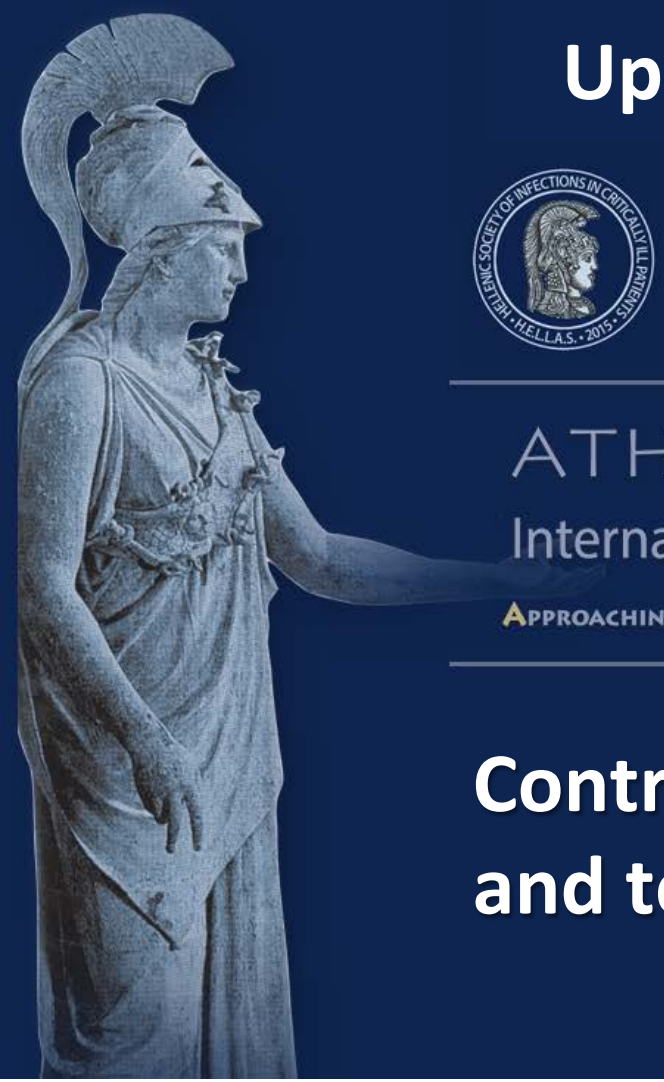
Update on MRSA critical Infections



ATHENA 2017
International Conference
APPROACHING THE SEVERELY INFECTED PATIENT

28-30 NOVEMBER 2017
ATHENS GREECE

Contribution of new antibiotics to today and tomorrow G+ infections challenges

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Disclosures

Research grants for work on investigational compounds discussed in this presentation from

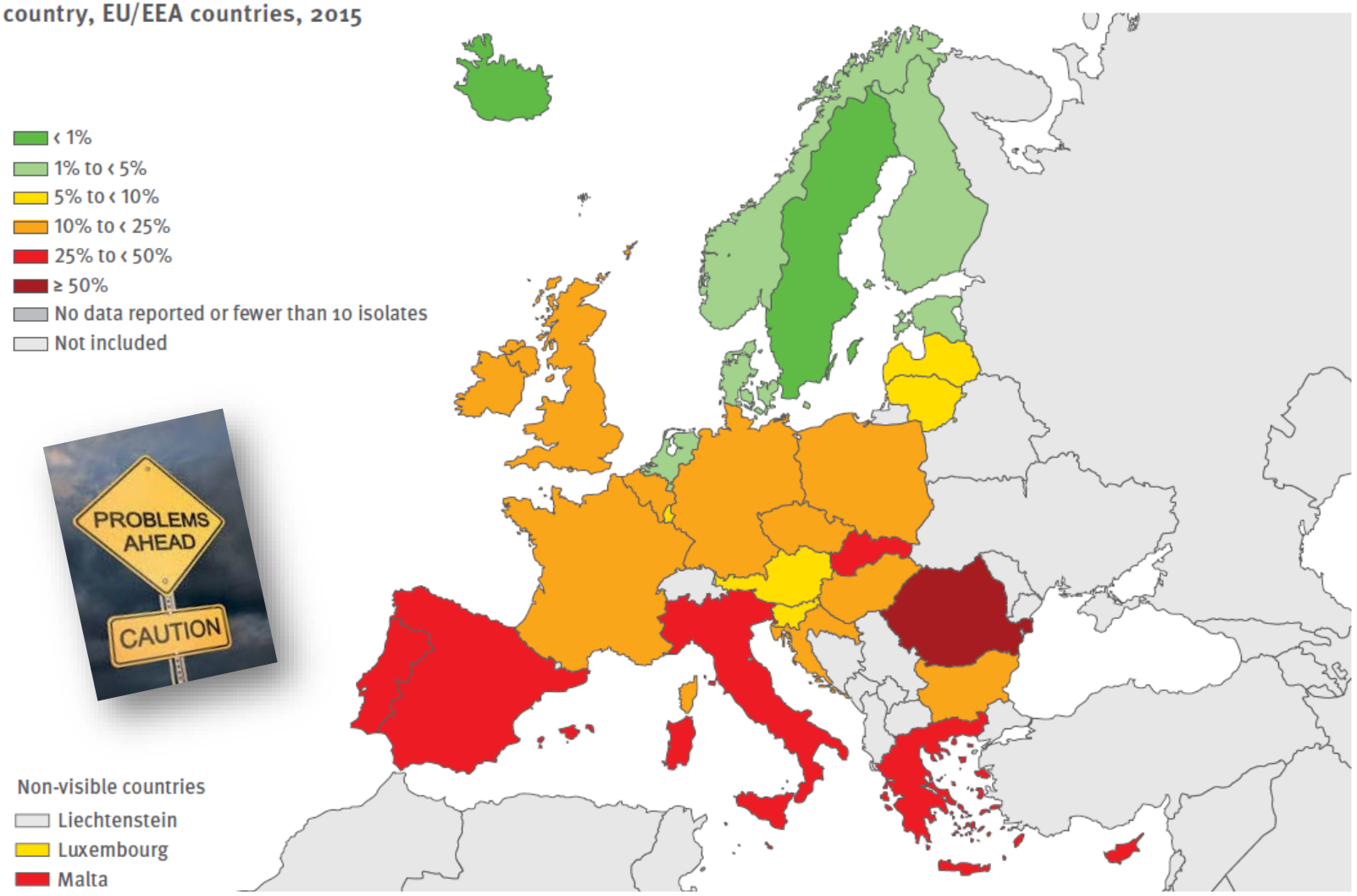
- Cerexa
- Melinta therapeutics
- The Medicine Company
- Theravance
- Trius therapeutics

Speaker honorarium from

- Bayer Healthcare
- The Medicine Company
- Merck & Co.

MRSA in Europe

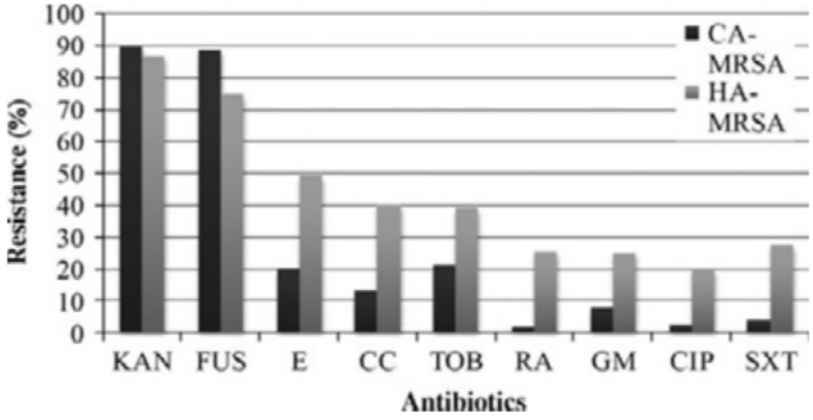
Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2015



https://ecdc.europa.eu

Co-resistance in MRSA from Greece

Drugka et al, Clin Microbiol Infect 2014; 20: O796–O803



vancomycin →
- Beware of MIC > 1 mg/L
- IV only
- Therapeutic monitoring (renal toxicity)

daptomycin →
- Dose uncertain
- Availability in some countries

linezolid →
- Bacteriostatic
- Severe adverse events if prolonged therapy
- Inhibition of Mono Amino Oxidases

MRSA infections: current guidelines

Un example for skin and skin structure infections

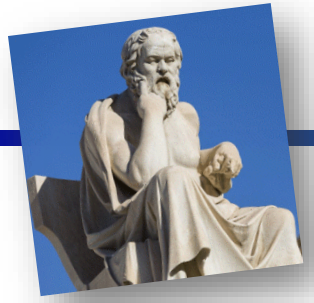
Antimicrobial therapy recommended for methicillin-resistant *Staphylococcus aureus* skin and soft tissues infections

	BSAC 2009	SIS 2009	GISIG 2010	ISID/ISC 2011	IDSA 2011	SEQ 2013
Vancomycin			A	A-1	A-1	+
Teicoplanin			A	A-1		+
Glycopeptides	A-1					
Daptomycin	A-1		C	A-1	A-1	+
Telavancin					A-1	
Linezolid	A-1	C-1	D	A-1	A-1	+
Clindamycin		C-1			A-2/A-3	
Erythromycin		C-1				
Tigecycline	B-1		B	A-1		

Strength of recommendation: A, good evidence; B, moderate evidence; C, poor evidence. Quality of evidence: 1, at least one randomized controlled trial; 2, at least one nonrandomized trial; 3, expert's opinion. No strength of recommendation was given for the SEQ 2013 guidelines. The drugs proposed in this article are indicated by '+'. BSAC, British Society of Antimicrobial Chemotherapy; GISIG, Gruppo Italiano di Studio Infezioni Gravi; IDSA, Infectious Diseases Society of America; ISID/ISC, Italian Society of Infectious Diseases/International Society of Chemotherapy; SEQ, Sociedad Espanola de Quimioterapia; SIS, Surgical Infection Society.

Montravers et al, Curr Opin Infect Dis. 2016; 29:131-8

MRSA infections: where is the therapeutic challenge ?



