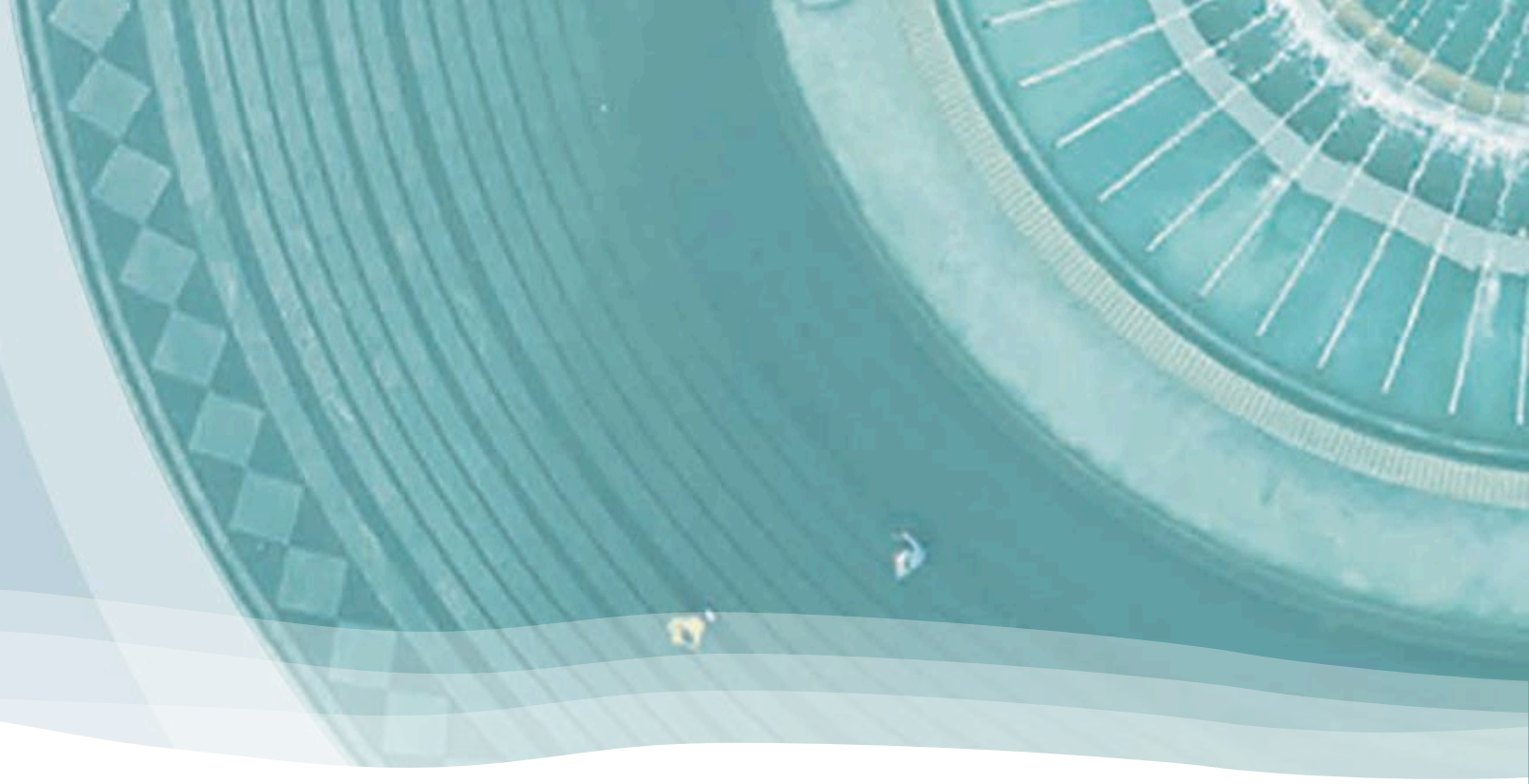


13th ACCP 2023

DELAFLOXACINA

Marianna Meschiari

Clinic of Infectious Diseases
University of Modena and Reggio Emilia
Modena, Italy

UNIVERSITAS STUDIORUM MUTINENSIS ET REGIENSIS 1175

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

Disclosure

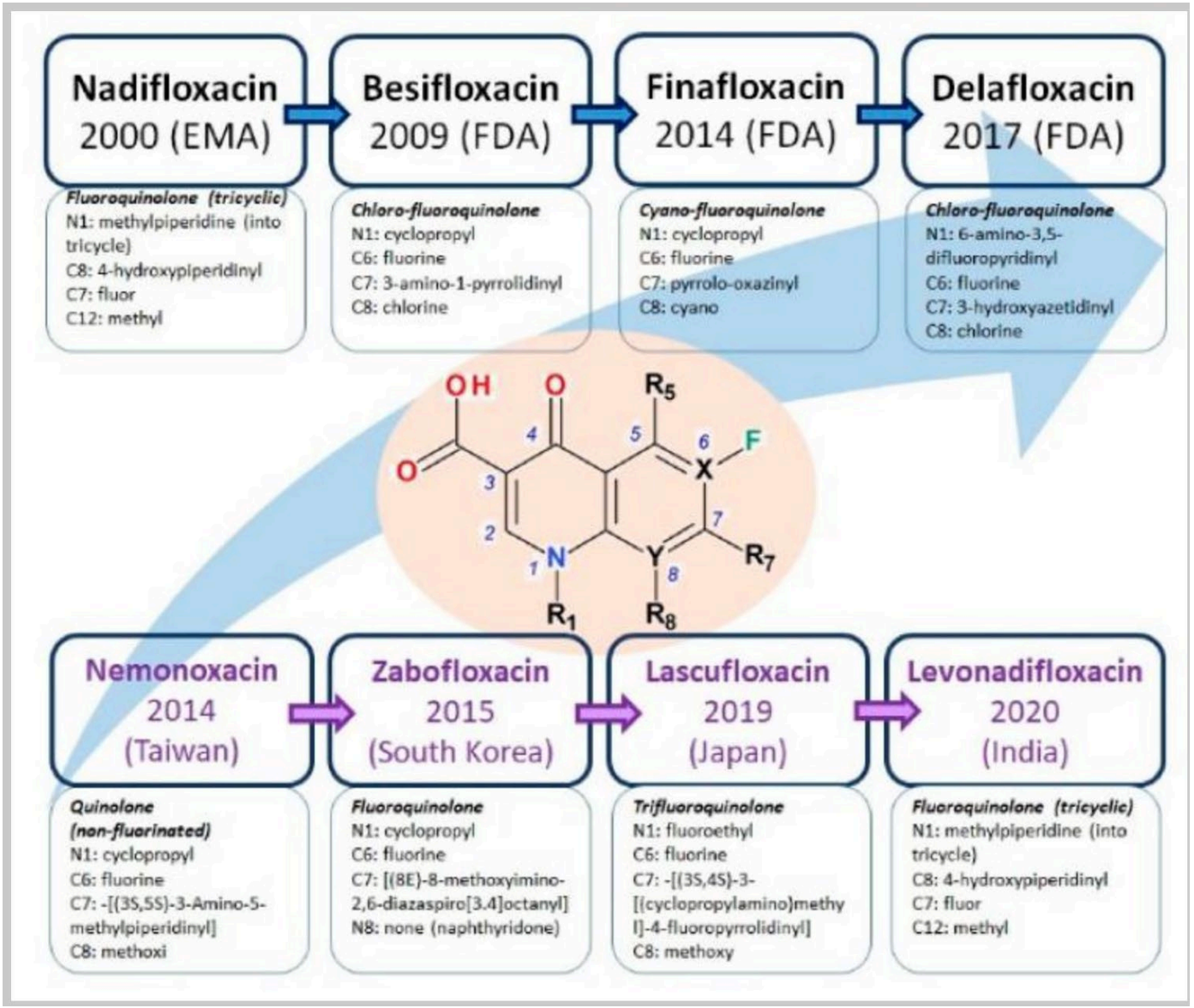
ai sensi dell’art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiaro

che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

MSD
Angelini
Pfizer
ViiV
Shionogi
BioMérieux

New FQNs chronology in therapy (since 2000)



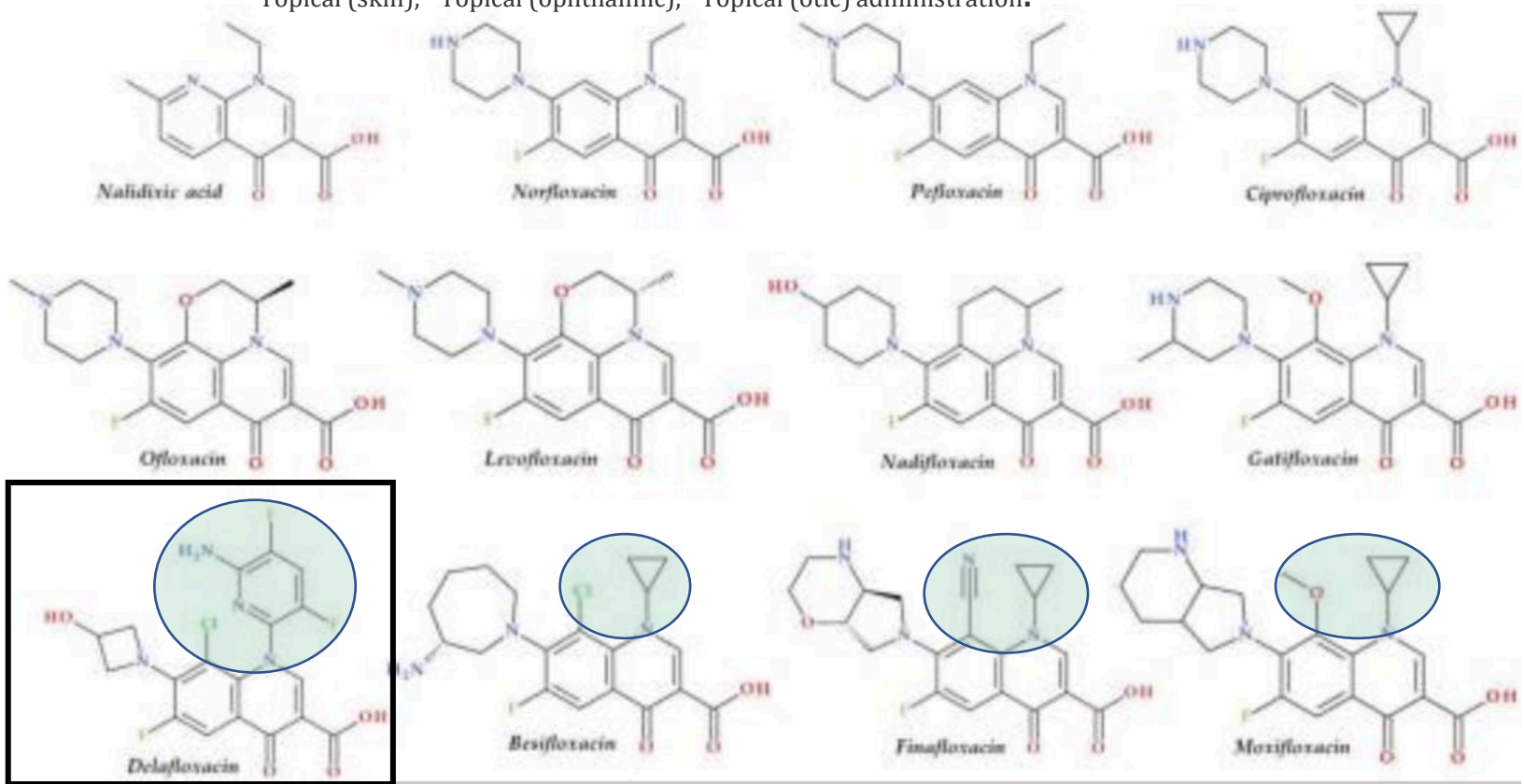
- The evolution of the class of antibacterial quinolones includes the introduction in therapy of highly successful compounds.
- In the last two decades, several representatives of antibacterial quinolones received approval for therapy.

NEW TOPOISOMERASE INHIBITORS

Chemical structures of FQs used in therapy and approved by the EMA and FDA

	1st Generation	2nd Generation	3rd Generation	4th Generation
QNs/FQs	Nalidixic Acid	Ciprofloxacin, Nadifloxacin [1], Norfloxacin, Ofloxacin, Pefloxacin	Gatifloxacin [2], Levofloxacin	Besifloxacin [2], Delafloxacin, Finafloxacin [3], Moxifloxacin

[1] Topical (skin), [2] Topical (ophthalmic), [3] Topical (otic) administration.



