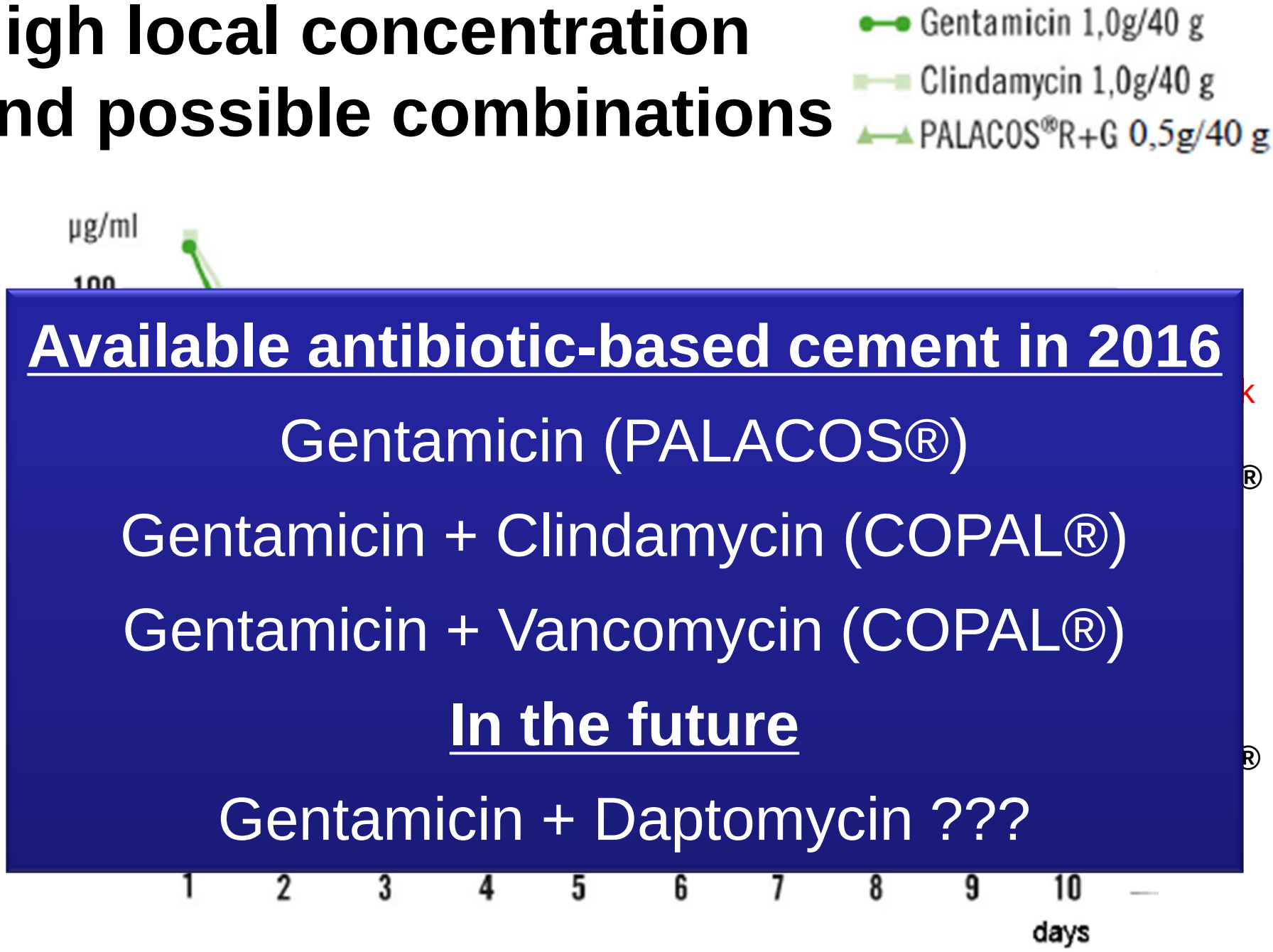
Antibiotic-based cement



« Masquelet » for septic pseudarthrosis



High local concentration and possible combinations



Available antibiotic-based cement in 2016

Gentamicin (PALACOS®)

Gentamicin + Clindamycin (COPAL®)

Gentamicin + Vancomycin (COPAL®)

In the future

Gentamicin + Daptomycin ???