Current challenges in managing MRSA infections

1. Empirical *vs.* targeted therapy ?

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Appropriateness of empirical therapy and mortality

MRSA **bacteremia**: impact of initial therapy

	Alive, $N=286$	Dead, $N=224$	P value
Septic shock at onset	17/280 (6.1)	48/220 (21.8)	<0.001
Source of infection[a]			<0.001
cellulitis/skin abscess	42 (14.7)	32 (14.3)	
surgical site infection	35 (12.2)	12 (5.4)	
bone/joint	31 (10.8)	7 (3.1)	
catheter-related bacteraemia	41 (14.3)	14 (6.3)	
endocarditis	5 (1.7)	12 (5.4)	
other endovascular	18 (6.3)	9 (4)	
hospital-acquired pneumonia	10 (3.5)	22 (9.8)	
ventilator-associated pneumonia	16 (5.6)	20 (8.9)	
other source of infection	33 (11.5)	28 (12.5)	
primary/unknown	55 (19.2)	68 (30.4)	
MRSA isolated from non-blood source	132/286 (46.2)	49/224 (21.9)	<0.001
Polymicrobial bacteraemia	10/286 (3.5)	11/224 (4.9)	0.425
Persistence of bacteraemia ≥7 days[b]	31/192 (16.1)	13/119 (10.9)	0.199
Management			
inappropriate empirical therapy	174/286 (60.8)	168/224 (75)	0.001
vancomycin, empirical	96/286 (33.6)	50/224 (22.3)	
other appropriate, empirical[c]	16/286 (5.6)	6/224 (2.7)	
central catheter not removed[d]	32/64 (50)	34/45 (75.6)	0.007
foreign body not removed[d]	25/31 (80.6)	23/28 (82.1)	0.883

→ Inappropriate empirical therapy is a risk of mortality

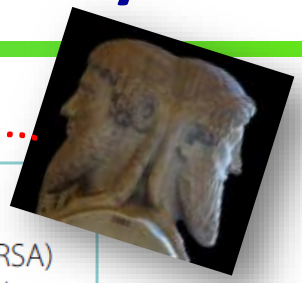
→ Vancomycin is useful to reduce the risk

Adapted from Paul et al, JAC 2010; 65: 2658–65

Appropriateness of empirical therapy and mortality

MRSA **bacteremia**: impact of initial therapy

but controversy ...



Abstract

Background: The purported value of empirical therapy to cover methicillin-resistant *Staphylococcus aureus* (MRSA) has been debated for decades. The purpose of this study was to evaluate the effects of inappropriate empirical antibiotic therapy on clinical outcomes in patients with healthcare-associated MRSA bacteremia (HA-MRSAB).

Methods: A prospective, multicenter, observational study was conducted in 15 teaching hospitals in the Republic of Korea from February 2010 to July 2011. The study subjects included adult patients with HA-MRSAB. Covariate adjustment using the propensity score was performed to control for bias in treatment assignment. The predictors of in-hospital mortality were determined by multivariate logistic regression analyses.

Results: In total, 345 patients with HA-MRSAB were analyzed. The overall in-hospital mortality rate was 33.0 %. Appropriate empirical antibiotic therapy was given to 154 (44.6 %) patients. The vancomycin minimum inhibitory concentrations of the MRSA isolates ranged from 0.5 to 2 mg/L by E-test. There was no significant difference in mortality between propensity-matched patient pairs receiving inappropriate or appropriate empirical antibiotics (odds ratio [OR] = 1.20; 95 % confidence interval [CI] = 0.71–2.03). Among patients with severe sepsis or septic shock, there was no significant difference in mortality between the treatment groups. In multivariate analyses, severe sepsis or septic shock (OR = 5.45; 95 % CI = 2.14–13.87), Charlson's comorbidity index (per 1-point increment; OR = 1.52; 95 % CI = 1.27–1.83), and prior receipt of glycopeptides (OR = 3.24; 95 % CI = 1.08–9.67) were independent risk factors for mortality.

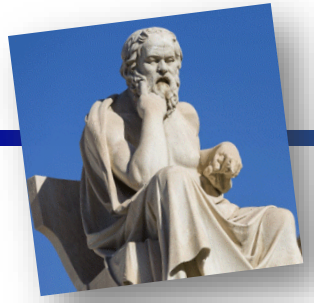
Conclusion: Inappropriate empirical antibiotic therapy was not associated with clinical outcome in patients with HA-MRSAB. Prudent use of empirical glycopeptide therapy should be justified even in hospitals with high MRSA prevalence.

Keywords: Methicillin-resistant *Staphylococcus aureus*, Bacteremia, Risk factors, Treatment outcome, Anti-bacterial agents

→ Inappropriate empirical therapy is not a risk of mortality

→ Previous glycopeptide use is at risk !

Yoon et al, BMC 2016; 16:331



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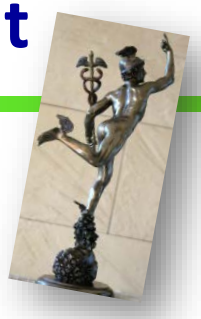
2. De-escalation ?

Do we need to stop MRSA coverage when microbiological data are available ?

Impact of rapid diagnostic on bacteremia management



MRSA detection (MALDI-TOF/PCR) in patients with **bacteremia**

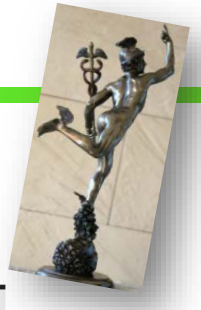
Characteristic	Pre-MALDI-TOF group (n = 133)	Post-MALDI-TOF group (n = 94)	p-Value
Patients with MRSA bacteremia (%)	27.82	26.59	0.88
Length of hospitalization (days)	28.27 ± 32.16	28.62 ± 28.75	0.26
Average time to positivity of blood cultures	2.16 ± 1.51 days	2.08 ± 1.93 days	0.201
Turnaround time to identification and susceptibility	3.95 ± 1.70 days	2.06 ± 1.95 days	< 0.0001
Adequate empirical antibiotic therapy, , n (%)	47 (59,49.%)	39 (51.31%)	0.41
Adjustment to optimal therapy, , n (%)	38 (48.71%)	61 (81.33%)	< 0.0001
Unknown antibacterial therapy data, , n (%)	36 (27.67%)	19 (20.21%)	0.43

→ Early identification of MRSA reduces the length of therapy with no impact on length of stay

→ De-escalation possible!

Adapted from Romero-Gomez et al, Eur J Clin Microbiol Infect Dis. 2017 doi: 10.1007/s10096-017-3086-5

Impact of MRSA nasal screening on targeted therapy



MRSA PCR detection in **HAP** patients

MRSA-targeted antibiotic therapy outcomes

Parameter	Pre-PCR (n = 27)	PCR (n = 30)	Difference	P value
Duration of therapy				
Hours	74 ± 48.9	27.4 ± 18.7	46.6	<0.0001
Days	4.0 ± 2.0	2.13 ± 0.86	1.9	<0.0001
Total i.v.[a] vancomycin doses	4.2 ± 3.1	1.7 ± 1.5	2.44	0.005
Total i.v. vancomycin (mg)	5,394.4 ± 3,483.5	2,865 ± 2,579.8	2,529.4	0.003

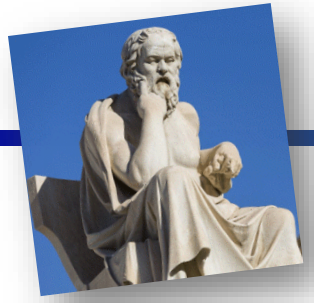
Clinical outcomes

Outcome	Pre-PCR	PCR	Difference	P value
Days to clinical improvement	1.78 ± 2.52	2.27 ± 3.34	−0.49	0.54
No. (%) with acute kidney injury	7 (26)	1 (3.3)	22.7	0.02
Length of hospital stay (days)	11.04 ± 9.5	8.2 ± 7.8	2.84	0.22
Mortality (no. [%])	4 (14.8)	2 (6.7)	8.1	0.41

→ Early identification of MRSA reduces the length of therapy with no impact on length of stay

→ De-escalation possible!

Baby et al, AAC 2017; 61: e02432-16



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3. Treatment duration ?

How much time do we need to treat, depending on

- the drug used ?
- the site of infection ?

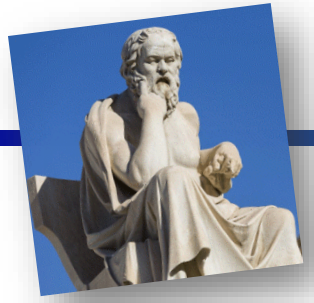
Treatment duration for MRSA infections

The example of IDSA guidelines

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

IDSA guidelines; CID 2011; 52:e18



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How much time do we need to treat, depending on

- the drug used ?
- the site of infection ?

4. Hospitalization / Home therapy ?

Which criteria do we need to take into account to treat patients at home ?

Conditions for discharge in patients with SSTI

Checklist for early discharge of patients with acute bacterial skin and skin-structure infection

Discharge checklist	Comments
Results of blood cultures and other tests	Negative cultures, reduction of inflammatory indices, normalizing white blood cell count
Evaluation of all co-morbidities	No significant alterations of chronic diseases, glycaemic control in patients with diabetes, no systemic signs of infection
Switch to oral therapy or plan for outpatient parenteral antibiotic therapy	Plan for length of antibiotic therapy after discharge, access to day-hospital services, ability to take oral medications
Use of long-acting antibiotics	In empiric therapy or as early switch to these antibiotics
Follow up scheduled	Follow up within 7 days from discharge
Education to wound care	Correct management of chronic wounds
Continued cares in structures enabled or home-care evaluation	Transfer to long-term care facilities or evaluation by primary-care physician within 48 h from discharge

mainly related to AB properties

Russo et al, Clin Microbiol Infect 2016; 22: S27–S36

Pros and Cons of new drugs

Anti Gram-positive recently approved drugs

company	drug	class	indications	MRSA	MDRSP	VRE
Theravance	Telavancin	lipoglyco-peptide	cSSSI / HABP/VABP	✓	✓	VanB only
Durata Ther.	Dalbavancin	lipoglyco-peptide	ABSSSI	✓	✓	VanB only
The MedCo	Oritavancin	lipoglyco-peptide	ABSSSI	✓	✓	✓
Forrest Astra-Zeneca	Ceftaroline	β-lactam	ABSSSI / CABP	✓	✓	✓
Basilea	Ceftobiprole*	β-lactam	CABP / HAP	✓	✓	✓
MSD	Tedizolid	oxazolidinone	ABSSSI	✓	✓	✓
Melinta	Delafloxacin	fluoroquinolone	ABSSSI	✓	✓	✓