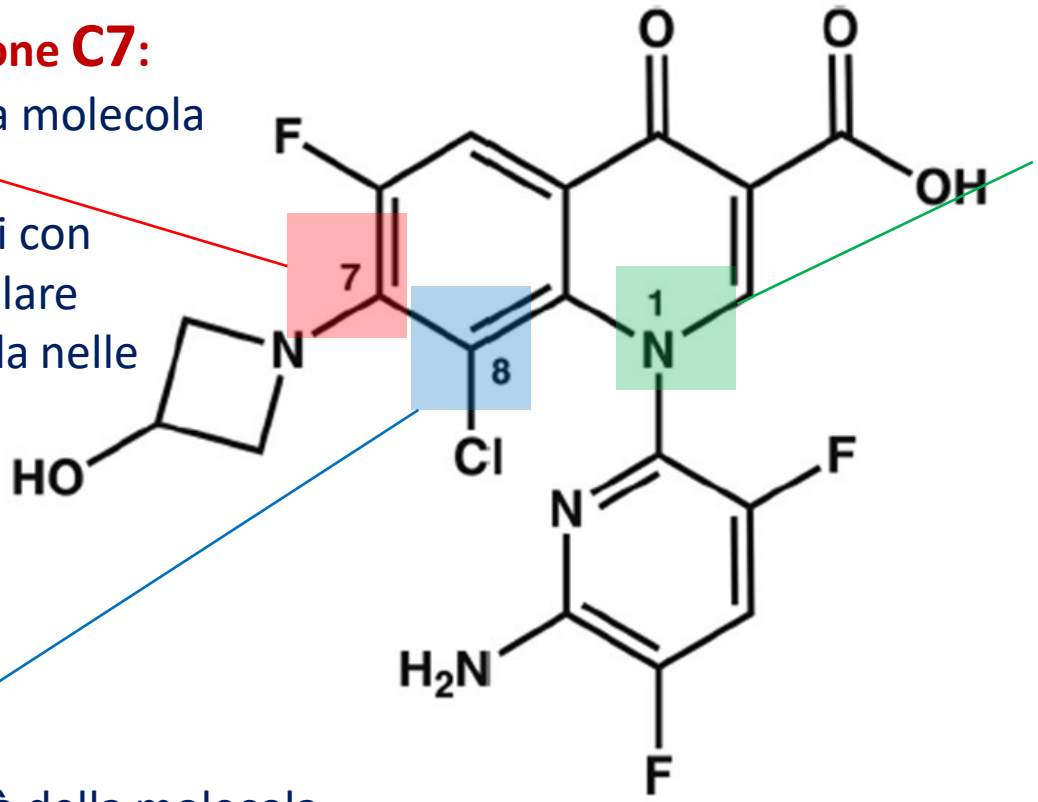
- Chemical structure of new fluoroquinolones in clinical development.
- New compounds are acquired from one generation to another with a **broader spectrum** of activity and **improved pharmacokinetic properties**
- The substituents in position 1 and 8 known to confer high intrinsic activity are on a green background.

Rusu A, et al. Overview of Side-Effects of Antibacterial Fluoroquinolones: New Drugs versus Old Drugs, a Step Forward in the Safety Profile? Pharmaceutics. 2023 Mar 1;15(3):804.

Chemical structure: shape, size and polarity

3 singole sostituzioni nella struttura chimica della molecola conferiscono vantaggio alla molecola:

Assenza gruppo basico in posizione C7:
Conferisce carattere **anionico** alla molecola a pH neutro
Lo rende una acido debole quindi con maggiore penetrazione intracellulare e una maggiore attività battericida nelle condizioni acide

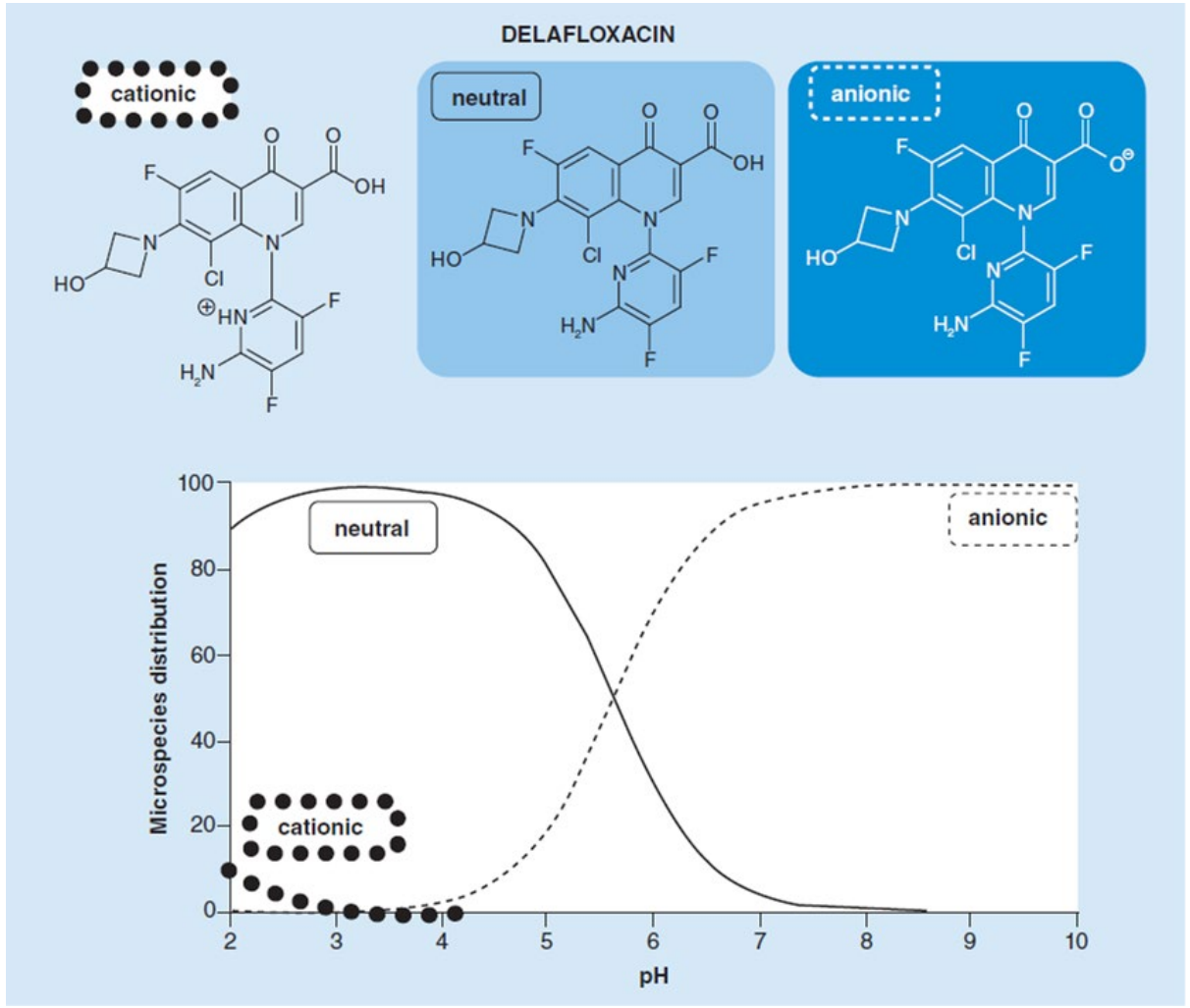


Anello eteroaromatico in posizione N1:
Aumenta la **superficie accessibile della molecola.**
Si ritiene che la collaborazione tra questo sostituente e il gruppo debolmente polare in C8 possa influenzare la potenza **contro i batteri gram-positivi resistenti** ai chinoloni, aumentando volume di distribuzione e biodisponibilità

Atomo di cloro in posizione C8:
Responsabile della **debole polarità** della molecola.
Contribuisce alla potenza verso i batteri gram-positivi.
Si ipotizza che questa sostituzione in C8 possa anche ridurre lo sviluppo di resistenze da parte di *S. aureus*

Mogle et al, J Antimicrob Chemother 2018; 73: 1439–1451; Jorgensen et al, Infect Dis ther (2018) 7:197-217

Chemical behaviour of delafloxacin in relation to pH

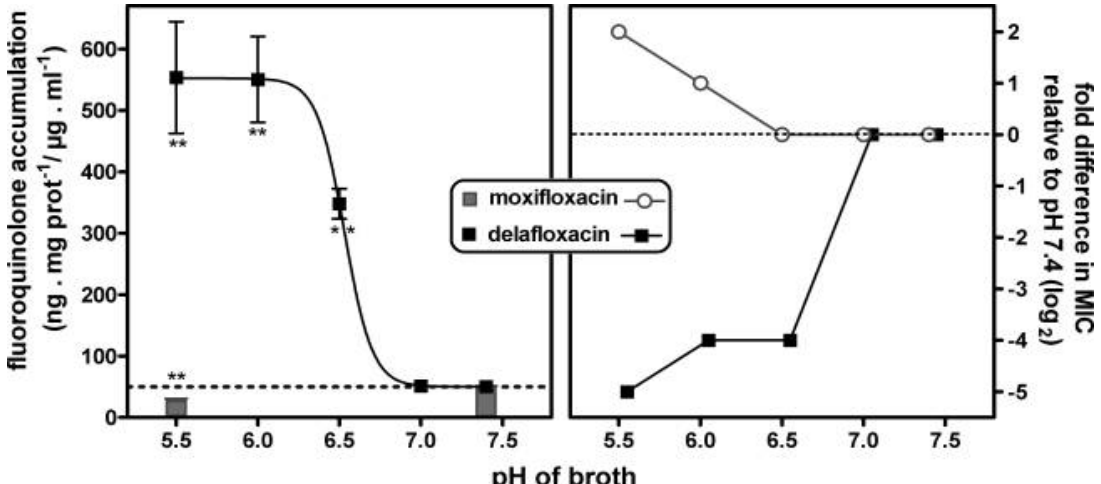


Van Bambeke et al, Future Microbiol. (2015) 10(7), 1111–1123
Lemaire S, *et al. Antimicrob Agents Chemother*. 2011;55(2):649-658.

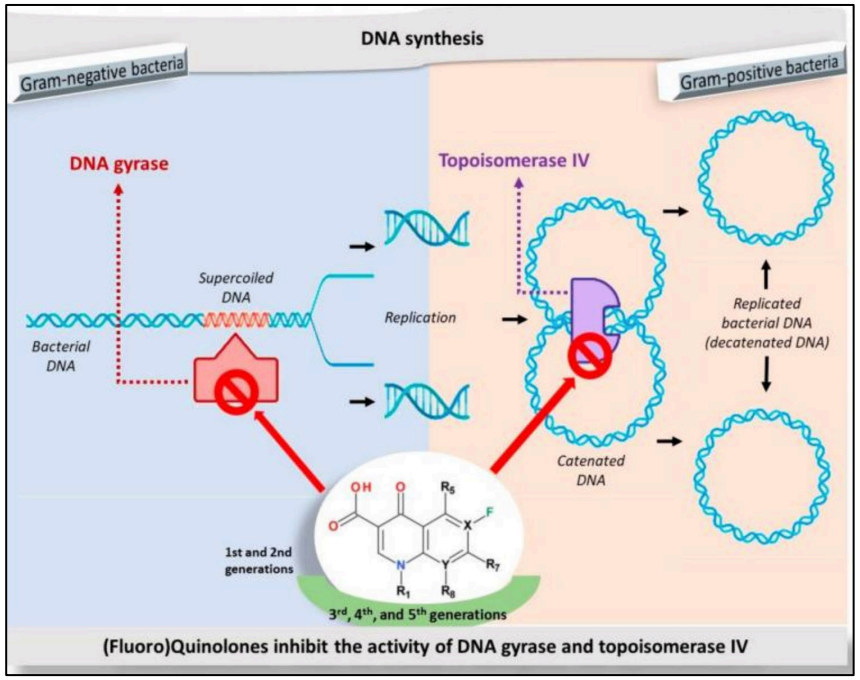
- **A pH fisiologico** (~7–7,4), delafloxacina si trova principalmente come **anione (>gram +)**, ma **a pH** leggermente **acido** (≤5,5), si trova soprattutto in forma **non carica**