New drugs with new mechanisms of action

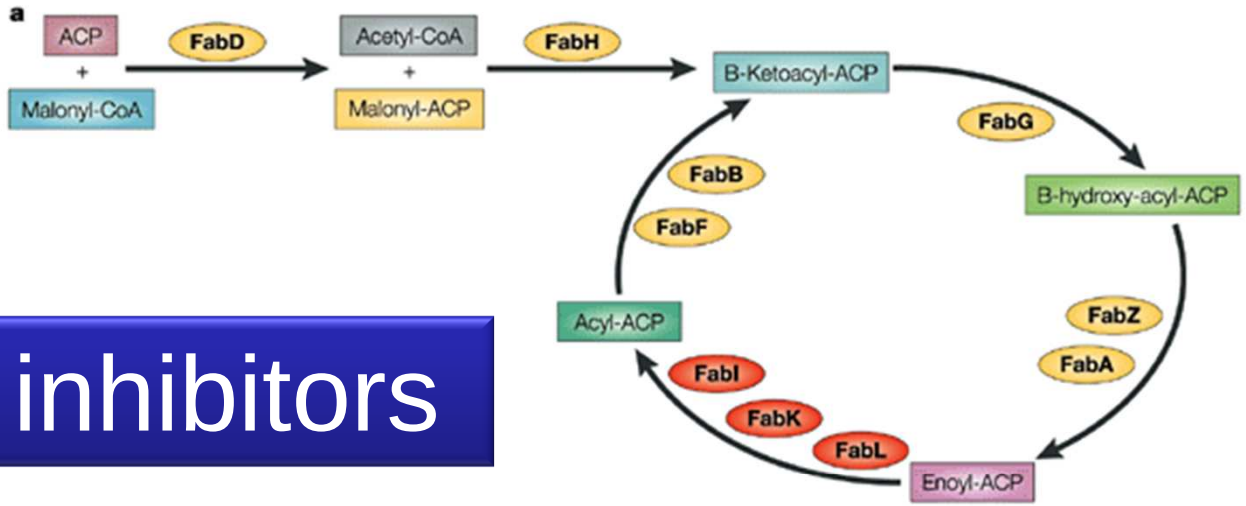
- Most of new drugs are not « antibiotics » that could be used **in adjunctive therapy**
  - Monoclonal/polyclonal antibodies
    - Targeting virulence factors (PVL, α-toxin, MSCRAMMs)
  - Bacteriophages
- **FabI inhibitors** (could be antipersister)
- **Teixobactin**
- **Anti-virulence agents**
  - **Targeting the agr or the SarA system**