* licensed in 14 countries: AT, BE, CA, CH, DE, DK, ES, FI, FR, IT, LU, NO, SE, UK

Susceptibility breakpoints

Breakpoints *vs*. susceptibility of current MRSA isolates

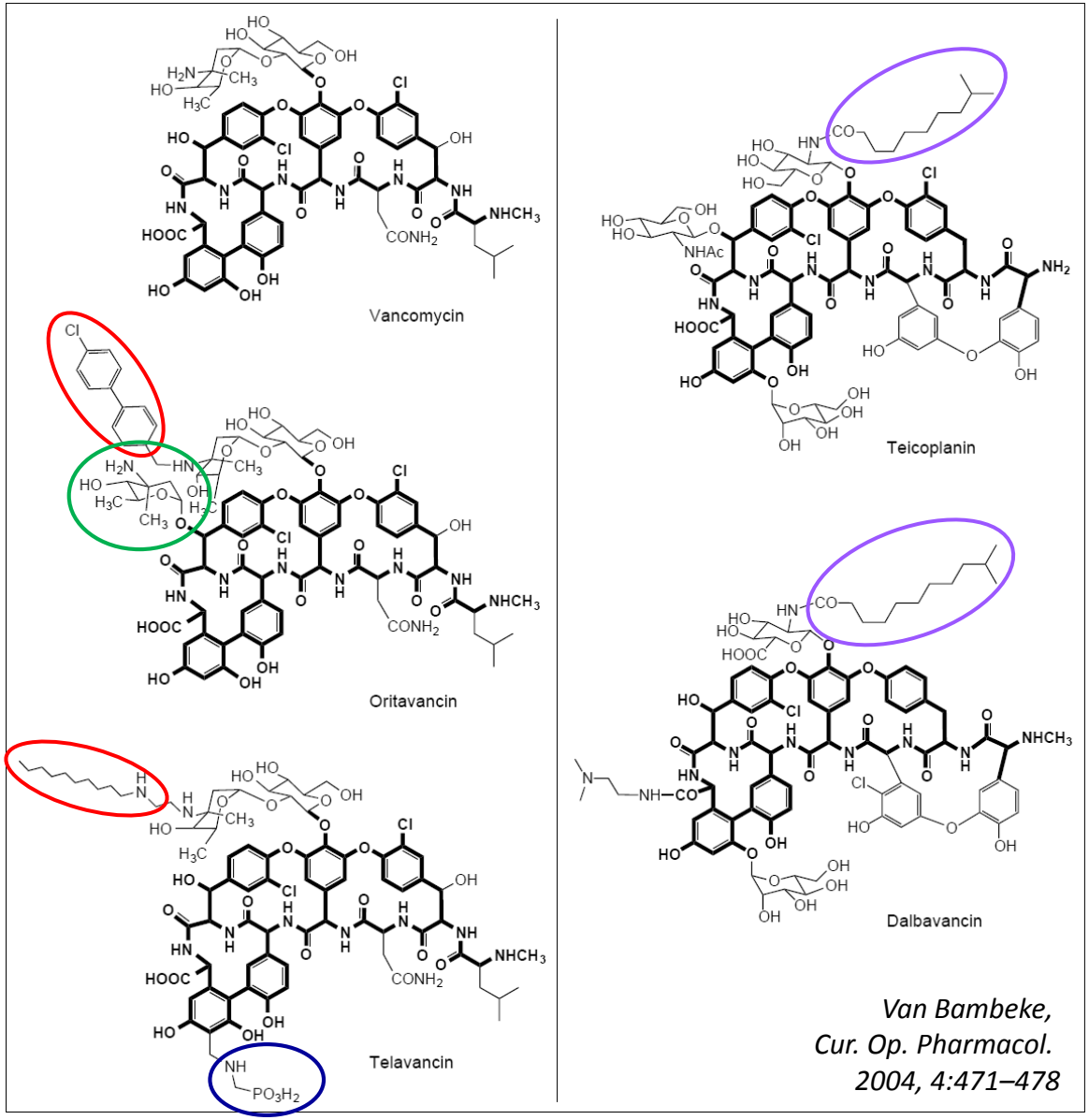
	antibiotic	breakpoint		susceptibility		
		S	R	MIC_{50}	MIC_{90}	range
EUCAST	telavancin	≤ 0.125	> 0.125	0.03	0.06	≤ 0.015 - 0.25
	dalbavancin	≤ 0.125	> 0.125	0.06	0.06	≤ 0.008 - 0.25
	oritavancin	≤ 0.125	> 0.125	0.03	0.03	≤ 0.008 - 0.25
	ceftobiprole	≤ 2	> 2	1	1	0.25 - 2
	ceftaroline	≤ 1	> 1	0.5	1	0.06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