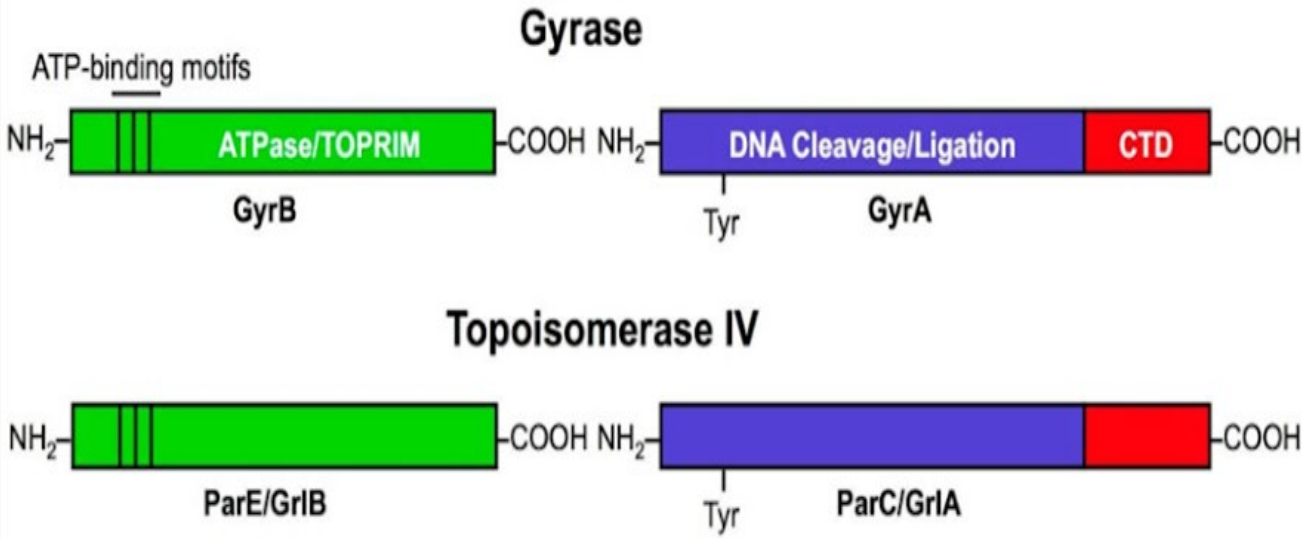
- **La forma non ionizzata di un farmaco è considerata più diffusibile attraverso le membrane biologiche** e questo spiega perchè delafloxacina si accumula di più nei batteri a pH acido (> diffusione, anche ELF)

- Rispetto a moxifloxacina, quando il pH cellulare scendeva da 7.0 a 6.0, si è osservato un aumento dell'accumulo di delafloxacina di **10 volte superiore**, ed una riduzione delle MIC di 4-5 diluizioni



Dual-targeting mechanism of action lead to minor resistances





-Resistance to FQs results from **chromosomal mutations** in the quinolones resistance-determining regions (**QRDRs**) of DNA gyrase (gyrA) and/or topoisomerase IV (parC/grlA).

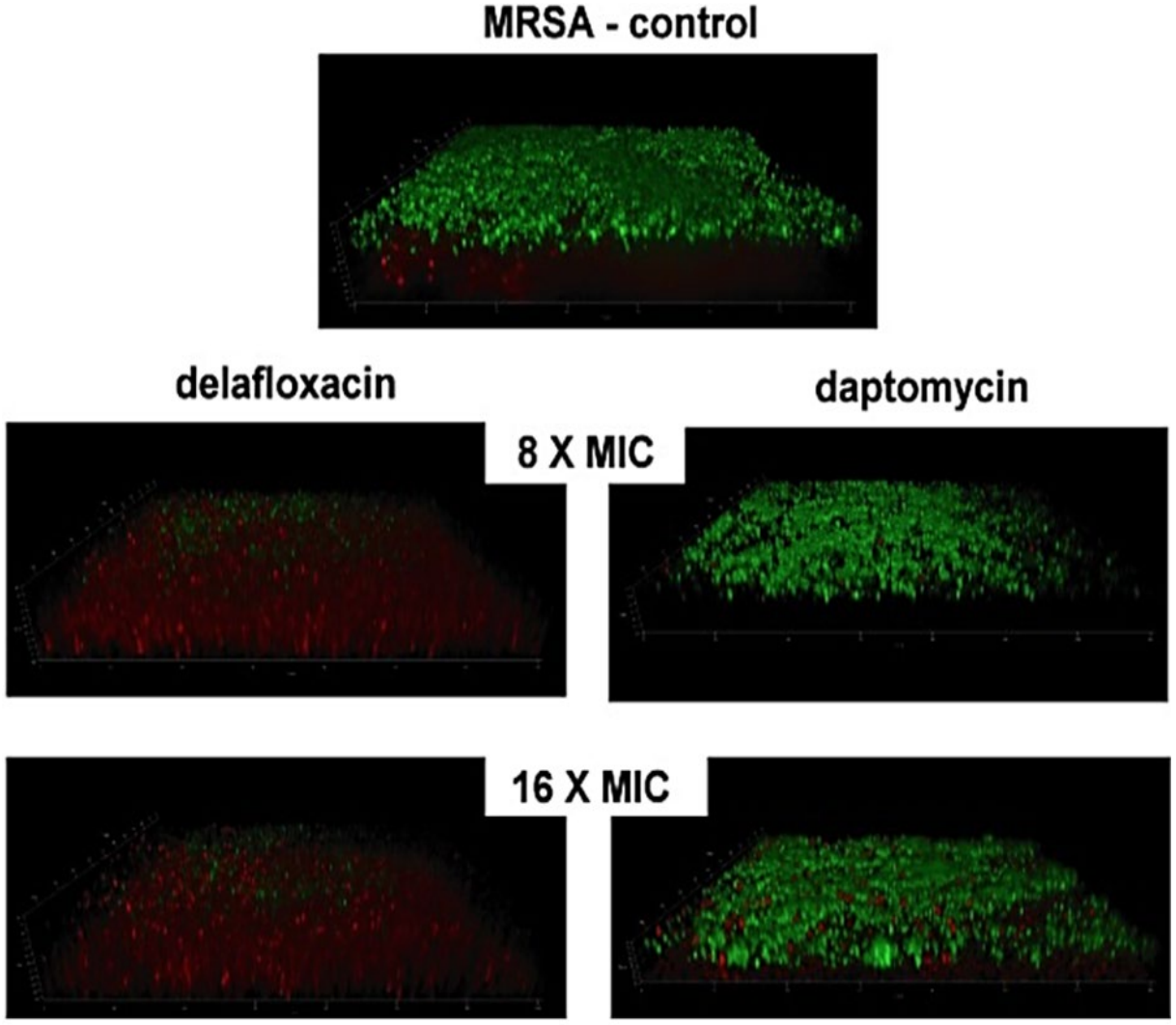
Delafloxacin, compared with other FQs, has **greater affinity for DNA gyrase** which acts ahead of the replication fork and faster.

Delafloxacin retains its bactericidal activity even against bacteria displaying the quinolone-resistant phenotype secondary to single and/or double mutations in the QRDR

Jorgensen et al, Infect Dis Ther (2018) 7:197–217

Delafloxacin has potent activity against *Staphylococcus aureus* biofilm, including MRSA

The effectiveness of various antibiotics (vancomycin, fusidic acid, moxifloxacin, daptomycin and delafloxacin) on MSSA and MRSA biofilms was studied

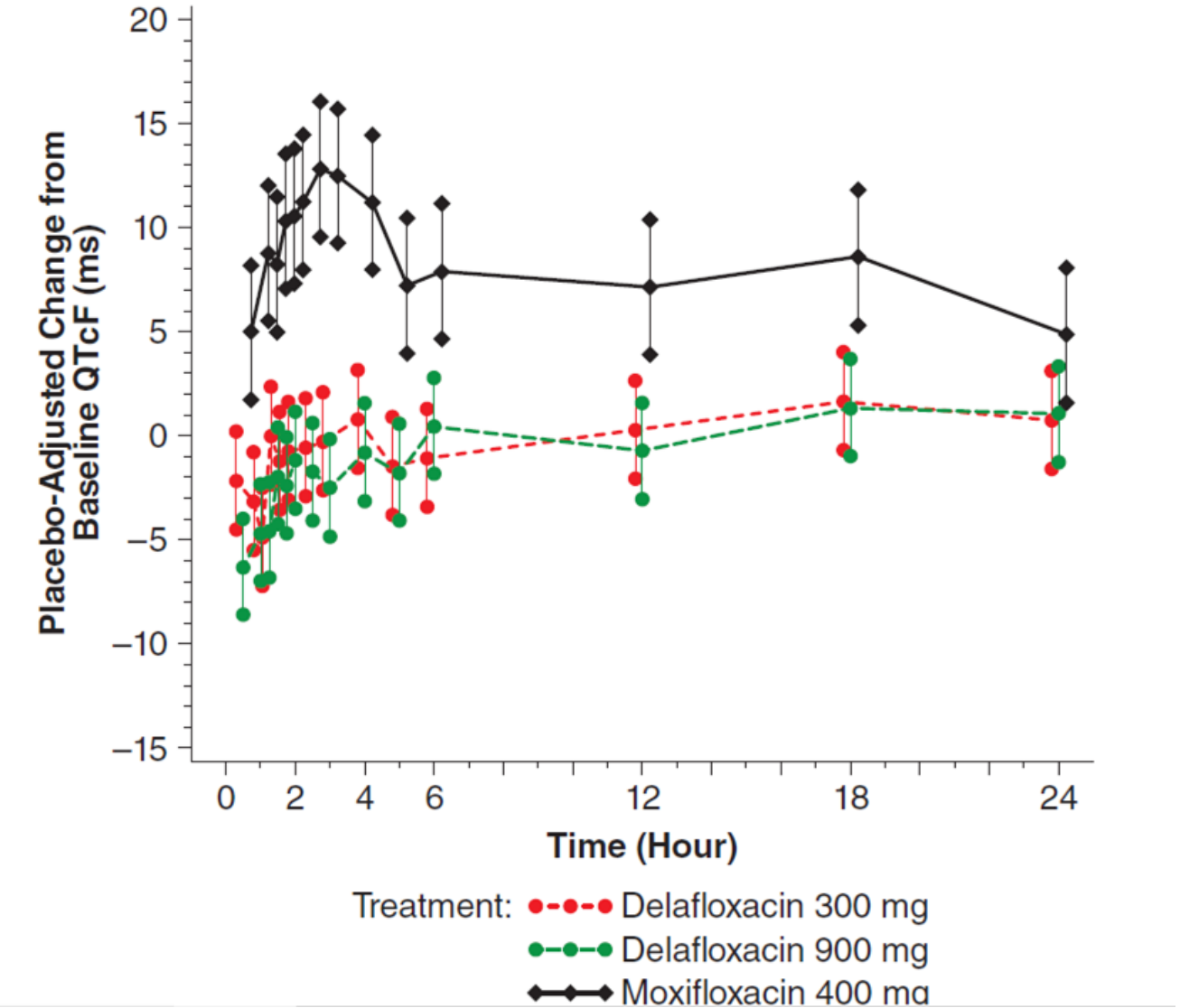


Green: viable cells; Red: dead cells

- Only delafloxacin and daptomycin significantly reduced the cell viability of both bacteria at any depth in the biofilm
- **Delafloxacin appeared more effective than daptomycin**, both at concentrations 8 and 16 times the MIC, **in reducing MRSA biofilm**

Bauer J, et al. Antimicrob Agents Chemother. 2013;57(6):2726-2737.

Delafloxacin was not associated with significant QT prolongation



- Studio crossover randomizzato, in doppio cieco, controllato con placebo, a 4 periodi su 52 adulti sani che ha valutato **l'effetto di delafloxacina sull'intervallo QT (QTc) corretto**.
- Sono stati confrontati **delafloxacina a 300 mg** per via endovenosa (i.v.; terapeutico), **delafloxacina a 900 mg i.v**. (sopraterapeutico), **moxifloxacina a 400 mg** per via orale (p.o.; controllo positivo), e **placebo**
- Ad ogni time point valutato dopo la somministrazione di **delafloxacina**, il limite superiore dell'intervallo di confidenza (CI) del 90% per la variazione corretta con il placebo rispetto al basale nel QTcF (QTcF) era inferiore a 10 ms (massimo, 3,9 ms 18 h dopo la somministrazione), indicando **l'assenza di un aumento clinicamente significativo nell'intervallo QTc**.