Appl Microbiol Biotechnol (2002) 58:695–703
DOI 10.1007/s00253-001-0918-z

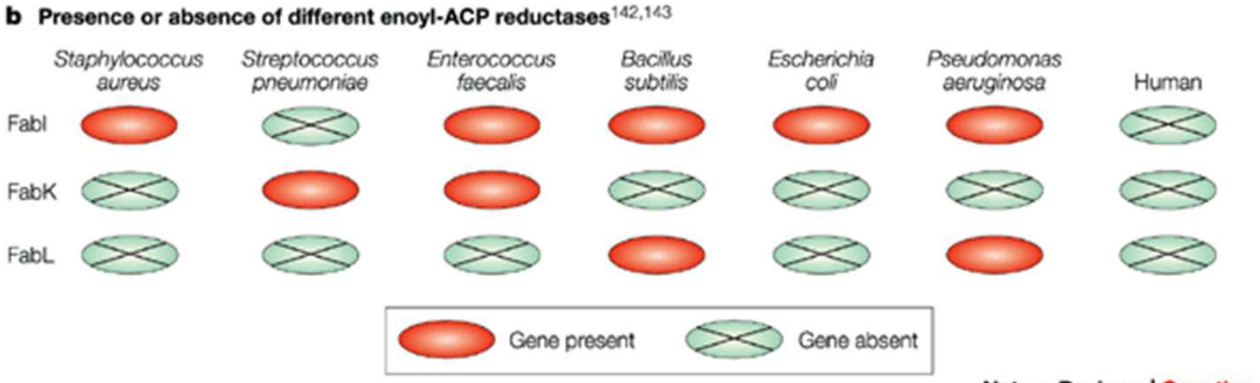
MINI-REVIEW

R.J. Heath · S.W. White · C.O. Rock

Inhibitors of fatty acid synthesis as antimicrobial chemotherapeutics



FabI inhibitors



Miesel L. Nat Rev Genet. 2003 Jun;4(6):442-56.

Activity of Debio1452, a FabI Inhibitor with Potent Activity against *Staphy* ... spp., Includi ...

Robert K. Fla ...
JMI Laboratories ...

26th ECCMID
Amsterdam, Netherlands
9 – 12 April 2016
ESCMID

Impressive intracellular activity

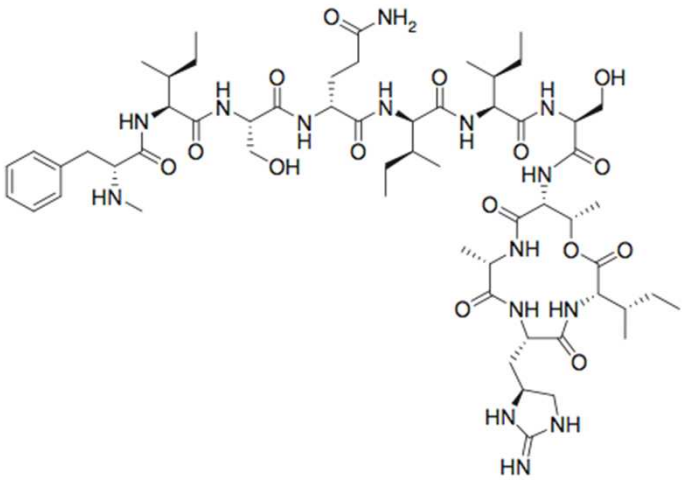
TABLE 2 ... of *S. aureus* ...

Antimicrobial agent (no. tested)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)
MRSA (...			
Debic ...			.015
Rifam ...			>2
Oxaci ...			
Eryth ...			>4
Clind ...			>2
Dapto ...			
Vanco ...			
Linezolid	1	1	0.5 to 2
Levofloxacin	>4	>4	≤0.5 to >4
Tetracycline	≤0.25	>8	≤0.25 to >8
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4

ClinicalTrials.gov

A Phase 2, Randomized, Double-Blind, Multicenter Study of Safety, Tolerability, and Efficacy of **Debio 1450** vs Vancomycin (IV)/Linezolid (Oral) in the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Due to Staphylococcus Sensitive or Resistant to Methicillin

Teixobactin



ARTICLE

doi:10.1038/nature14098

A new antibiotic kills pathogens without detectable resistance

Losee L. Ling[1]*, Tanja Schneider[2,3]*, Aaron J. Peoples[1], Amy L. Spoering[1], Ina Engels[2,3], Brian P. Conlon[4], Anna Mueller[2,3], Till F. Schäberle[3,5], Dallas E. Hughes[1], Slava Epstein[6], Michael Jones[7], Linos Lazarides[7], Victoria A. Steadman[7], Douglas R. Cohen[1], Cintia R. Felix[1], K. Ashley Fetterman[1], William P. Millett[1], Anthony G. Nitti[1], Ashley M. Zullo[1], Chao Chen[4] & Kim Lewis[4]

- **New class** of antibiotics
- Binds to **lipid II and lipid III**, important precursor molecules of peptidoglycan and teichoic acid, respectively
- Produced by unculturable bacteria from soils named *Eleftheria terrae*

Ling LL. Nature. 2015 Jan 22;517(7535):455-9.