Lipoglycopeptides

dimerization

- prolonged half-life
- membrane anchoring

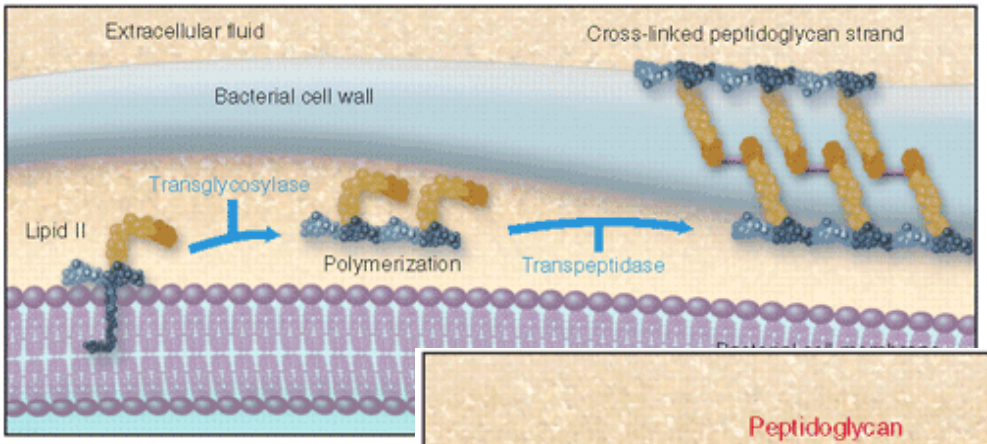
decreased half-life

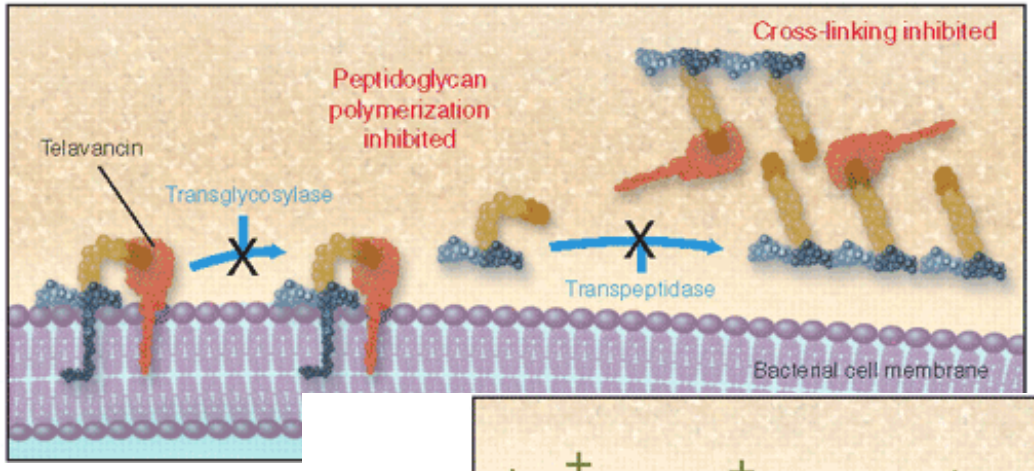


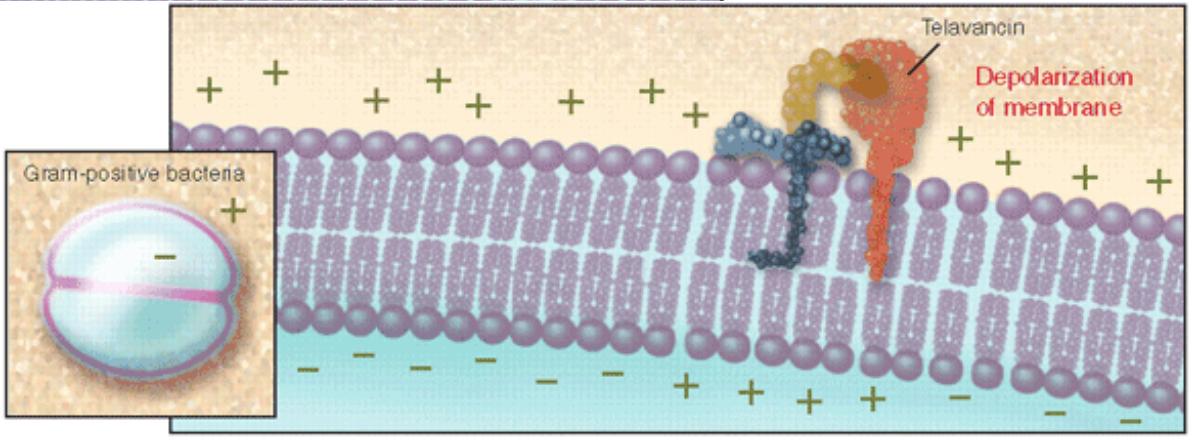
prolonged half-life

Van Bambeke, Cur. Op. Pharmacol. 2004, 4:471–478

Lipoglycopeptides: dual mode of action







highly bactericidal

Attwood & LaPlante, Am J Health Syst Pharm. 2007;64:2335-48

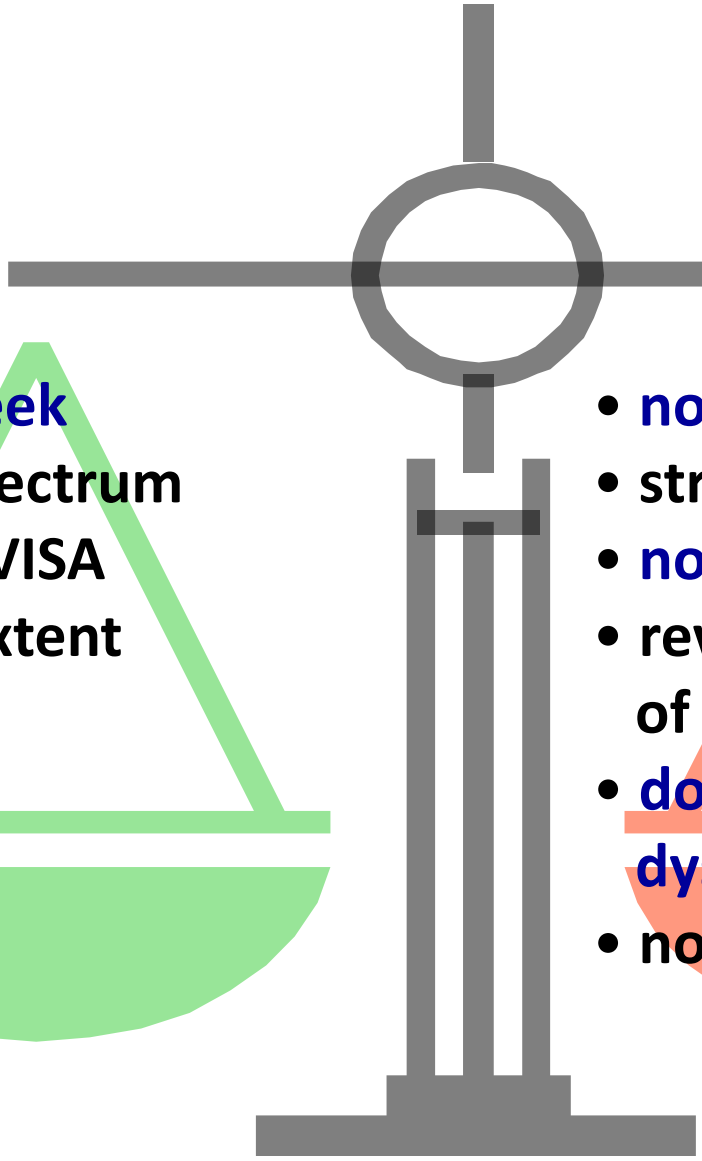
Lipoglycopeptides: pharmacokinetics

parameter	VAN	ORI	TLV	TEC	DAL
Dosage	15 mg/kg	1200 mg	10 mg/kg	6 mg/kg	1000 mg
Cmax (mg/L)	20-50	138	93	43	287
AUC (mg.h/L)	260	1110 (24h) 2800 (tot)	668	600	3185 (24h) 23443 (tot)
(%) prot. binding	55	85	95	88-94	99
T ½ (h)	1 (β) 3-9 (γ)	14 (β) 245 (γ)	8	10 (β) 168 (γ)	346 (γ)

twice daily | single dose | once daily | every 2 days | once-a-week (2 doses)

Van Bambeke, Drugs 2015; 75:2073–95

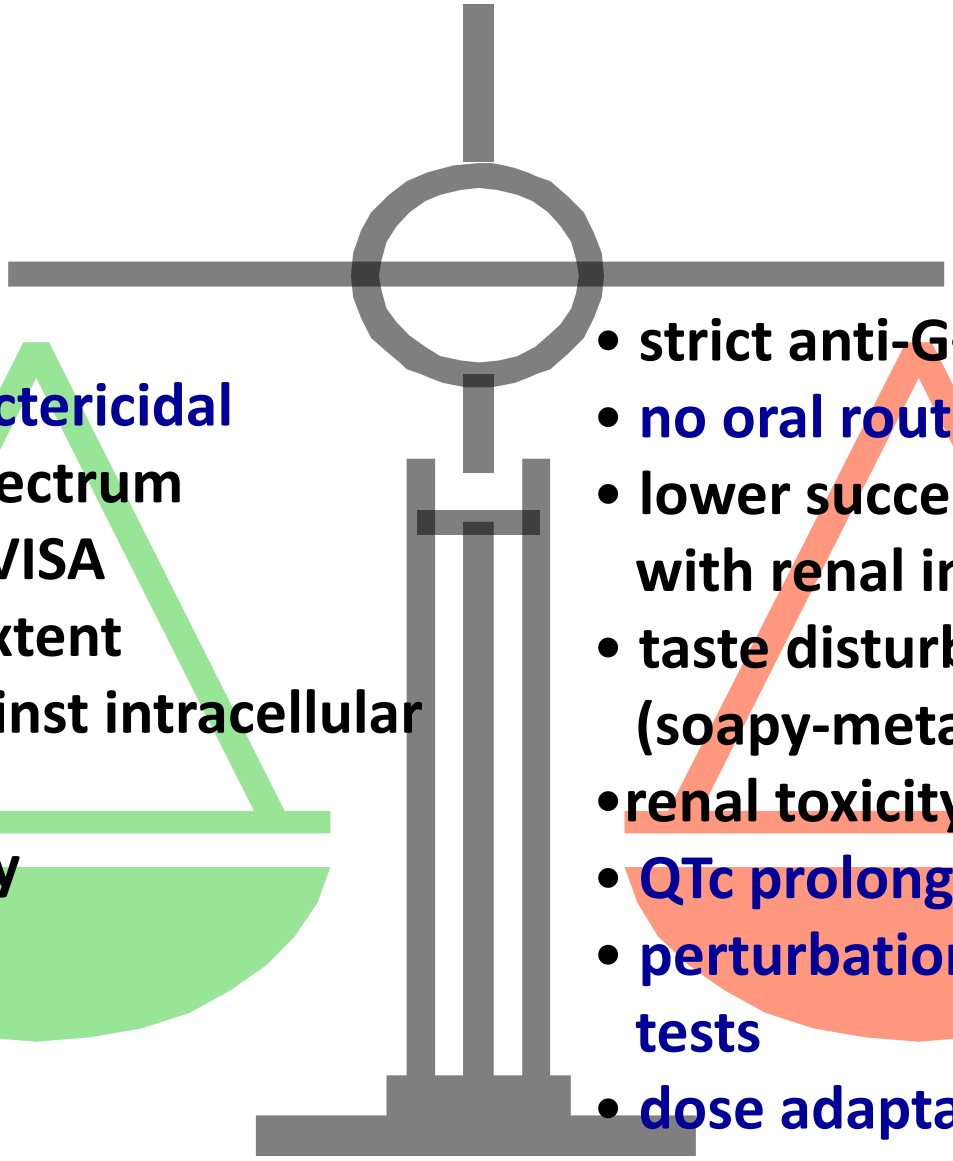
Dalbavancin : pros and cons



- once-a-week
- narrow spectrum
- active on VISA to some extent

- not rapidly bactericidal
- strict anti-G+
- no oral route
- reversible inhibition of transaminases
- dose adaptation if renal dysfunction
- not dialyzable

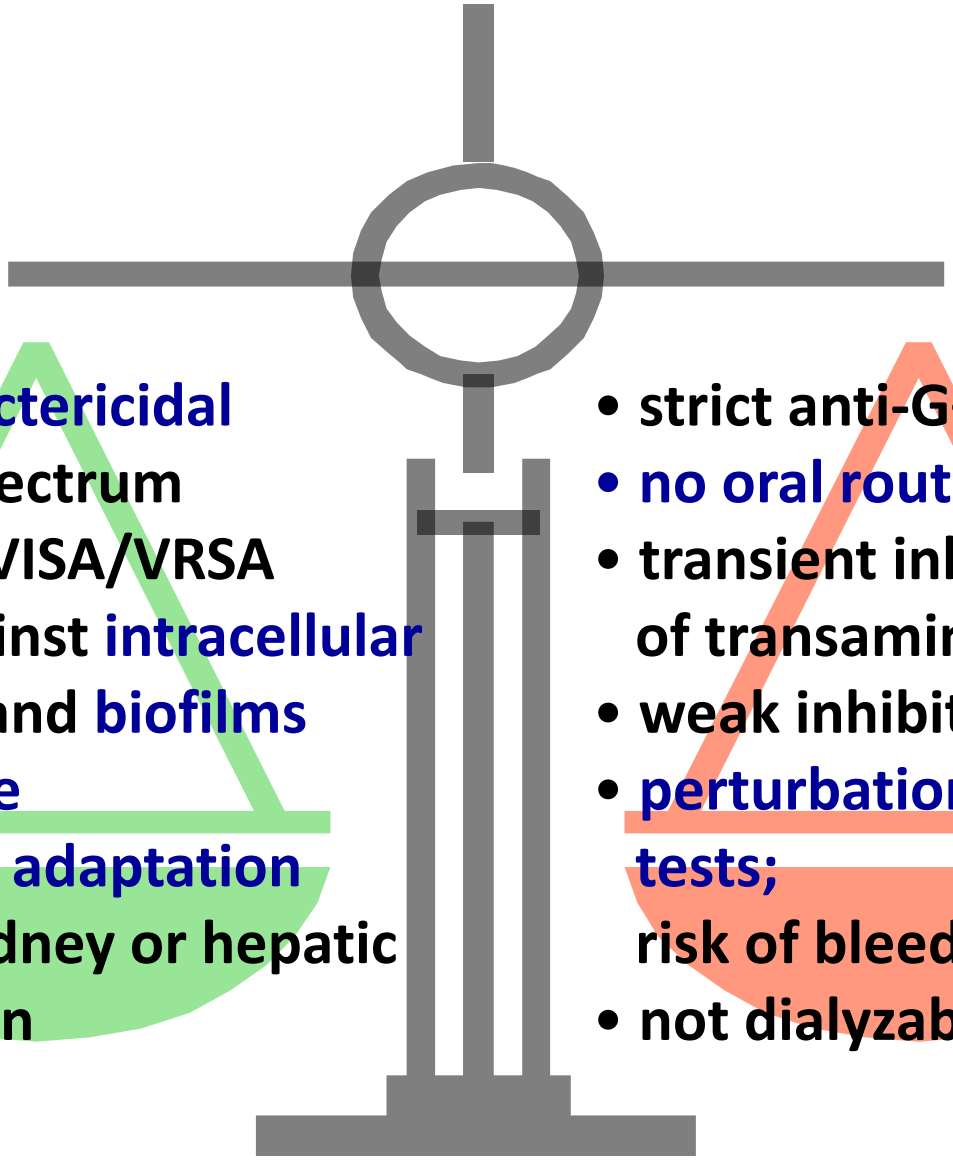
Telavancin : pros and cons



- rapidly bactericidal
- narrow spectrum
- active on VISA to some extent
- active against intracellular *S. aureus*
- once-a-day