Litwin et al. Antimicrob Agents Chemother. 2015;59(6):3469-73

Gram-positive

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.[1]
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]
β-hemolytic staphylococci	All	17	Levofloxacin	0.5	2	0.03–2	[42]
		17	Delafloxacin	0.008	0.015	≤0.002–0.015	[42]
S. pneumoniae	FQ-S	69	Levofloxacin	1	1	0.5–2	[23]
		69	Moxifloxacin	0.12	0.12	0.06–0.25	[23]
		69	Delafloxacin	0.008	0.015	0.004–0.015	[23]
	FQ-R	33	Levofloxacin	16	32	2–32	[23]
		33	Moxifloxacin	2	4	0.25–8	[23]
		33	Delafloxacin	0.12	0.5	0.015–0.5	[23]
E. faecalis	FQ-S	18	Levofloxacin	1	1	0.5–2	[18,23]
		18	Moxifloxacin	0.25	0.5	0.12–0.5	[23]
		18	Delafloxacin	0.06	0.06	0.03–0.12	[23]
	FQ-R	26	Levofloxacin	32	128	16–128	[23]
		26	Moxifloxacin	8	32	2–64	[23]
		26	Delafloxacin	0.25	8	0.06–32	[23]
E. faecium	FQ-S	14	Levofloxacin	1	4	0.5–4	[23]
		14	Moxifloxacin	1	2	0.12–4	[23]
		14	Delafloxacin	0.12	1	0.06–2	[23]
	FQ-R	28	Levofloxacin	32	64	8–>128	[23]
		28	Moxifloxacin	16	16	1–32	[23]
		28	Delafloxacin	4	8	0.25–16	[23]
C. difficile	All	12	Levofloxacin	2	4	2–4	[18]
		12	Delafloxacin	≤0.015	≤0.015	≤0.015	[18]

[1]Comparison of MIC distributions among antibiotics should be performed using data from a same bibliographic reference.
FQ-S: Fluoroquinolone susceptible; FQ-R: Fluoroquinolone resistant (based in most cases on CLSI susceptibility breakpoints for marketed comparators).

- **Delafloxacin** exhibits very **low MIC values** against Gram-positive pathogens *(S.aureus, S.epidermidis, S.pneumoniae, E. faecalis, E.faecium)* with values **2 to 4 times lower than those of moxifloxacin**, which is considered today as ***the most potent anti-Gram-positive fluoroquinolone on the market.***

- The **MICs of delafloxacin remain low against FQ-R** bacteria (levofloxacin, moxifloxacin), with maximum values of 2 mg/l, 1 mg/l and 0.5 mg/l observed in
- *S. aureus,*
- *coagulase-negative staphylococci and*
- *S. pneumoniae*

Future Microbiol. 2015;10(7):1111-23

Gram-negative

Organism group (no. of isolates tested)/ antimicrobial agent	% of isolates susceptible by the following criteria: CLSI	EUCAST	MIC (μg/ml) 50%	90%	Range
Enterobacteriaceae (2,250)					
Delafloxacin			0.06	4	≤0.004 to >4
Levofloxacin	83.8	81.9	≤0.12	>4	≤0.12 to >4
Ampicillin-sulbactam	47.4	47.4	16	>32	0.5 to >32
Aztreonam	86.3	83.6	≤0.12	>16	≤0.12 to >16
Cefepime	90.8	87.8	≤0.5	2	≤0.5 to >16
Ceftazidime	86.3	82.8	0.25	16	0.03 to >32
Ceftriaxone	80.3	80.3	0.12	>8	≤0.06 to >8
Ciprofloxacin	81.6	79.3	≤0.03	>4	≤0.03 to >4
Gentamicin	90.7	89.0	≤1	4	≤1 to >8
Meropenem	97.5	97.9	0.03	0.06	≤0.015 to >32
Piperacillin-tazobactam	89.3	85.7	2	32	≤0.5 to >64
Tigecycline	99.2[b]	95.2	0.25	1	0.03 to 4
Pseudomonas aeruginosa (200)					
Delafloxacin			0.25	>4	0.015 to >4
Levofloxacin	72.5	62.5	0.5	>4	≤0.12 to >4
Amikacin	93.5	89.5	2	16	≤0.25 to >32
Aztreonam	55.5	3.5	8	>16	0.25 to >16
Cefepime	83.0	83.0	2	16	≤0.5 to >16
Ceftazidime	78.5	78.5	2	>32	0.25 to >32
Ceftriaxone			>8	>8	1 to >8
Ciprofloxacin	75.0	70.0	0.25	>4	≤0.03 to >4
Colistin	98.5	100.0	2		
Gentamicin	85.5	85.5	≤1		
Meropenem	74.4	74.4	0.5		
Piperacillin-tazobactam	78.0	78.0	8		

Pfaller MA et al. 2017. Antimicrob Agents Chemother 61:e02609-16

* Against *Enterobacter spp.,* delafloxacin appears less active than levofloxacin.

*Among isolates with the ESBL phenotype, susceptibility rates were just 17.3% and 5.7%, for E. coli and K. pneumoniae isolates, respectively

Organism	Phenotype	Delafloxacin MIC_{90}	Delafloxacin Range	Levofloxacin MIC_{90}	Levofloxacin Range	Ciprofloxacin MIC_{90}	Ciprofloxacin Range
Escherichia coli	All	4	≤ 0.004 to > 4	> 4	≤ 0.12 to > 4	> 4	≤ 0.03 to > 4
	ESBL	> 4	0.008 to > 4	> 4	≤ 0.12 to > 4	> 4	≤ 0.03 to > 4
Klebsiella pneumoniae	All	> 4	0.015 to > 4	> 4	≤ 0.12 to > 4		
	ESBL	> 4	0.06 to > 4	> 4	≤ 0.12 to > 4		

Spectrum of action of delafloxacin

Gram-positive micro-organisms[1]

- *Staphylococcus aureus* (including Methicillin-resistant *S.aureus* [MRSA])
- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Staphylococcus lugdunensis*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus)*
- *Streptococcus dysgalactiae*
- *Streptococcus mitis* group (including *Streptococcus cristatus, Streptococcus gordonii, Streptococcus oralis, Streptococcus mitis, and Streptococcus sanguinis)*
- *Streptococcus pyogenes*
- *Enterococcus faecalis*

Gram-negative micro-organisms[1]

- *Escherichia coli*
- *Enterobacter cloacae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

****In contrast to ciprofloxacin and levofloxacin,**
delafloxacin exhibited good activity **against anaerobes:**
Clostridium perfringens,
Bacteroides fragilis,
Prevotella sp,
Peptostreptococcus,
Bacteroides thetaiotamicron
Cutibacterium acnes,
Propionibacterium avidum,
Actinomyces spp.

Other organisms (CAP)

Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Streptococcus pneumoniae
Haemophilus influenzae
Moraxella catarrhalis

Unusual organisms: Non-fermentative Gram-negative bacilli (DTT)

Achromobacter spp.
Burkholderia multivorans
Burkholderia cenocepacia
S. maltophilia

Giordano PA, et al. Clin Infect Dis. 2019;68(Suppl 3):S223–S232.
Saravolatz LD et al. Clin Infect Dis 2018
Adrien Turban, et al . Antibiotics 2023, 12, 1241

MIC EUCAST: Breakpoints of delafloxacin

Organism	MIC breakpoints (mg/L)	
	Susceptible (S≤)	Resistant (R>)
Staphylococcus aureus	0.25	0.25
Streptococcus pyogenes	0.03	0.03
Streptococcus dysgalactiae	0.03	0.03
Streptococcus agalactiae	0.03	0.03
Streptococcus anginosus group	0.03	0.03
Escherichia coli	0.125	0.125

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	Observations	(T)ECOFF	Confidence interval
Acinetobacter baumannii	0	0	0	4	27	84	149	127	60	32	71	133	1463	1	0.25 - 2
Citrobacter freundii	0	0	0	4	43	104	38	26	39	48	45	15	396	(0.25)	0.06 - 0.25
Citrobacter koseri	0	0	4	42	277	107	38	21	3	4	1	4	506	(0.125)	0.03 - 0.125
Enterobacter cloacae	0	4	7	22	160	972	979	193	85	60	88	110	2878	0.5	0.125 - 0.5
Enterococcus faecalis	0	2	7	15	72	471	813	258	95	202	86	4	2103	0.5	0.125 - 0.5
Enterococcus faecium	0	0	2	1	9	22	24	18	6	22	39	49	1092	ID	
Escherichia coli	0	29	120	1288	3862	1898	491	598	270	205	890	1603	12325	0.125	0.06 - 0.5
Haemophilus influenzae	3123	117	42	20	10	5	6	11	0	0	0	0	3339	ID	
Haemophilus parainfluenzae	215	138	115	33	8	2	8	5	5	1	1	0	540	ID	
Klebsiella aerogenes	0	1	0	4	26	189	360	201	54	34	9	22	916	0.5	0.25 - 1
Klebsiella oxytoca	0	1	0	0	34	358	505	103	32	8	8	4	1059	0.5	0.125 - 0.5
Klebsiella pneumoniae	0	5	3	25	311	1872	1516	312	228	201	266	388	6323	0.25	0.125 - 0.5
Proteus mirabilis	0	1	2	39	408	892	176	37	54	114	213	96	2081	0.25	0.06 - 0.25
Proteus vulgaris	0	0	1	2	16	14	14	5	2	3	3	1	61	ID	
Pseudomonas aeruginosa	0	19	14	35	81	160	456	2200	2301	737	578	386	8131	2	0.5 - 4

According to EUCAST, due to insufficient evidence the clinical breakpoints for these pathogens have not yet been established:

- *Haemophilus influenzae,*
- *Moraxella catarrhalis,*
- *Enterococci*
- *Gram negative different from E.coli*

MIC distributions for Delafloxacin, 2023-11-11

Delafloxacina & *S.aureus*

TABLE 1 Summary of delafloxacin activity by MIC against baseline *S. aureus* isolates from an ABSSSI site or blood overall and by geographic region[a]

	United States (n = 717)					Europe (n = 283)					Overall (n = 1,042)				
		MIC (μg/ml)					MIC (μg/ml)					MIC (μg/ml)			
Organism	No.	Range	50%	90%	% LVX-NS	No.	Range	50%	90%	% LVX-NS	No.	Range	50%	90%	% LVX-NS
S. aureus	511	0.002–4	0.008	0.25	44.4	145	0.002–0.5	0.004	0.008	2.8	685	0.002–4	0.008	0.25	33.7
MRSA	281	0.004–4	0.12	0.25	68.0	7	0.004–0.5			42.9	294	0.002–4	0.12	0.25	66.0
MSSA	234	0.002–0.5	0.008	0.12	15.8	138	0.002–0.12	0.004	0.008	0.7	395	0.002–0.5	0.008	0.03	9.6

Aggregated data of patients enrolled in the two phase III studies of delafloxacin in ABSSSI

33.7% were R to levofloxacin (66.0% of the MRSA)

Delafloxacin showed potent activity against both S.aureus and **MRSA** isolates, with MIC50/90 values of 0.008/0.25 mg/ml and **0.12/0.25 mg/ml**, respectively.

In comparison, the MIC50/90 values of levofloxacin were 0.25/4 mg/ml and 4/8 mg/ml, respectively.

McCurdy S, et al. Antimicrob Agents Chemother. 2017;61(9):e00772-17, e00772-17.

Delafloxacina & *Pseudomonas aeurginosa*

TABLE 1 Comparison of susceptibility of *Pseudomonas aeruginosa* to delafloxacin and ciprofloxacin

Ciprofloxacin	Ciprofloxacin MIC (mg/L) Mean ± SEM	Delafloxacin MIC (mg/L) Mean ± SEM [Paired with Ciprofloxacin comparator]	*p* value
Total isolate (n = 50)	3.20 ± 0.58	1.13 ± 0.16	0.0005***
Sensitive [S ≤ 0.5 mg/L] (n = 10)	0.27 ± 0.04	0.17 ± 0.02	0.01*;
Intermediate [I = 1.0 mg/L] (n = 12)	1.15 ± 0.10	0.78 ± 0.12	0.01*;
Resistant [R ≥ 2.0 mg/L] (n = 28)	4.89 ± 0.88	1.28 ± 0.21	0.001**
Reference Strain (ATCC 27 853)	0.19	0.25	–

Activity of Delafloxacin and Comparator Fluoroquinolones against Multidrug-Resistant Pseudomonas aeruginosa in an In Vitro Cystic Fibrosis Sputum Model

52 isolates in patient affected with ***cystic fibrosis***:

delafloxacin vs cipro

→

Overall, isolates were statistically more sensitive to delafloxacin (***p = 0.0005***) than to ciprofloxacin.