Teixobactin

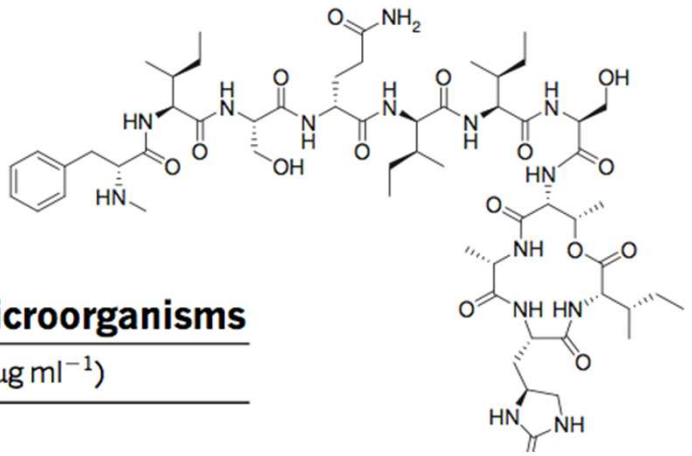
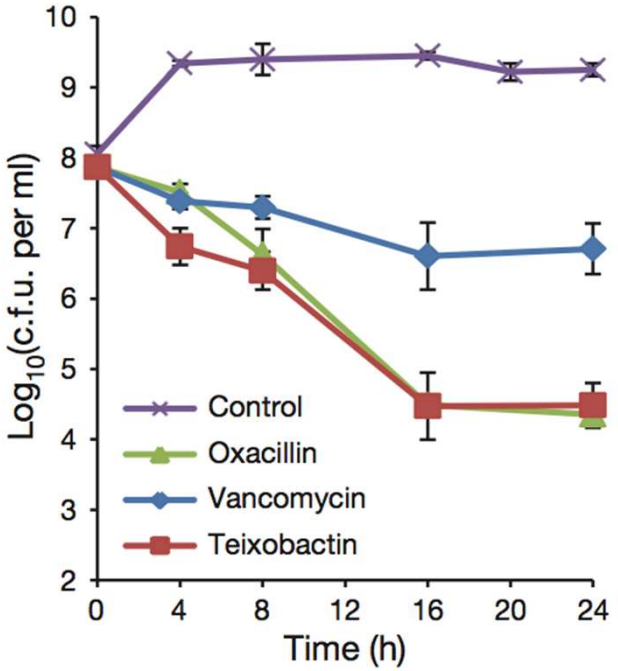


Table 1 | Activity of teixobactin against pathogenic microorganisms

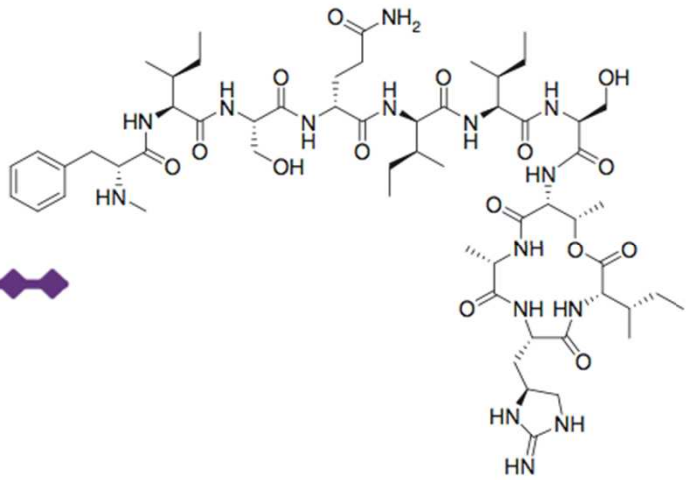
Organism and genotype	Teixobactin MIC (μg ml^{-1})
S. aureus (MSSA)	0.25
S. aureus + 10% serum	0.25
S. aureus (MRSA)	0.25
Enterococcus faecalis (VRE)	0.5
Enterococcus faecium (VRE)	0.5
Streptococcus pneumoniae (penicillin^{R})	≤ 0.03
Streptococcus pyogenes	0.06
Streptococcus agalactiae	0.12
Viridans group streptococci	0.12
B. anthracis	≤ 0.06
Clostridium difficile	0.005
Propionibacterium acnes	0.08
M. tuberculosis H37Rv	0.125
Haemophilus influenzae	4
Moraxella catarrhalis	2
Escherichia coli	25
Escherichia coli (*asmB1*)	2.5
Pseudomonas aeruginosa	>32
Klebsiella pneumoniae	>32