- strict anti-G+
- no oral route
- lower success rate in patients with renal impairment (SSTI)
- taste disturbance (soapy-metallic)
- renal toxicity ?
- QTc prolongation
- perturbation of coagulation tests
- dose adaptation if renal dysfunction

Oritavancin : pros and cons

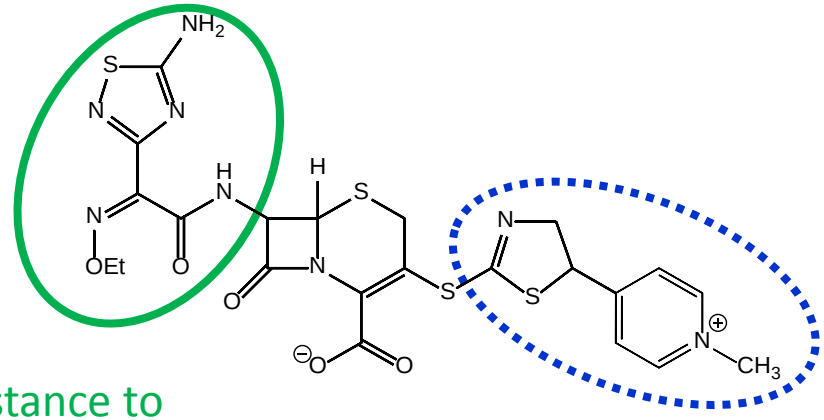


- rapidly bactericidal
- narrow spectrum
- active on VISA/VRSA
- active against intracellular *S. aureus* and biofilms
- single dose
- no dosage adaptation for age, kidney or hepatic dysfunction

- strict anti-G+
- no oral route
- transient inhibition of transaminases
- weak inhibitor of 2C9/19
- perturbation of coagulation tests; risk of bleeding with warfarin
- not dialyzable

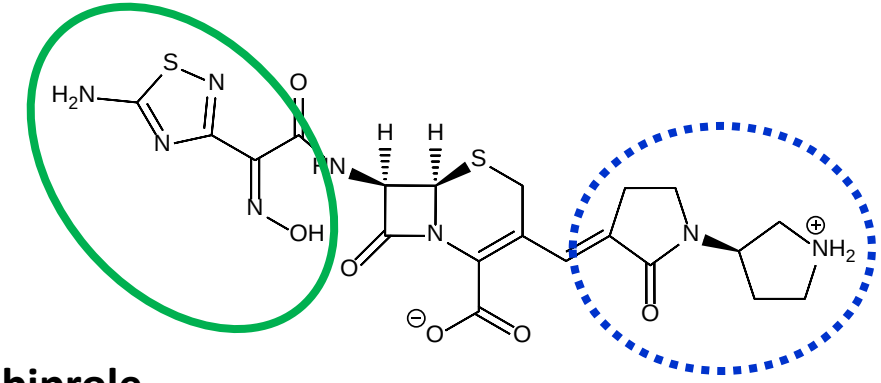
Anti-MRSA cephalosporins

ceftaroline



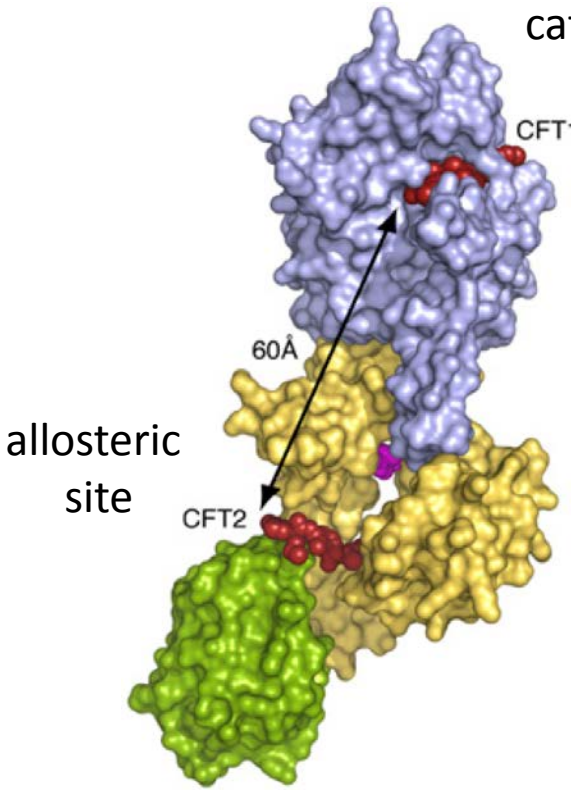
Resistance to β-lactamases

Binding to PBP2a



ceftobiprole

ceftaroline & PBP2a

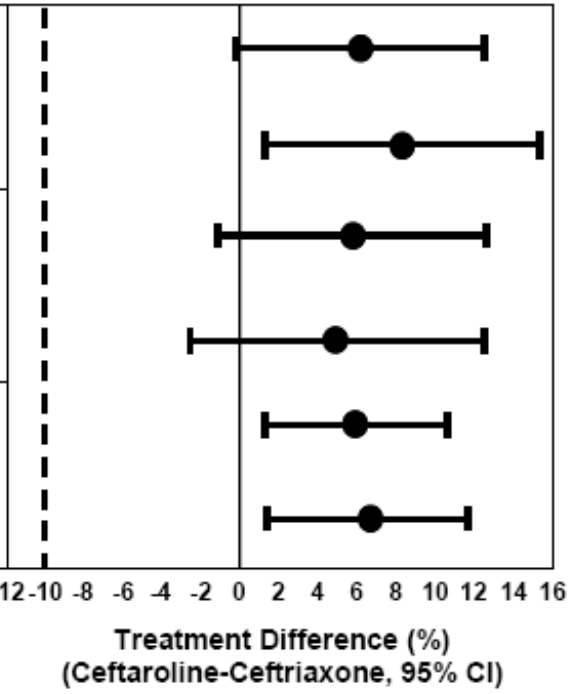


Otero et al, PNAS 2013; 110:16808–13

Ceftaroline & community-acquired pneumonia

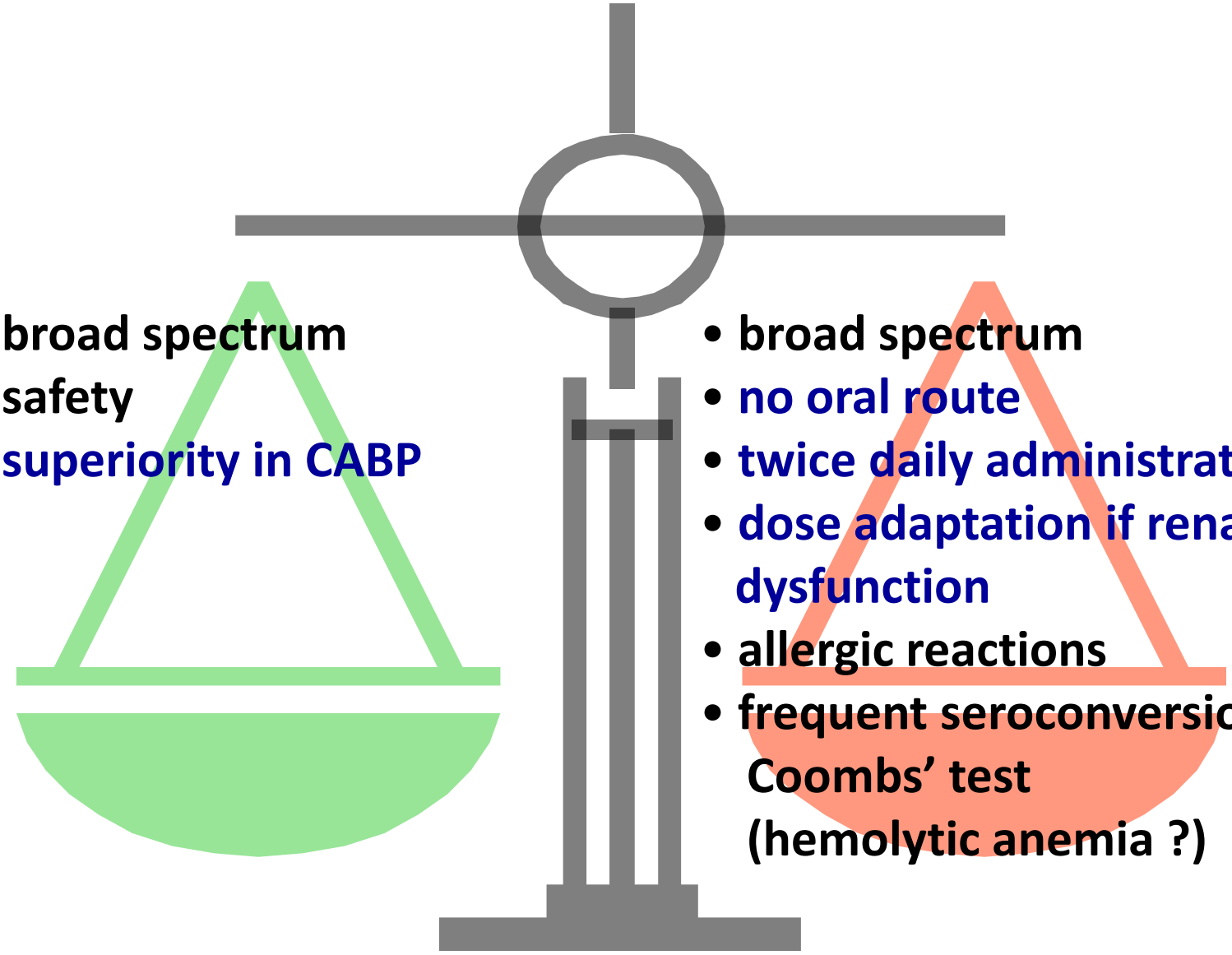
Figure 6.6–1. Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations

Study/Population		Clinical Response at TOC % (n/N) Ceftaroline	Ceftriaxone
P903-08	MITTE	**83.8** (244/291)	**77.7** (233/300)
	CE	**86.6** (194/224)	**78.2** (183/234)
P903-09	MITTE	**81.3** (235/289)	**75.5** (206/273)
	CE	**82.1** (193/235)	**77.2** (166/215)
COMBINED	MITTE	**82.6** (479/580)	**76.6** (439/573)
	CE	**84.3** (387/459)	**77.7** (349/449)