→

4/12 (**33.3%**) isolates with intermediate resistance to ciprofloxacin were **sensitive to delafloxacin.**

→

10/28 (35.7%) ciprofloxacin-resistant isolates were sensitive to delafloxacin, with only 17.9% of ciprofloxacin-resistant isolates resistant to delafloxacin.

Delafloxacin shows potential in treating ciprofloxacin-resistant Pseudomonas aeruginosa.

Fluoroquinolone cross-reactivity data remains inconclusive and is limited to case reports..

Millar et al Clin Respir J. 2021 Jan;15(1):116-120
Vaughn D. Craddock, Antibiotics 2023, 12, 1078. https://doi.org/10.3390/antibiotics12061078

Resistance development to delafloxacin

Resistance development in *Escherichia coli* to delafloxacin at pHs 6.0 and 7.3 compared to ciprofloxacin

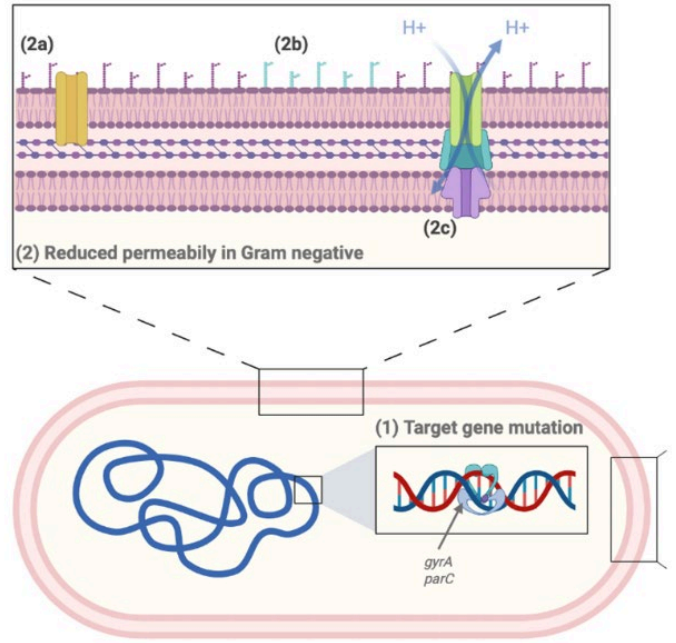
- This study identifies a **multifactorial mechanism** for the resistance evolution of delafloxacin in *E. coli*, which involves new mutational sites in topoisomerase genes and mutations in efflux-related genes (predominantly at pH 6.0).
- *Resistance to DLX evolved much slower in acidic ph.*
- cross-resistance to CIP in those challenged with DLX was less frequent.

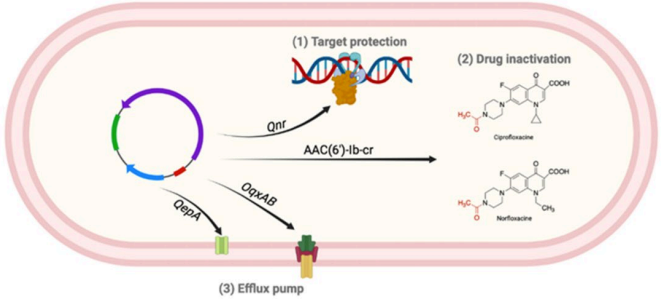
High-Level Delafloxacin Resistance through the Combination of Two Different Mechanisms in *Staphylococcus aureus*

- The study identifies resistance among 59 S. aureus clinical isolates, **16 %** categorized as resistant to delafloxacin:

1) mutation in the 84 position (E84K and E84V) of topoisomerase IV (ParC)

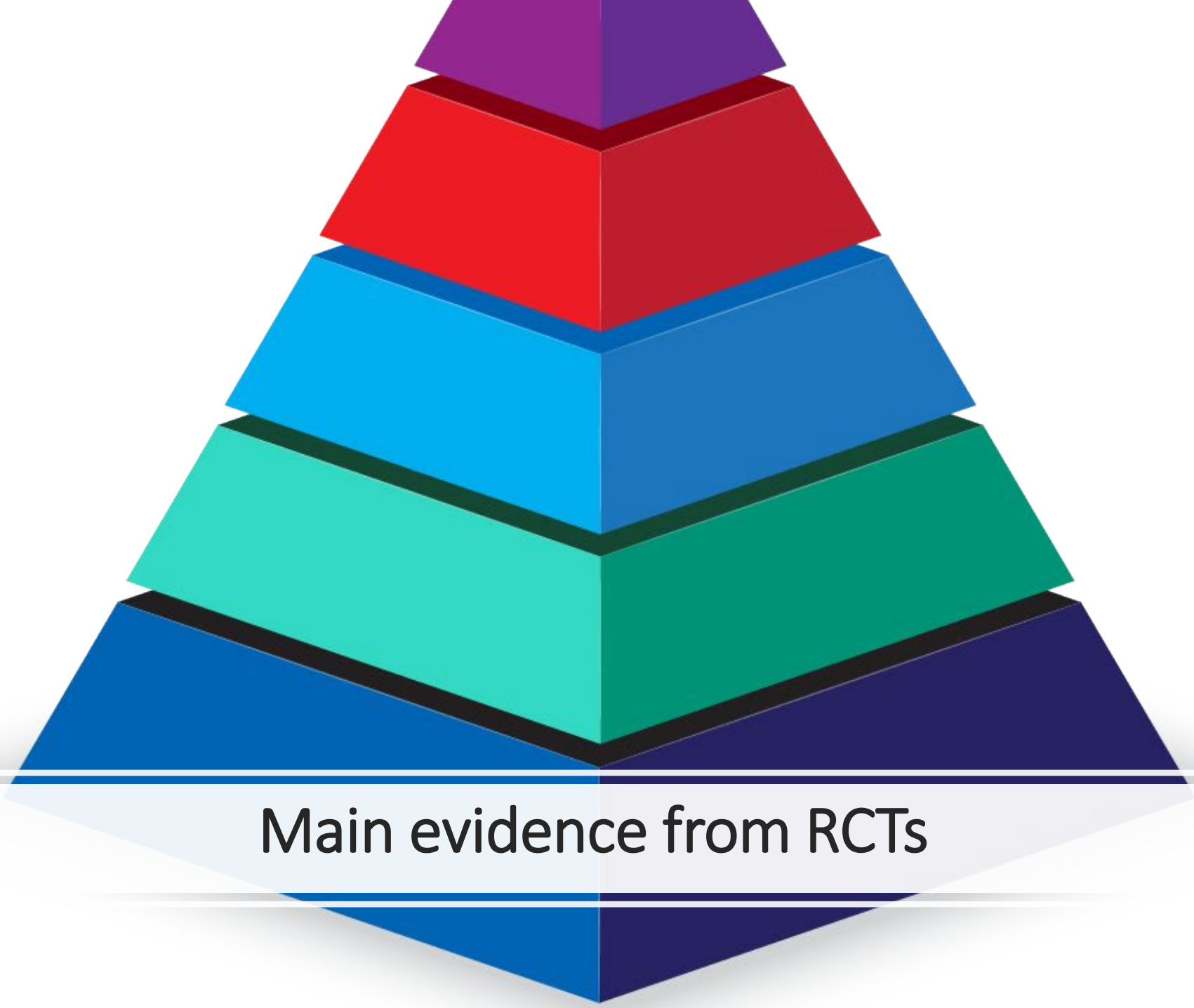
2) the acquisition of a plasmid-encoded qacC gene (coding for an MFS-type efflux pump)





(1) Target gene mutation occurs in QRDRs, mostly in gyrA and parC.
(2) (2a) Modification in membrane porins expression or QRDRs, mostly in gyrA and parC.
(2b) Outer membrane (LPS modification)
(3) Efflux pump expression
(4) Plasmid-mediated resistance mechanisms to FQs

Bösch A, et al.Antimicrob Agents Chemother. 2023 Oct 26:e0162522.
De la Rosa, J.M.O ; Int. J. Antimicrob. Agents 2023, 61, 106795.



Main evidence from RCTs

Flow Chart: Clinical development of delafloxacin

3,117 pazienti hanno ricevuto delafloxacina

32 studi

24 studi di fase 1

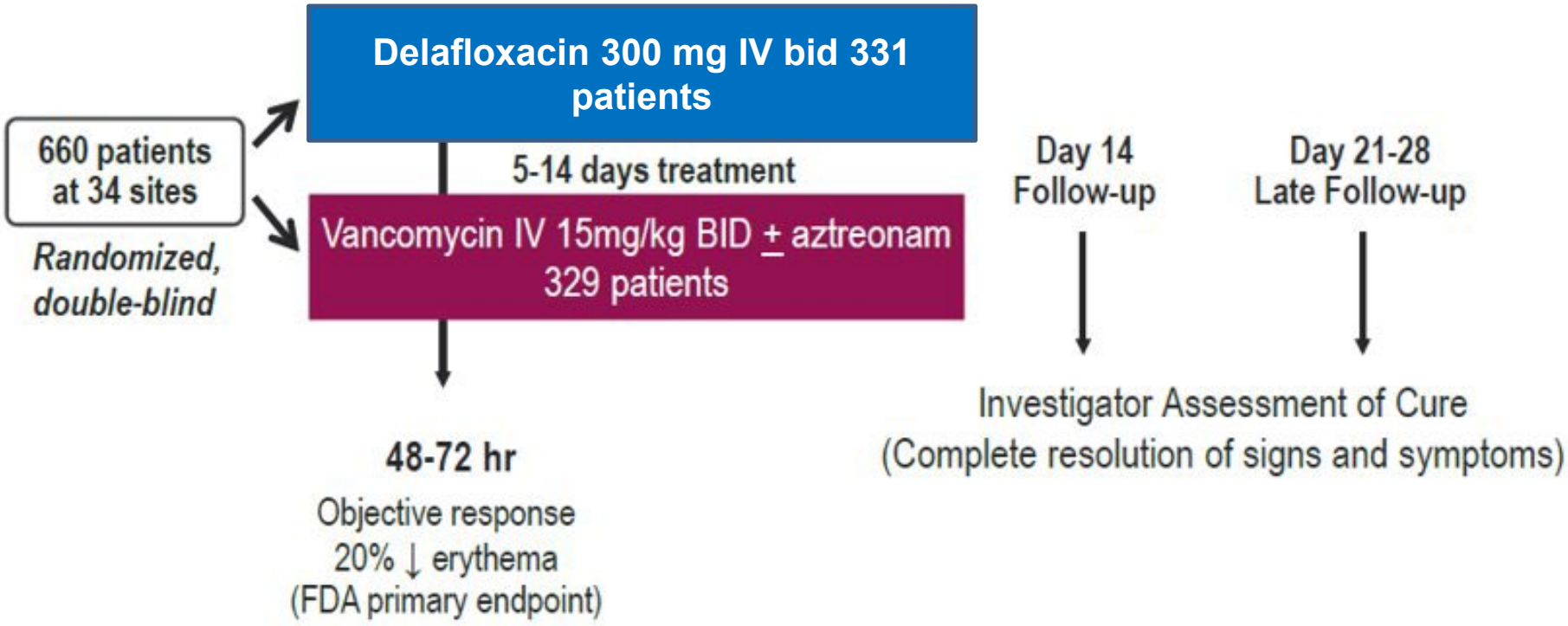
- 17 studi di **PK** (n = 881)
  - 2 studi pz con **disfunzione renale ed epatica** (n = 83)
    - 1 studio di **interazioni farmacologiche** (n = 22)
      - 1 studio su **BAL** (n = 30)
- 1 studio di **fotosensitività** **Delafloxacina orale** (n = 52)
  - 1 studio su **intervallo QT** **Delafloxacina orale** (n = 68)
    - 1 studio su **intervallo QTcorretto** **Delafloxacina ev** (n = 52)

8 studi di fase 2 e 3

- Fase 2
  2 studi in **ABSSSI**
  (n = 406) [36,37]
  - **Fase 3**
    2 studi in **ABSSSI**
    (n = 1,510) [4,5]
- Fase 2
  2 studi per altre indicazioni
  (**CAP e riacutizzazioni BPCO**)
  (n = 589)
  - Fase 3
    1 studio per un'altra indicazione
    (**Gonorrea non complicata**)
    (n = 460)
    - **Fase 3**
      1 studio nelle **CAP**
      (n = 850)

O'Riordan W, et al. Clin Infect Dis. 2018;67(5):657–666. Pullman J, et al. J Antimicrob Chemother. 2017;72:3471-3480. O'Riordan W, et al. Int J Infect Dis. 2015;30:67-73. Kingsley J, et al. J Antimicrob Chemother. 2016;71(3):821-829.