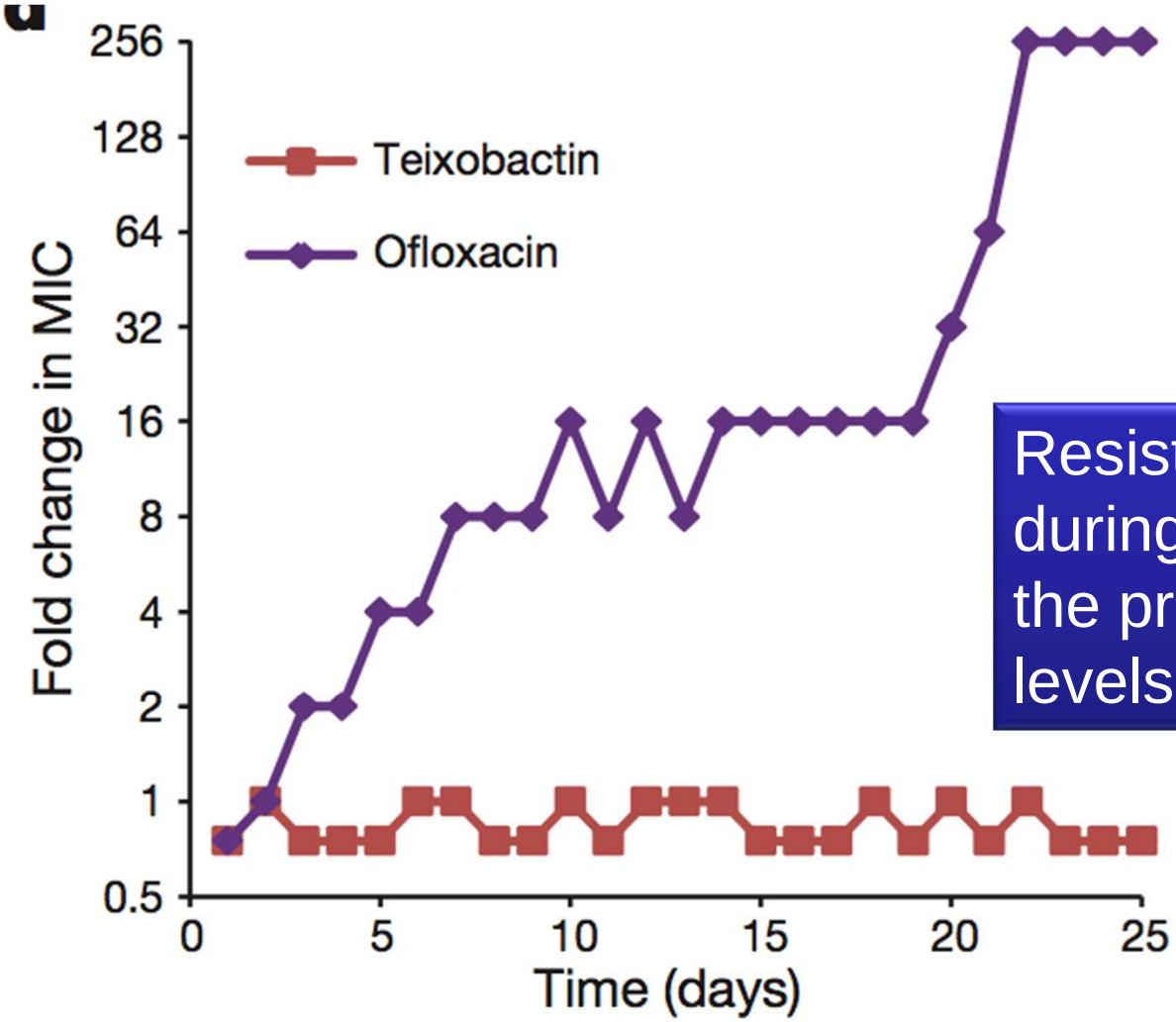
The MIC was determined by broth microdilution. MSSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant enterococci.