FDA briefing document; September 2010

Ceftaroline : pros and cons

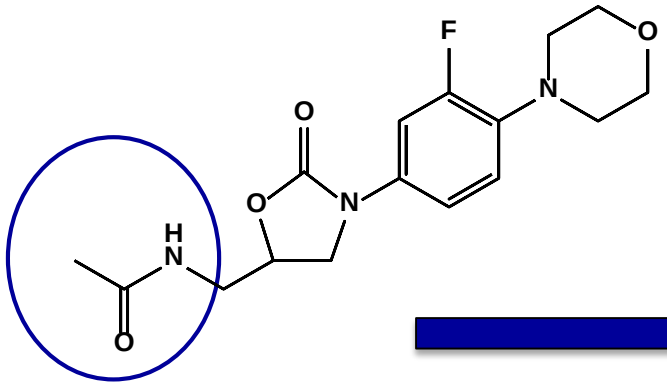


- broad spectrum
- safety
- superiority in CABP

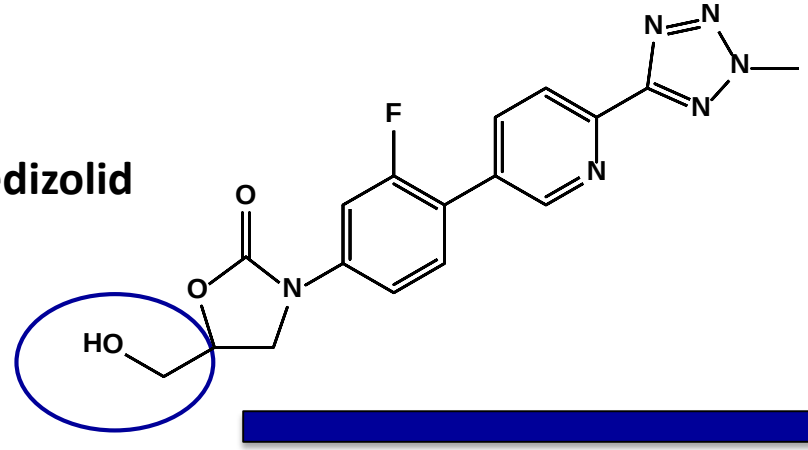
- broad spectrum
- no oral route
- twice daily administration
- dose adaptation if renal dysfunction
- allergic reactions
- frequent seroconversion of Coombs' test (hemolytic anemia ?)

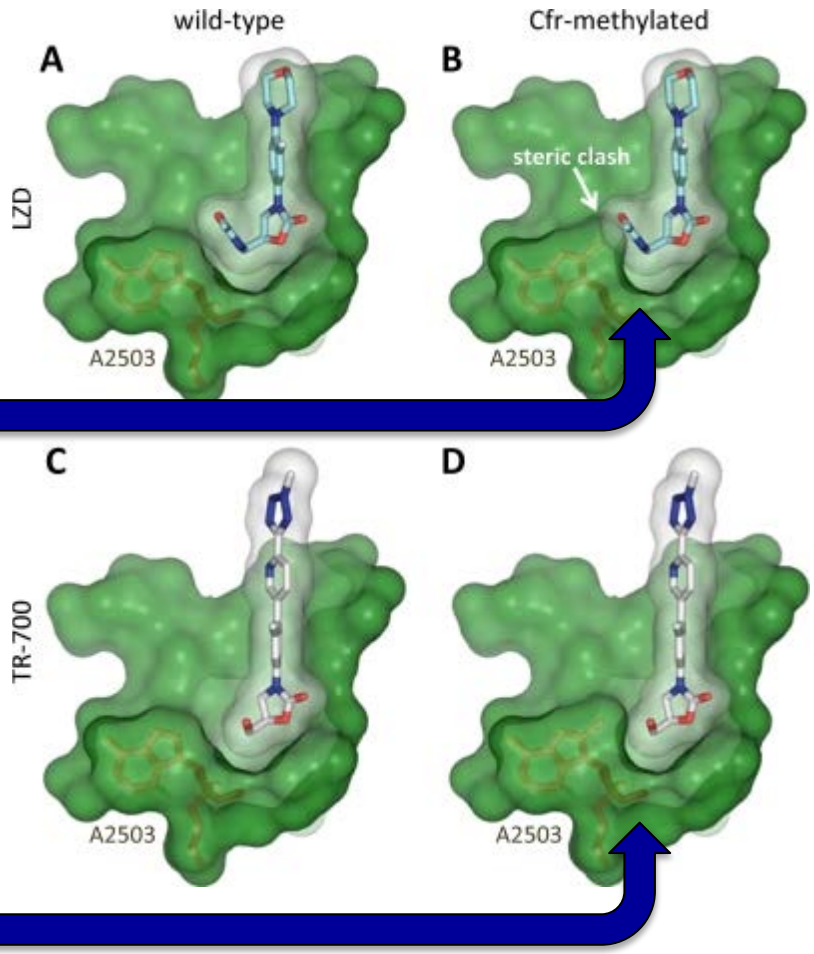
Oxazolidinones: tedizolid vs linezolid

linezolid



tedizolid





Binding of tedizolid
to methylated ribosomes (*cfr*)

Locke et al, AAC 2010; 54: 5337–43

Clinical efficacy

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

- Efficacy and Safety of
  - 6-day Oral Tedizolid (200 mg 1x/day)
    10-day Oral Linezolid (600 mg 2x/day)
- Intent-to-treat analysis

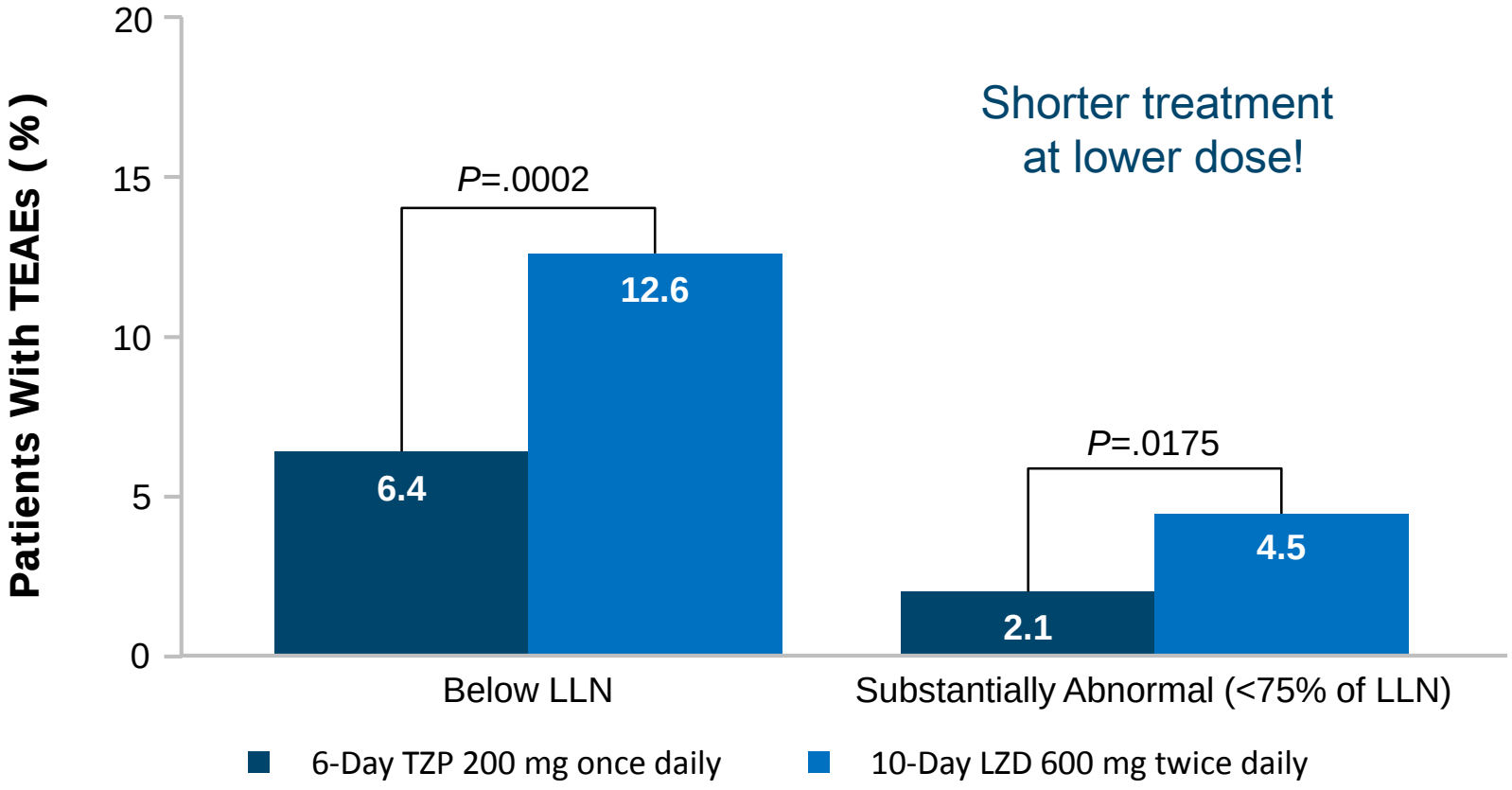
TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
At the 48- to 72-h assessment (ITT analysis set)			
Treatment responder, No. (%) [95% CI]	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 (−6.1 to 6.2)
Cellulitis/erysipelas, No./total (%)	101/135 (74.8)	100/139 (71.9)	
Major cutaneous abscess, No./total (%)	80/100 (80.0)	84/98 (85.7)	
Wound infection, No./total (%)	83/97 (85.6)	82/98 (83.7)	
Treatment nonresponder or indeterminate, No. (%)[a]	68 (20.5)	69 (20.6)	
Treatment nonresponder	27 (8.1)	35 (10.4)	
Indeterminate	41 (12.3)	34 (10.1)	
Missing lesion measurements	22 (6.6)	24 (7.2)	
Missing temperature data	37 (11.1)	32 (9.6)	