A comparison of the efficacy and safety of intravenous followed by oral delafloxacin with vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections:
a phase 3, multinational, double-blind, randomized study



Primary endpoint:

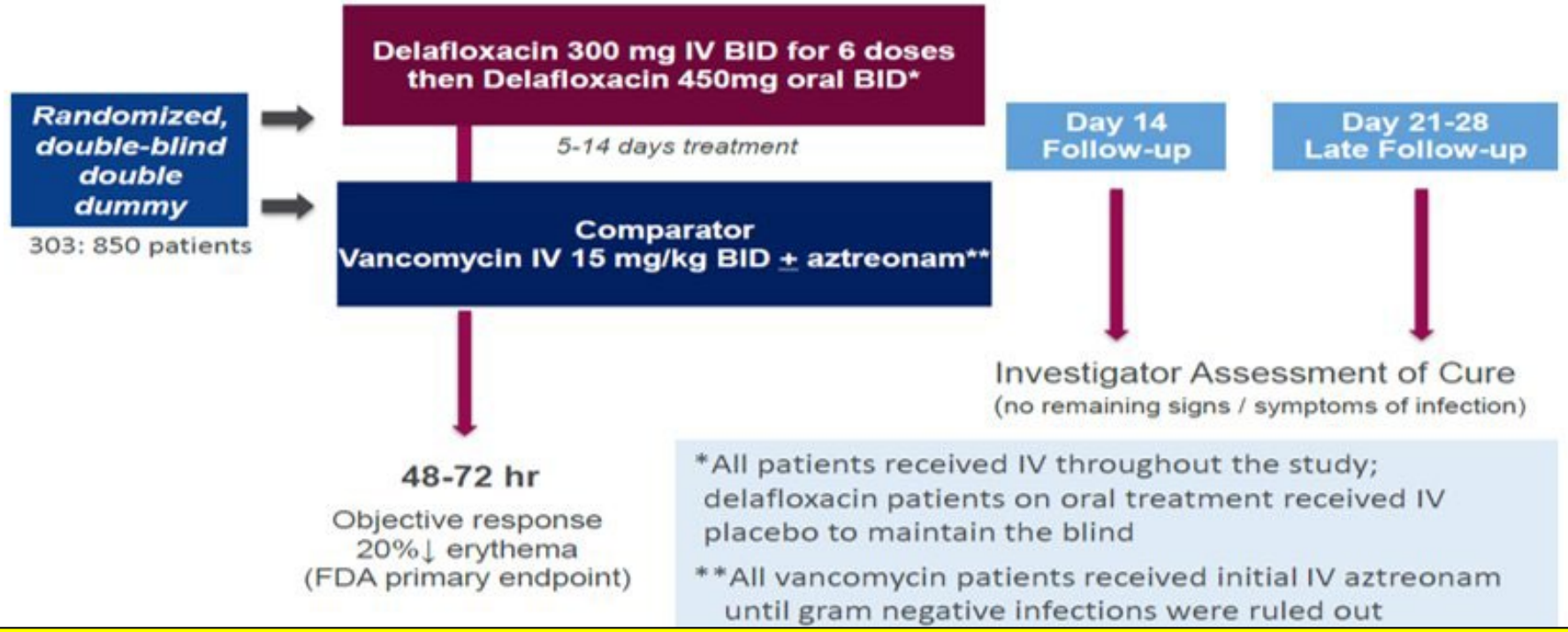
FDA: Reduction > 20% of the erythema area at 48-72 h after onset of erythema

EMA : Investigator's assessment of clinical recovery (no residual signs or symptoms) at follow-up visit in the ITT population

Pullman J, et al. J Antimicrob Chemother. 2017;72:3471-3480.

A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin With Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: *A Phase 3, Multinational, Double-Blind, Randomized Study*

Randomized (1:1),
with randomization stratified by
- infection category and
- BMI



Exclusion criteria:
- infection associated with prosthetic material or human/animal bites, osteomyelitis, decubitus ulcer, diabetic foot ulcer, septic arthritis, necrotizing fasciitis or burns (>10%).
- Liver disease, end-stage renal disease, cardiac disease, malignancy, history of seizure disorder and pregnancy or lactation.

Primary endpoint:

FDA: Reduction > 20% of the erythema area at 48-72 h after onset of erythema

EMA : Investigator's assessment of clinical recovery (no residual signs or symptoms) at follow-up visit in the ITT population

O'Riordan W, et al. Clin Infect Dis. 2018;67(5):657–666

Clinical outcomes of delafloxacin for ABSSSIs

Phase II trials (N 406)	**Antibiotics**		
Trial 1 ***O'Riordan W, et al. 2017***	**Delafloxacin 300 mg**	**Tigecycline 50 mg**	
Clinical cure	33/35 (94.3%)	31/34 (91.2%)	
Trail 2 **Kingsley J, et al. 2016**	**Delafloxacin 300 mg**	**Linezolid 600 mg**	**Vancomycin 15 mg/kg**
Clinical cure	57/81 (70.4%)	50/77 (64.9%)	53/98 (54.1%)
Phase III trials (N 1500)	**Antibiotics**		
Trial 1 ***Pullman J, et al. 2017***	**Delafloxacin 300-mg Intravenous**	**Vancomycin 15 mg/kg + Aztreonam**	**Treatment Difference (2-sided 95% CI)**
Clinical response	259 (78.2%)	266 (80.9%)	-2.6
Success ITT	270 (81.6%)	274 (83.3%)	-2.7
Trials 2 ***O'Riordan W, et al. 2018***	**Delafloxacin 300-mg Intravenous and 450-mg Oral**	**Vancomycin 15 mg/kg + Aztreonam**	**Treatment Difference (2-sided 95% CI)**
Clinical response	354 (83.7%)	344 (80.6%)	3.1
Success ITT	369 (87.2%)	362 (84.8%)	2.5

Equivalent efficacy for delafloxacin was also demonstrated for the CE, ME, and MITT analyses.

Adapted from: Eric R. Ocheretyaner & Tae Eun Park (2018) Delafloxacin: a novel fluoroquinolone with activity against methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa, Expert Review of Anti-infective Therapy, 16:7, 523-530, DOI: 10.1080/14787210.2018.1489721

Studio O'Riordan - Caratteristiche di popolazione al basale

Characteristic	Delafloxacin (n = 423)	Vancomycin + Aztreonam (n = 427)	Overall (N = 850)
Age, y, mean ± SD (range)	51.2 ± 15.98 (18–89)	50.2 ± 16.03 (19–93)	50.7 ± 16.00 (18–93)
Age category, y, No. (%)			
≤65	344 (81.3)	352 (82.4)	696 (81.9)
65–75	79 (18.7)	75 (17.6)	154 (18.1)
>75	35 (8.3)	31 (7.3)	66 (7.8)
Male sex, No. (%)	262 (61.9)	276 (64.6)	538 (63.3)
Race, No. (%)			
White	348 (82.3)	355 (83.1)	703 (82.7)
Black/African American	13 (3.1)	18 (4.2)	31 (3.6)
American Indian/Alaska Native	12 (2.8)	7 (1.6)	19 (2.2)
Asian	11 (2.6)	15 (3.5)	26 (3.1)
Native Hawaiian/Other Pacific Islander	2 (0.5)	2 (0.5)	4 (0.5)
Other	37 (8.7)	30 (7.0)	67 (7.9)
Ethnicity, No. (%)			
Hispanic or Latino	132 (31.2)	99 (23.2)	231 (27.2)
Region, No. (%)			
Europe	165 (39.0)	173 (40.5)	338 (39.8)
North America	202 (47.8)	196 (45.9)	398 (46.8)
Asia	9 (2.1)	14 (3.3)	23 (2.7)
Latin America	47 (11.1)	44 (10.3)	91 (10.7)
BMI, kg/m^2, mean ± SD	30.4 ± 7.44	30.7 ± 7.54	30.5 ± 7.49
≥30	211 (49.9)	214 (50.1)	425 (50.0)
Diabetes, No. (%)	53 (12.5)	54 (12.6)	107 (12.6)
Prior antibiotic use, No. (%)	89 (21.0)	111 (26.0)	200 (23.5)
Baseline pain score, mean ± SD	7.4 ± 2.30	7.2 ± 2.40	
Medical history relevant to substance abuse including IVDA, No. (%)[a]	129 (30.5)	125 (29.3)	
Duration of exposure, d			
No.	417	425	
Mean ± SD	7.3 ± 2.97	7.0 ± 2.92	
Median	6.5	6.5	
Min, Max	0.5, 14.0	0.5, 14.5	

Abbreviations: BMI, body mass index; IVDA, intravenous drug abuse; SD, standard deviation.

[a]Medical history was coded using the Medical Dictionary for Regulatory Activities version 16.1. At each level of summarization, a subject was counted once if the subject reported 1 or more events. Preferred terms used: drug dependence, drug abuse, substance use, drug abuser, substance abuse, and substance abuser.

Patient characteristics:

- Most patients were aged >65 years
- 30% of patients had a BMI ≥30 kg/m2
- 10% Diabetes
- Prior antibiotic use in 15-20% of patients

O'Riordan et al., Clinical Infectious Diseases 2018;67(5):657–66

Microbiological response rate (MRR) per pathogen at follow-up

Pathogen	Per-Pathogen Objective Responders at 48–72 h, ME at 48–72 h Analysis Set		Per-Pathogen Microbiological Response (Documented or Presumed Eradication)[a], ME at Follow-up Analysis Set	
	Delafloxacin (n = 264)	Vancomycin + Aztreonam (n = 250)	Delafloxacin (n = 231)	Vancomycin + Aztreonam (n = 212)
Staphylococcus aureus	139/152 (91.4)	122/142 (85.9)	129/131 (98.5)	114/118 (96.6)
MRSA	61/64 (95.3)	43/46 (93.5)	48/50 (96.0)	32/33 (97.0)
MSSA	80/89 (89.9)	79/96 (82.3)	83/83 (100.0)	82/85 (97.0)
Streptococcus anginosus[b]	28/28 (100)	20/20 (100)	24/24 (100.00)	16/16 (100.0)
Streptococcus pyogenes	12/16 (75)	7/12 (58.3)	13/14 (92.9)	11/11 (100.0)
Klebsiella pneumoniae	8/9 (88.9)	9/10 (90)	8/8 (100.0)	8/8 (100.0)
Pseudomonas aeruginosa	7/9 (77.8)	7/7 (100)	9/9 (100.0)	6/6 (100.0)
Escherichia coli	9/9 (100)	6/10 (60)	7/7 (100.0)	9/10 (90.0)
Staphylococcus haemolyticus	6/9 (66.7)	5/6 (83.3)	7.7 (100)	5.5 (100)
Enterobacter cloacae	6/8 (75)	5/8 (62.5)	8/8 (100.0)	7/8 (87.5)
Streptococcus agalactiae	6/8 (75)	8/10 (80)	6/6 (100)	9/10 (90.0)
Enterococcus faecalis	8/8 (100)	8/12 (66.7)	7/8 (87.5)	11/12 (91.7)
Staphylococcus lugdunensis	2/3 (66.7)	3/6 (50)	3/3 (100)	6/6 (100)

Among the 839 patients with an ABSSSI culture at baseline, *S.aureus* was the micro-organism most frequently identified in 58.2% of isolates in the Delafloxacin group and 57.0% of isolates in patients on vancomycin/aztreonam.

MRSA was detected **in 24%** and 18% of patients on delafloxacin and vancomycin/aztreonam, respectively.