Ling LL. Nature. 2015 Jan 22;517(7535):455-9.

Teixobactin



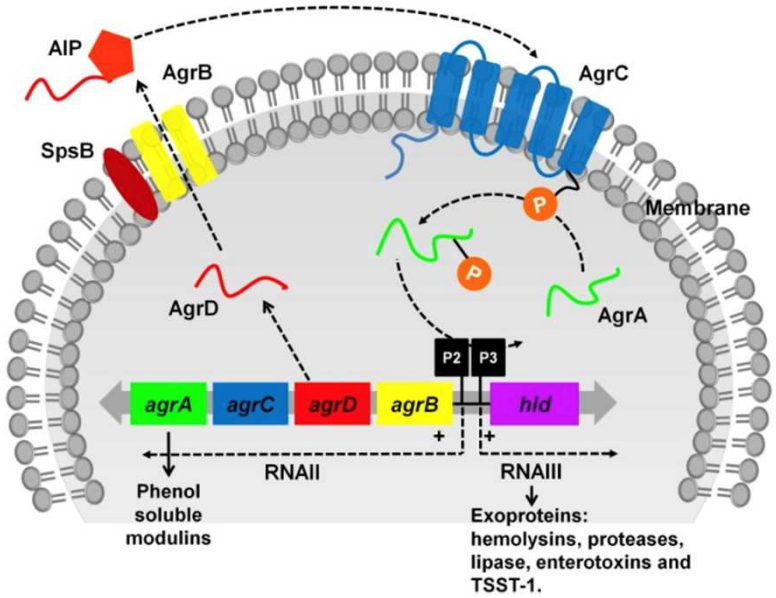


Resistance acquisition during serial passaging in the presence of sub-MIC levels of antimicrobials

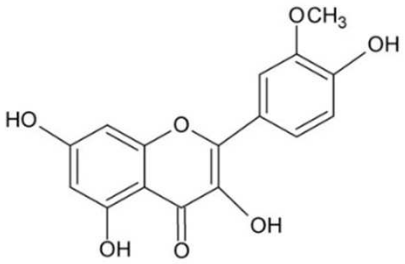
Ling LL. Nature. 2015 Jan 22;517(7535):455-9.

Anti-virulence agents

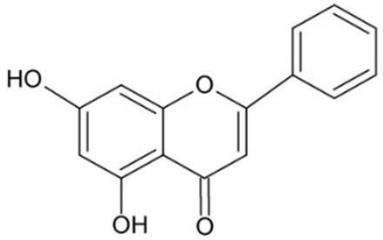
- Number of bioactive component isolated from natural products
- That did not affect the bacterial growth
- Inhibit the agr of SarA regulator system