Safety: Platelet counts – Pooled Phase 3 Studies

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

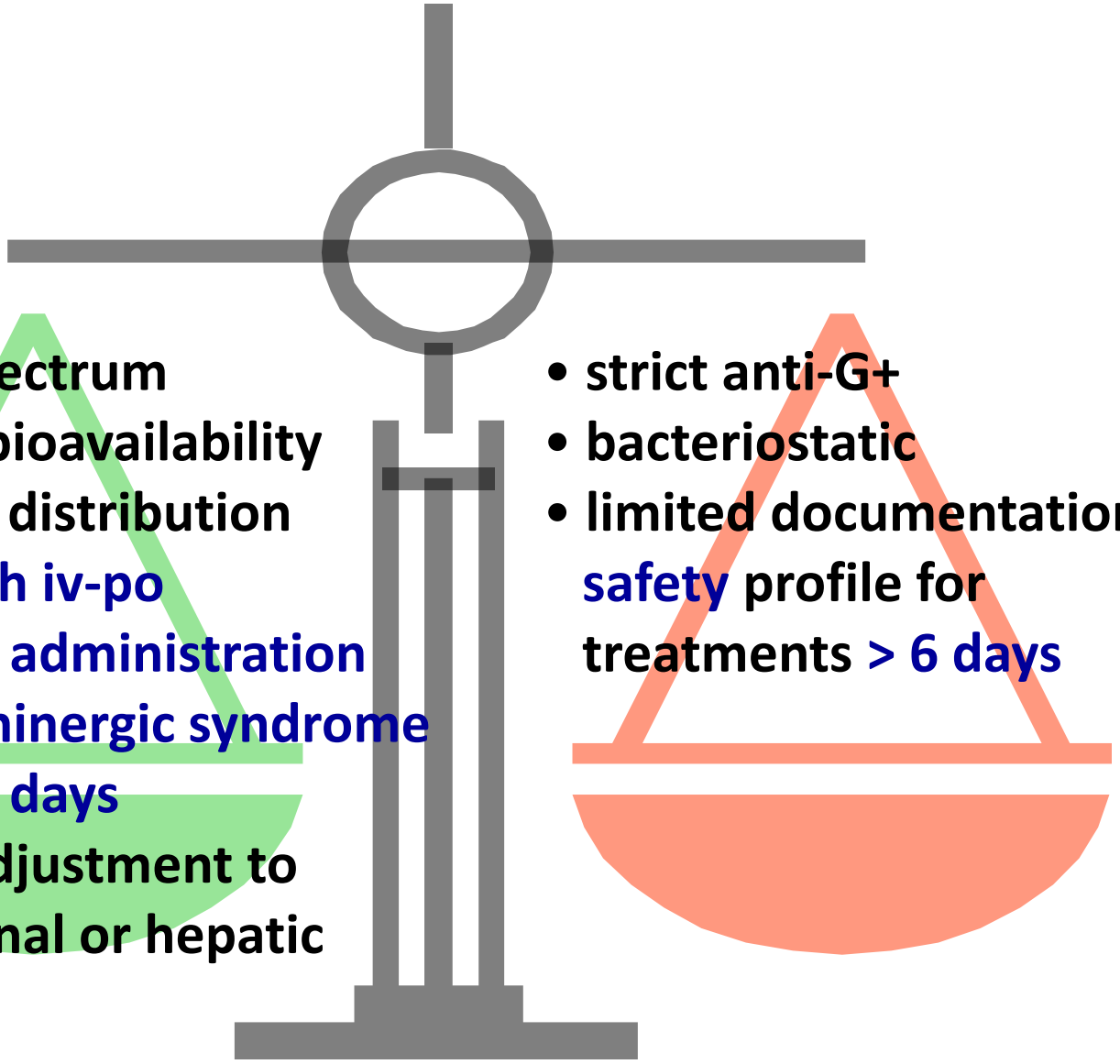


TEAE=treatment-emergent adverse events; LLN=lower limit of normal; TZP=tedizolid; LZD=linezolid.

[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).

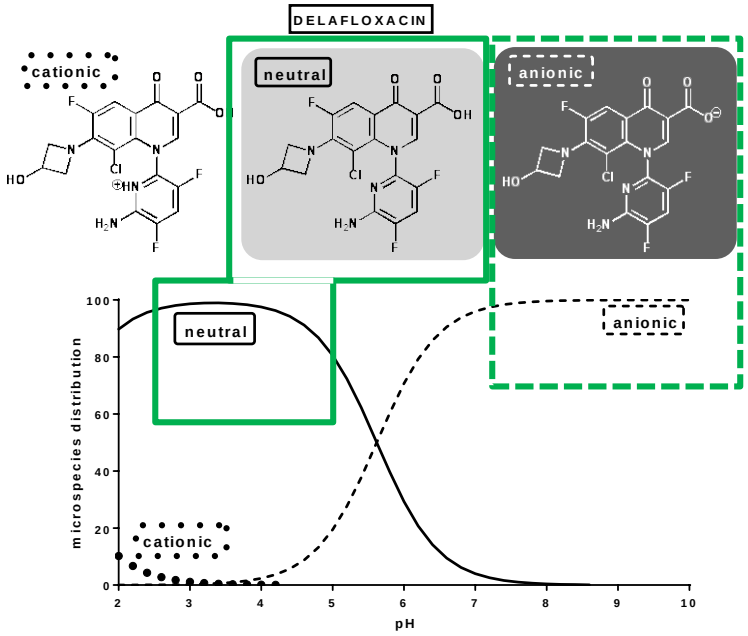
Tedizolid: pros and cons

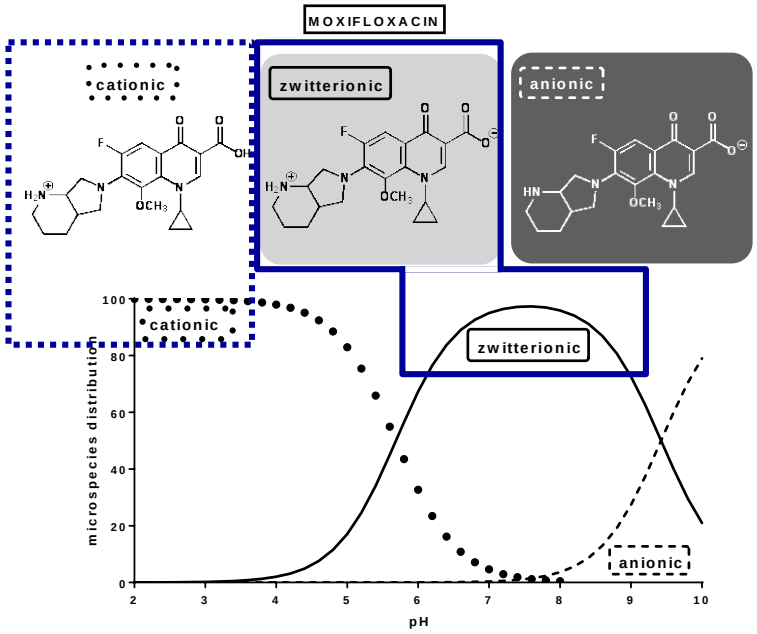


- narrow spectrum
- excellent bioavailability and tissue distribution
- easy switch iv-po
- once daily administration
- no serotoninergic syndrome
- active in 6 days
- no dose adjustment to weight, renal or hepatic function

- strict anti-G+
- bacteriostatic
- limited documentation of safety profile for treatments > 6 days

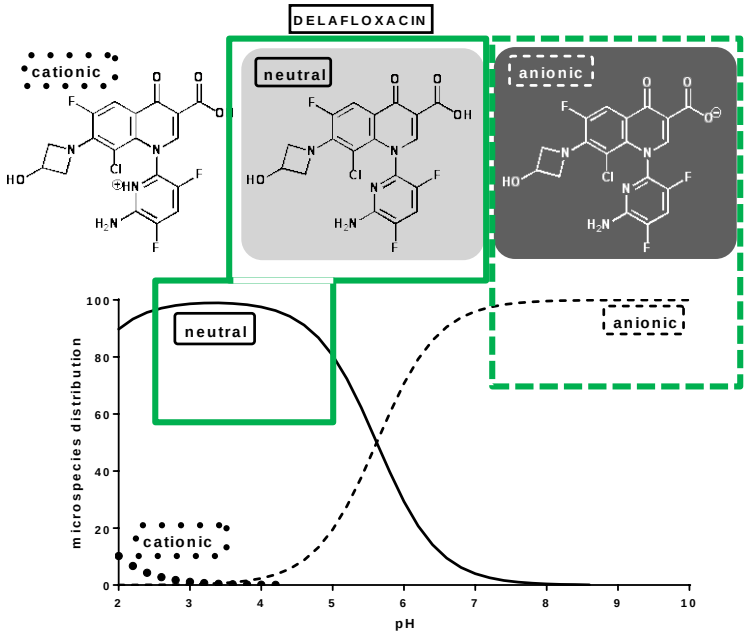
Delafloxacin, the first “non-zwitterionic” quinolone