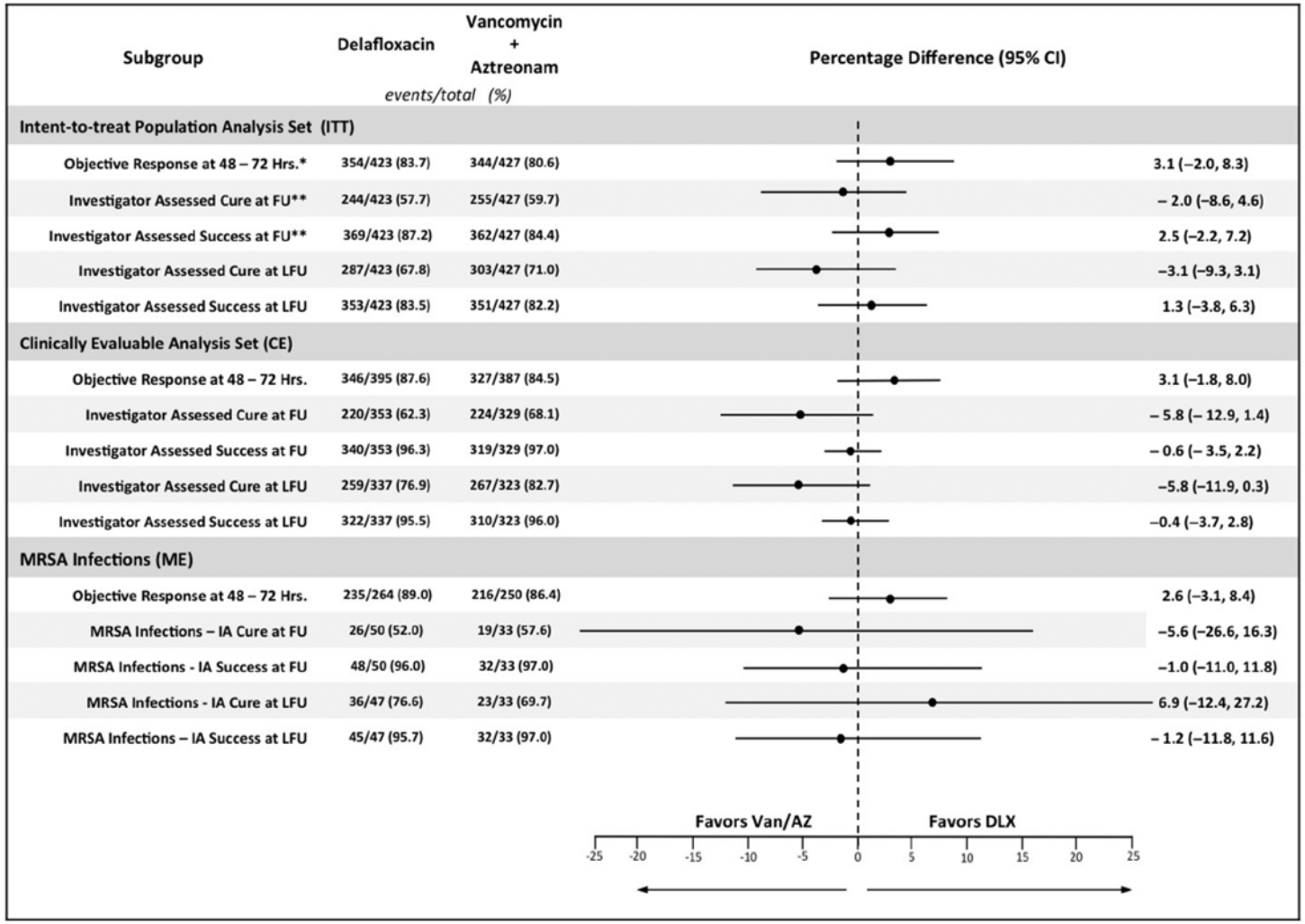
Overall, 96% of MRSA isolates were sensitive to delafloxacin (delafloxacin MIC ≤ 0.25 µg/mL)

The microbiological response rate was similar for patients with MRSA infections: 96% in the delafloxacin-treated group and 97% in the vanco/aztreonam-treated group

Too few gram-negative isolates were collected to allow for meaningful analysis.

O'Riordan W, et al. Clin Infect Dis. 2018;67(5):657–666

Results



The percentage of clinical responders 48-72 h after the start of treatment was similar between the two groups, 83.7% for delafloxacin and 80.6% for vancomycin/aztreonam (**demonstrated non-inferiority**)

O'Riordan W, et al. Clin Infect Dis. 2018;67(5):657–666

O'Riordan - Safety

Adverse Event	Delafloxacin (n = 417)	Vancomycin + Aztreonam (n = 425)
Any TEAE regardless of causality affecting ≥2% of patients	182 (43.6)	167 (39.3)
Nausea	32 (7.7)	19 (4.5)
Diarrhea	32 (7.7)	14 (3.3)
Infection	16 (3.8)	15 (3.5)
Headache	14 (3.4)	16 (3.8)
Infusion site extravasation	13 (3.1)	10 (2.4)
Pyrexia	11 (2.6)	9 (2.1)
Vomiting	10 (2.4)	8 (1.9)
Increase in creatinine phosphokinase	5 (1.2)	10 (2.4)
Pruritus	4 (1.0)	9 (2.1)
TEAE related to study drug	87 (20.9)	89 (20.9)
TEAE of moderate or severe intensity	75 (18.0)	86 (20.2)
Any TEAE resulting in premature study drug discontinuation	10 (2.4)	12 (2.8)
Any related TEAE resulting in premature study drug discontinuation	5 (1.2)	10 (2.4)
Any SAE	16 (3.8)	17 (4.0)
Deaths	0. (0.0)	2 (0.5)

Data are presented as No. (%).

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

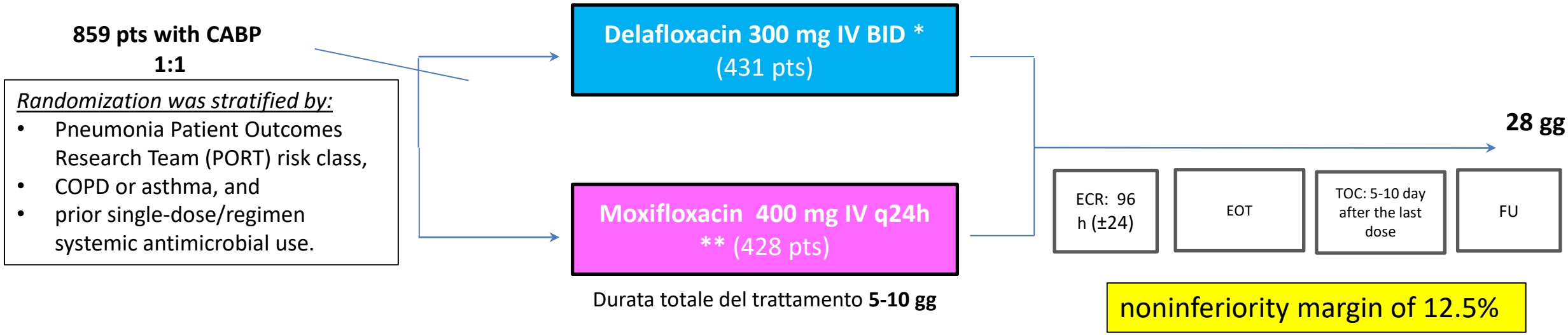
- One case of CDI occurred in a patient treated with delafloxacin but no cases of tendinitis or tendon rupture

- Treatment-emergent adverse events leading to study *drug discontinuation was higher* in the *vancomycin + aztreonam* group (1.2% vs 2.4%).

O'Riordan et al., Clinical Infectious Diseases 2018;67(5):657–66

A Phase 3 Study to Compare Delafloxacin With Moxifloxacin for the Treatment of Adults With Community-Acquired Bacterial Pneumonia (DEFINE-CABP)ç

a phase 3, randomized, double-blind, comparator-controlled, multicenter, global study



*According to clinical criteria, patients could switch to treatment by os after at least 6 i.v. doses

** if MRSA confirmed, patients could switch from moxifloxacin to linezolid

*** Abbrev: CABP: Community acquired bacterial pneumoniae; ECR: early clinical response; EOT: end of treatment; TOC: test of cure; FU: follow up

Key efficacy point:

FDA: The primary end point was early clinical response (**ECR**), defined as improvement at 96 (±24) hours after the first dose of study drug. Clinical response at test of cure (TOC) and microbiologic response were also assessed.

Horcajada et al In Open Forum Infectious Disease*. 2019 Dec 5;7(1):ofz514*

Studio Horcajada - Caratteristiche di popolazione al basale

Characteristic	Delafloxacin (n = 431)	Moxifloxacin (n = 428)	Total (n = 859)
Age, y			
Mean (SD)	60.7 (16.06)	59.3 (16.58)	60.0 (16.33)
Median	63.0	61.0	62.0
Min, max	18, 89	18, 93	18, 93
Age category, No. (%)			
<65 y	228 (52.9)	249 (58.2)	477 (55.5)
≥65 y	203 (47.1)	179 (41.8)	382 (44.5)
≥75 y	85 (19.7)	97 (22.7)	182 (21.2)
Sex, No. (%)			
Male	251 (58.2)	253 (59.1)	504 (58.7)
Female	180 (41.8)	175 (40.9)	355 (41.3)
Race, No. (%)			
White	398 (92.3)	388 (90.7)	786 (91.5)
Black or African American	22 (5.1)	33 (7.7)	55 (6.4)
Asian	5 (1.2)	5 (1.2)	10 (1.2)
American Indian or Alaska Native	4 (0.9)	0	4 (0.5)
Other	2 (0.5)	2 (0.5)	4 (0.5)
Region, No. (%)[a]			
Europe	371 (86.1)	365 (85.3)	736 (85.7)
South Africa	30 (7.0)	41 (9.6)	71 (8.3)
Latin America	29 (6.7)	17 (4.0)	46 (5.4)
North America	1 (0.2)	5 (1.2)	6 (0.7)
Weight, kg			
Mean (SD)	76.40 (17.389)	77.23 (16.765)	76.82 (17.076)
Median	75.00	75.65	75.00
Min, max	39.2, 160.0	33.5, 136.0	33.5, 160.0
BMI category, No. (%)			
<30 kg/m^2	328 (76.1)	316 (73.8)	644 (75.0)
≥30 kg/m^2	103 (23.9)	112 (26.2)	215 (25.0)
Diabetes, No. (%)			
Yes	70 (16.2)	61 (14.3)	131 (15.3)
COPD/asthma, No. (%)			
Yes	61 (14.2)	56 (13.1)	117 (13.6)
Multilobar pneumonia, No. (%)			
Yes	125 (29.0)	120 (28.0)	245 (28.5)
CrCl group, No. (%)[b]			
Severe (<30 mL/min)	5 (1.2)	7 (1.6)	12 (1.4)
Moderate (30–<60 mL/min)	80 (18.6)	79 (18.5)	159 (18.5)
Mild (60–<90 mL/min)	142 (32.9)	134 (31.3)	276 (32.1)
Normal (≥90 mL/min)	194 (45.0)	199 (46.5)	393 (45.8)
Missing	10 (2.3)	9 (2.1)	19 (2.2)
PORT risk class, No. (%)			
II	54 (12.5)	57 (13.3)	111 (12.9)
III	258 (59.9)	260 (60.7)	518 (60.3)
IV	115 (26.7)	103 (24.1)	218 (25.4)
V	4 (0.9)	8 (1.9)	12 (1.4)
PORT risk score			
Mean (SD)	84.5 (15.75)	84.7 (17.43)	84.6 (16.60)
Median	83.0	81.0	82.0
Min, max	50, 146	48, 161	48, 161
Bacteremia, No. (%)			
Yes	5 (1.2)	8 (1.9)	13 (1.5)
Pathogen identified at baseline	257 (59.6)	263 (61.4)	520 (60.5)

Abbreviations: BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CRF, case report form; CURB-65, confusion, urea, respiratory rate, blood pressure, age 65 or older; ITT, intent-to-treat; Max, maximum; Min, minimum; NIH, National Institutes of Health; PMN, polymorphonuclear neutrophil; PORT, Patient Outcomes Research Team; SEC, squamous epithelial cell.