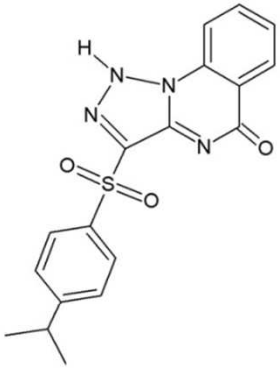
agr inhibitors



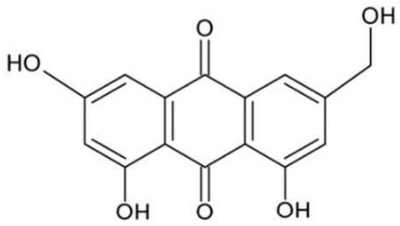
Isorhamnetin



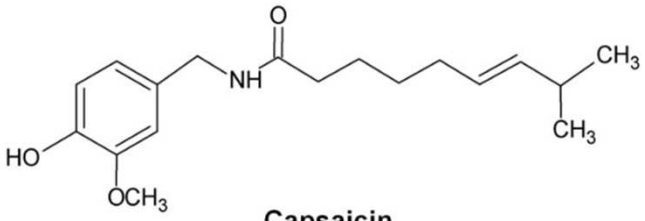
Chrysin



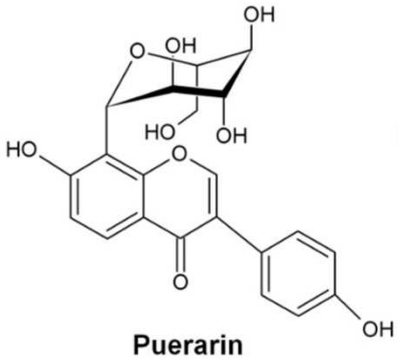
Savirin



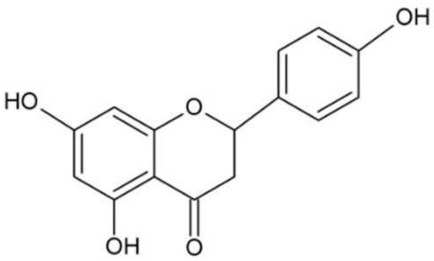
ω-hydroxyemodin (OHM)



Capsaicin



Puerarin



Naringenin

Kong C et al. Targeting *S. aureus* Toxins: A Potential form of Anti-Virulence Therapy. Toxins (Basel). 2016 Mar 15;8(3).