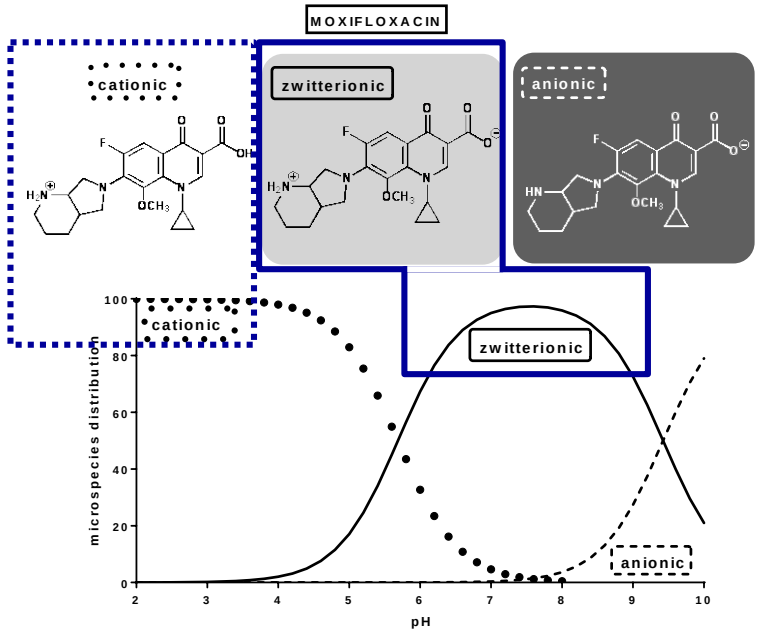




Van Bambeke, Future Microbiol. 2015; 10:1111–23

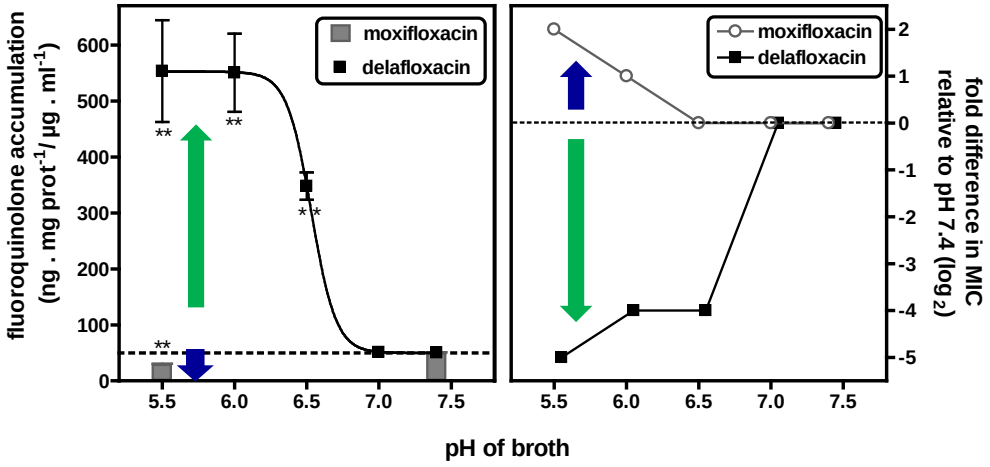
Delafloxacin, the first “non-zwitterionic” quinolone





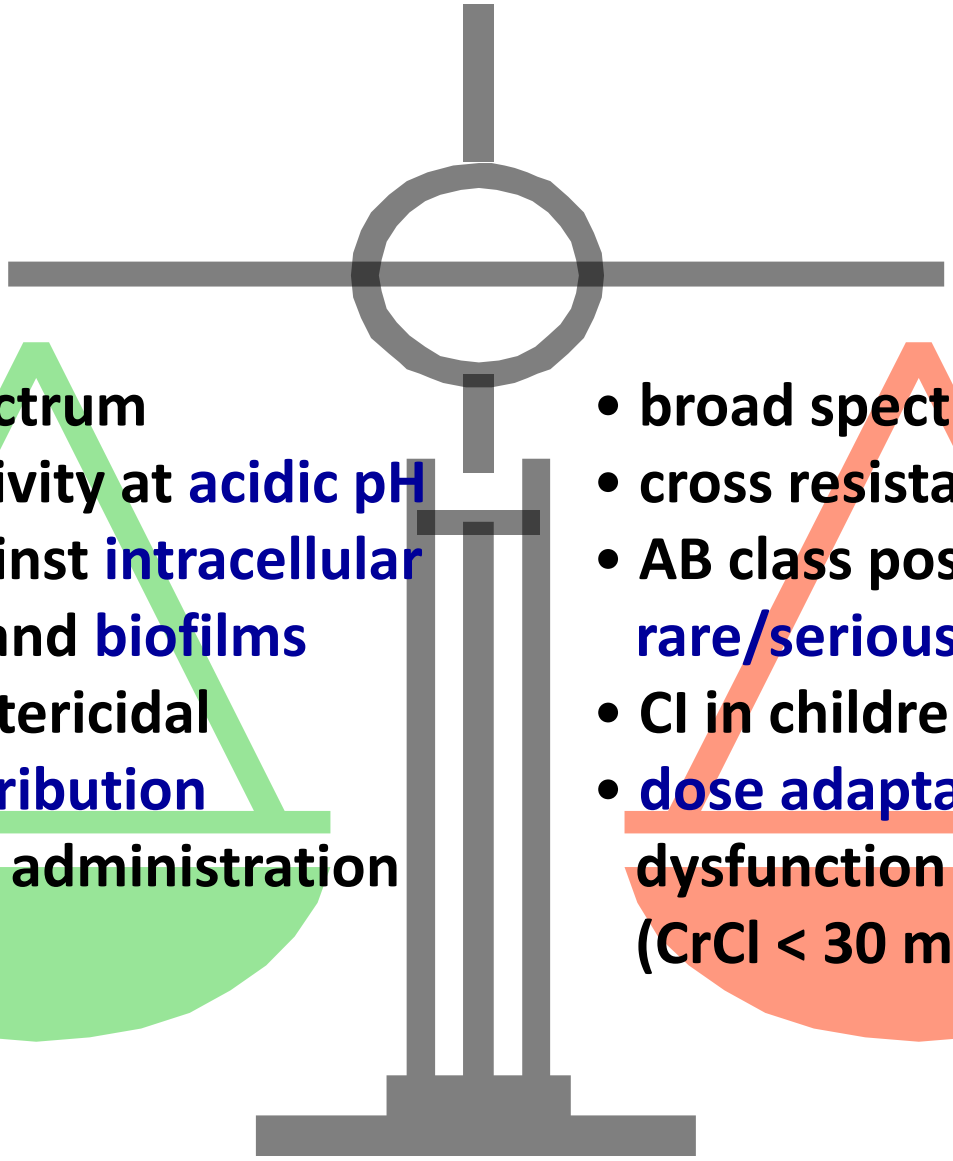
Increased

- uptake by bacteria
- activity at acidic pH



Van Bambeke, Future Microbiol. 2015; 10:1111–23; Lemaire et al, AAC 2011; 55:649-58

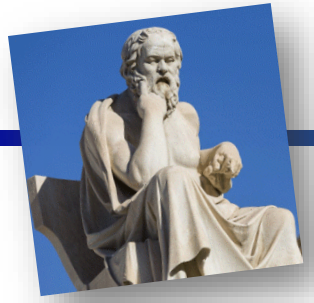
Delafloxacin: pros and cons



- broad spectrum
- higher activity at acidic pH
- active against intracellular *S. aureus* and biofilms
- highly bactericidal
- tissue distribution
- once daily administration
- oral or IV

- broad spectrum
- cross resistance with other FQ
- AB class possibly showing rare/serious adverse effects
- CI in children/pregnancy
- dose adaptation if renal dysfunction (CrCl < 30 mL/min)

From past to future therapies …



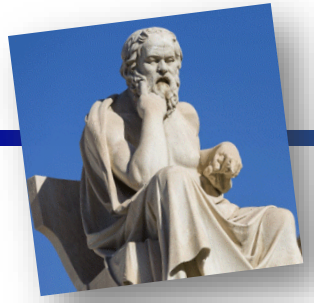
What do new drugs bring to our arsenal ?

1. Empirical *vs.* targeted therapy ?

2. De-escalation ?

antibiotic	spectrum
telavancin	G+
dalbavancin	G+
oritavancin	G+
ceftobiprole	**G+ G-**
ceftaroline	**G+ G-**
tedizolid	G+
delafloxacin	**G+ G-**

Broad coverage including MRSA

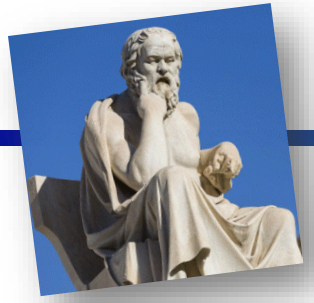


What do new drugs bring to our arsenal ?

3. Treatment duration ?

antibiotic	Treatment duration for SSTI (current: 7-14 days)
telavancin	7-14 days
dalbavancin	**2 doses** (D1 & D7)
oritavancin	**1 dose**
ceftobiprole	not indicated
ceftaroline	5-14 days
tedizolid	**6 days**
delafloxacin	5-14 days

shorter treatment



What do new drugs bring to our arsenal ?

4. Hospitalization / Home therapy ?

antibiotic	Easiness of use out of the hospital
telavancin	IV only
dalbavancin	**2 doses**
oritavancin	**1 dose**
ceftobiprole	IV only
ceftaroline	IV only
tedizolid	**IV-PO**
delafloxacin	**IV-PO**

infrequent dosing

good oral bioavailability

Take home message

Take home message

- Many new anti-MRSA drugs registered over the last years …
  and probably more to come in a near future !

- Main advantages of new drugs:
  - Activity on resistant strains
  - Pharmacokinetic profile
  - Safety profile

- Guidelines for MRSA infections out-of-date viz. these new drugs
  → how to position them ?
  More clinical data needed in specific indications…

Have a bright future …

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 1/2

company	drug	class	status	MRSA	MDRSP	VRE
Cempra	solithromycin	ketolide	Phase III CAPB	✓	✓	
TaiGen	nemonoxacin	fluoroquinolone	Phase III CAPB / ABSSSI	✓	✓	
Dong	zabofloxacin	fluoroquinolone	Phase III CAPB	✓	✓	
Activis	avarofloxacin	fluoroquinolone	Phase II completed CAPB / ABSSSI	✓	✓	
MerLion	finafloxacin	fluoroquinolone	Phase II ABSSSI	✓	✓	
GSK	GSK2140944	topoisomerase inhibitor	Phase II respiratory / ABSSSI	✓	✓	
Melinta	radezolid	oxazolidinone	Phase II CAPB / ABSSSI	✓	✓	✓

Constructed based on www.pewtrusts.org

Anti Gram-positive antibiotics in the pipeline (phases II/III) – 2/2

company	drug	class	status	MRSA	MDRSP	VRE
Paratek	omadacycline	aminomethyl cyclines	Phase III CAPB / ABSSSI	✓	✓	✓
Cempra	fusidic acid	fusidane	Phase III ABSSSI	✓		
Debiopharm	Debio1452	FabI inhibitor	Phase II S. aureus ABSSSI	✓		
Crystal-genomics	CG-400549	FabI inhibitor	Phase II ABSSSI / osteomyelitis	✓		
Theravance	TD-1792	glycopeptide + cephalosporine	Phase II completed cSSSI	✓	✓	
Nabriva	lefamulin	pleuromutilin	Phase II completed ABSSSI /CABP/HA-VABP	✓	✓	✓
Cellceutix	brilacidin	defensin-mimetic	Phase II completed ABSSSI	✓		✓

Constructed based on www.pewtrusts.org