SarA inhibitors

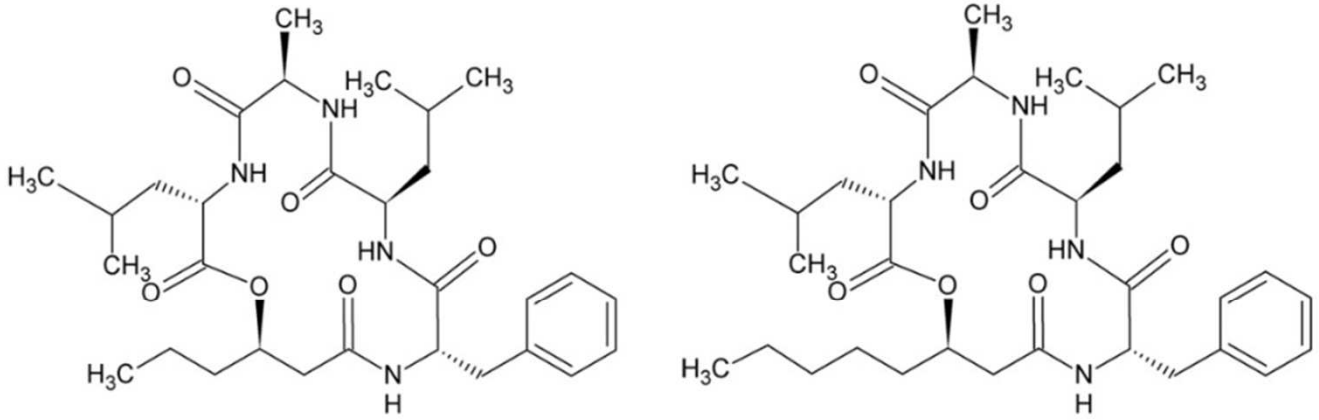


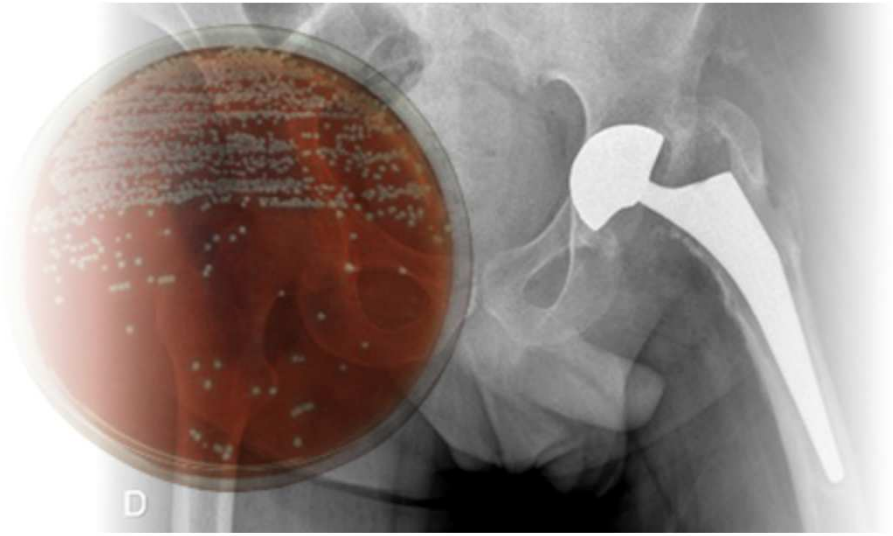
Figure 4. Chemical structure of solonamides isolated from *Photobacterium* sp. (redrawn from [140]).

Kong C et al. Targeting *S. aureus* Toxins: A Potential form of Anti-Virulence Therapy. Toxins (Basel). 2016 Mar 15;8(3).

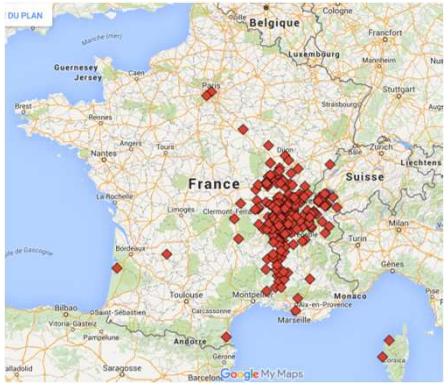
Conclusion

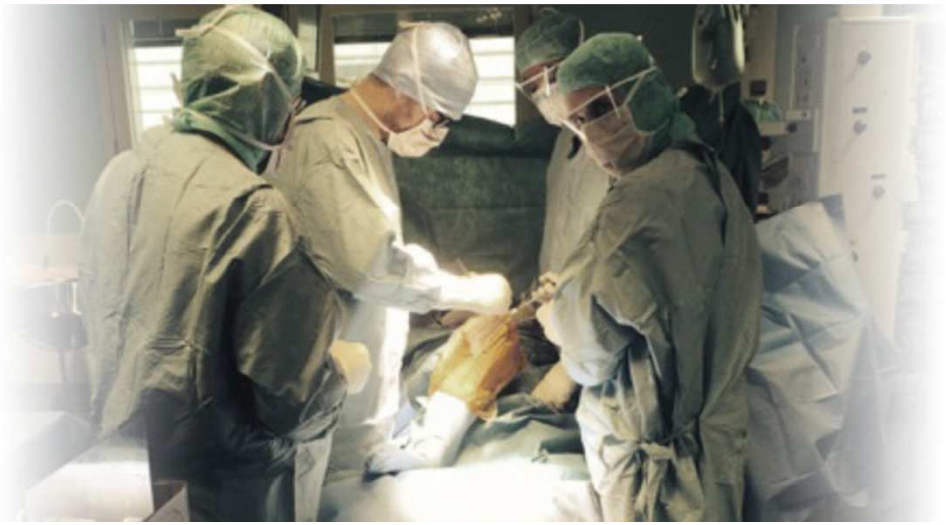
- A lot of « ***faire du neuf avec du vieux*** »
- With a **paradox**:
  - Limited approved indications, mainly in skin and soft tissue infections
  - Few data in other staphylococci infections
- But **promising local administration** and **combination strategies**
- Promising **new drugs** with new mechanisms of action

http://www.crioac-lyon.fr



- Published cases
- Open acces studies in pdf
- All thesis in pdf
- Newsletter





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