[a]Europe comprises Bulgaria, Georgia, Germany, Hungary, Latvia, Poland, Romania, Russia, Serbia, Spain, Slovenia, and Ukraine. North America comprises the United States. Latin America comprises Argentina, Columbia, Peru, and Dominican Republic.

[b]CrCl was based on the Cockcroft-Gault formula without correction for BSA.

The median duration of treatment was 9 days (median, 6 days IV and 2 days oral)

Horcajada et al., Open Forum Infectious Disease, feb 2023 DOI: 10.1093/ofid/ofz514

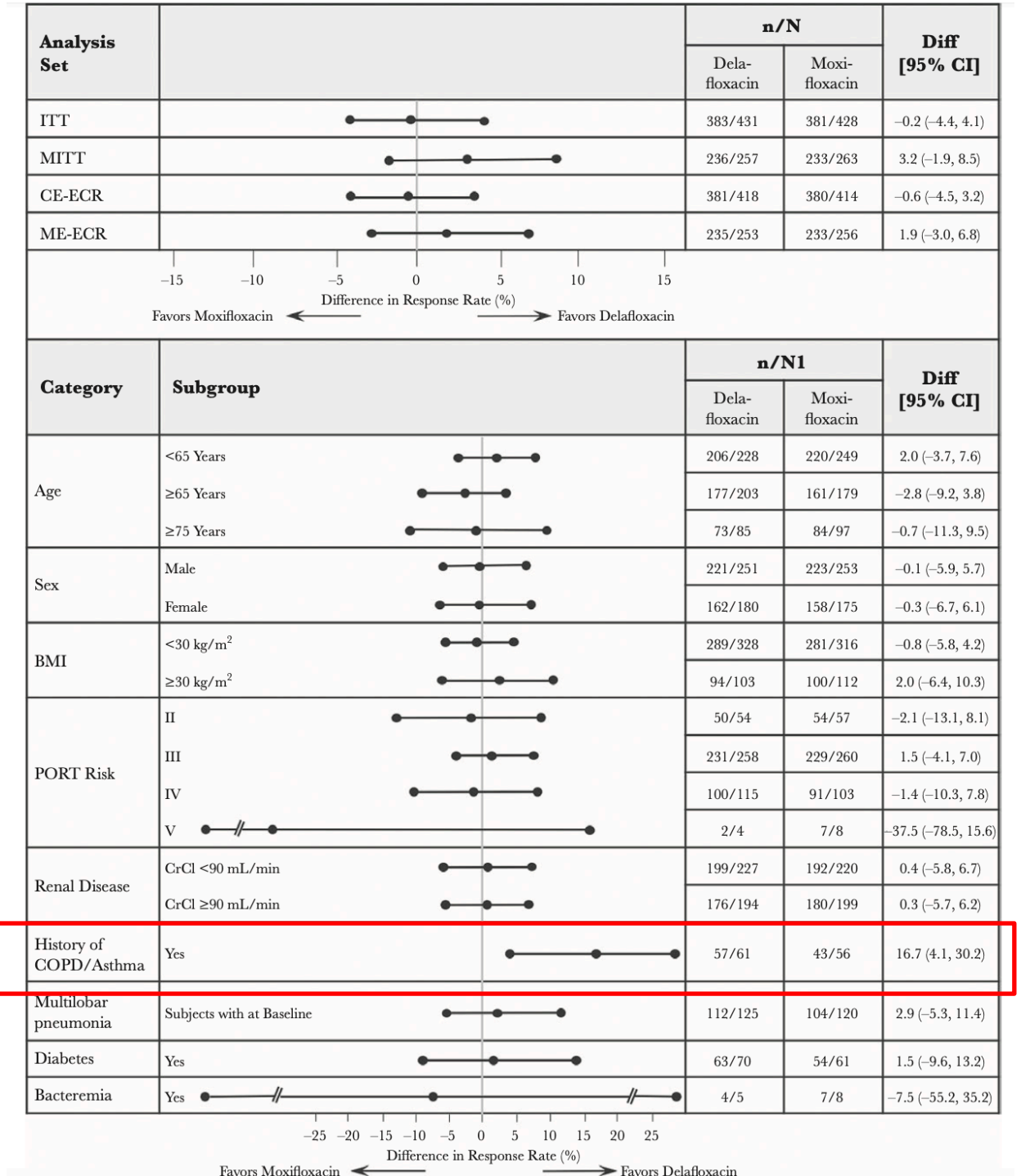
Pathogens Identified

Table 2. Pathogens Identified at Baseline in >1% of Subjects (MITT Population)

Baseline Pathogens	No. (%) of Subjects Total (n = 520)
Streptococcus pneumoniae	226 (43.5)
PSSP	102 (19.6)
PISP	25 (4.8)
PRSP	19 (3.7)
MDRSP	12 (2.3)
MRSP	35 (6.7)
Haemophilus parainfluenzae	76 (14.6)
Mycoplasma pneumoniae	65 (12.5)
Legionella pneumophila	62 (11.9)
Haemophilus influenzae	62 (11.9)
Staphylococcus aureus	57 (11.0)
MRSA	2 (0.4)
MSSA	55 (10.6)
Chlamydia pneumoniae	41 (7.9)
Klebsiella pneumoniae	33 (6.3)
Escherichia coli	27 (5.2)
Pseudomonas aeruginosa	24 (4.6)
Klebsiella oxytoca	10 (1.9)
Moraxella catarrhalis	12 (2.3)

Horcajada et al Infect Dis. 2019 Dec 5;7(1):ofz514

Early clinical response by analysis set and subgroup (ITT population)



Analysis Set		n/N Dela-floxacin	n/N Moxi-floxacin	Diff [95% CI]
ITT		383/431	381/428	−0.2 (−4.4, 4.1)
MITT		236/257	233/263	3.2 (−1.9, 8.5)
CE-ECR		381/418	380/414	−0.6 (−4.5, 3.2)
ME-ECR		235/253	233/256	1.9 (−3.0, 6.8)

−15 −10 −5 0 5 10 15

Difference in Response Rate (%)

Favors Moxifloxacin ← → Favors Delafloxacin

Category	Subgroup	n/N1 Dela-floxacin	n/N1 Moxi-floxacin	Diff [95% CI]
Age	<65 Years	206/228	220/249	2.0 (−3.7, 7.6)
	≥65 Years	177/203	161/179	−2.8 (−9.2, 3.8)
	≥75 Years	73/85	84/97	−0.7 (−11.3, 9.5)
Sex	Male	221/251	223/253	−0.1 (−5.9, 5.7)
	Female	162/180	158/175	−0.3 (−6.7, 6.1)
BMI	<30 kg/m^2	289/328	281/316	−0.8 (−5.8, 4.2)
	≥30 kg/m^2	94/103	100/112	2.0 (−6.4, 10.3)
PORT Risk	II	50/54	54/57	−2.1 (−13.1, 8.1)
	III	231/258	229/260	1.5 (−4.1, 7.0)
	IV	100/115	91/103	−1.4 (−10.3, 7.8)
	V	2/4	7/8	−37.5 (−78.5, 15.6)
Renal Disease	CrCl <90 mL/min	199/227	192/220	0.4 (−5.8, 6.7)
	CrCl ≥90 mL/min	176/194	180/199	0.3 (−5.7, 6.2)
History of COPD/Asthma	Yes	57/61	43/56	16.7 (4.1, 30.2)
Multilobar pneumonia	Subjects with at Baseline	112/125	104/120	2.9 (−5.3, 11.4)
Diabetes	Yes	63/70	54/61	1.5 (−9.6, 13.2)
Bacteremia	Yes	4/5	7/8	−7.5 (−55.2, 35.2)

−25 −20 −15 −10 −5 0 5 10 15 20 25

Difference in Response Rate (%)

Favors Moxifloxacin ← → Favors Delafloxacin

In ITT, ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group.

At TOC in the ITT population, the success rates were 90.5% in the delafloxacin treatment group and 89.7% in the moxifloxacin group.

Noninferiority of delafloxacin compared with moxifloxacin was demonstrated.

Response rates were similar in all subgroups analysed, except for subjects with COPD or asthma, where delafloxacin was better than moxifloxacin (93.4% vs. 76.8%; difference, 16.7%; 95% CI, 4.1% to 30.2%).

Abbreviations: CE, clinically evaluable; CI, con- fidence interval; ECR, early clinical response; ITT, intent-to-treat; LCL, 95% lower confidence limit; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; UCL, 95% upper confidence limit.

Horcajada et al Infect Dis. 2019 Dec 5;7(1):ofz514

Safety

Table 6. Treatment-Emergent Adverse Events of Special Interest by Type and Preferred Term (Safety Population)

	No. (%) of Subjects			
	Delafloxacin (n = 429)		Moxifloxacin (n = 427)	
MedDRA System Organ Class and Adverse Event (Preferred Term)	Total	Related[a]	Total	Related[a]
Total No. of AESIs[b]	35	25	34	16
Subjects with any AESI, No. (%)[b]	34 (7.9)	24 (5.6)	32 (7.5)	16 (3.7)
Hepatic-related events	22 (5.1)	16 (3.7)	12 (2.8)	8 (1.9)
Transaminases increased	13 (3.0)	11 (2.6)	6 (1.4)	4 (0.9)
ALT increased	4 (0.9)	2 (0.5)	2 (0.5)	1 (0.2)
Hepatic enzyme increased	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)
Hepatic steatosis	2 (0.5)	0	0	0
GGT increased	1 (0.2)	1 (0.2)	0	0
Hepatic lesion	0	0	1 (0.2)	0
Potential allergic reactions	8 (1.9)	6 (1.4)	4 (0.9)	3 (0.7)
Rash	2 (0.5)	2 (0.5)	0	0
Urticaria	2 (0.5)	2 (0.5)	0	0
Bronchospasm	1 (0.2)	0	1 (0.2)	0
Dermatitis allergic	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Gingival swelling	1 (0.2)	0	0	0
Hypersensitivity	1 (0.2)	1 (0.2)	0	0
Rash pruritic	0	0	1 (0.2)	1 (0.2)
Clostridium difficile diarrhea	2 (0.5)	2 (0.5)	1 (0.2)	0
C. difficile colitis	2 (0.5)	2 (0.5)	1 (0.2)	0
Hyperglycemia	2 (0.5)	0	7 (1.6)	2 (0.5)
Hyperglycemia	2 (0.5)	0	6 (1.4)	2 (0.5)
Blood glucose increased	0	0	1 (0.2)	0
Hypoglycemia	0	0	3 (0.7)	1 (0.2)
Hypoglycemia	0	0	3 (0.7)	1 (0.2)
Potential myopathy	0	0	5 (1.2)	2 (0.5)
Acute kidney injury	0	0	1 (0.2)	0
Blood creatinine phosphokinase increased	0	0	2 (0.5)	1 (0.2)
Blood creatinine increased	0	0	1 (0.2)	1 (0.2)
Myalgia	0	0	1 (0.2)	0
Potential QT prolongation	0	0	2 (0.5)	0
ECG QT prolonged	0	0	1 (0.2)	0
Sudden death	0	0	1 (0.2)	0

- Overall, 131 subjects (30.5%) in the delafloxacin group and 112 (26.2%) in the moxifloxacin group experienced TEAE.
- No subjects in either group manifested potential peripheral neuropathy, tendon disturbance, phototoxicity or potential aortic rupture/dissection.
- No subjects in the delafloxacin group experienced potential myopathy or QT interval prolongation, while 5 subjects (1.2%) and 2 subjects (0.5%) in the moxifloxacin group experienced potential myopathy or QT interval prolongation, respectively.
- A higher percentage of subjects in the delafloxacin group (5.1%) compared to the moxifloxacin group (2.8%) had hepatic TEAEs, with **increased transaminases** reported most frequently
- *Exclusion criteria in completed phase 3 trials also limit the generalizability of safety findings*

Horcajada et al Infect Dis. 2019 Dec 5;7(1):ofz514

Pharmacokinetic properties, route of administration

DELAFLOXACIN PK/PD

Absorption	• Peak plasma concentrations are reached at the end of the **1-hour** intravenous infusion. • **Oral bioavailability (59%)** : the 300 mg intravenous formulation and the 450 mg tablet are **bioequivalent in terms** of total exposure (AUC). • Delafloxacin can be administered with or without food as the total systemic exposure (AUC) is unchanged on an empty and full stomach. • Oral bioavailability can be significantly reduced if taken concomitantly with drugs or products that contain multi-valent metal cations such as **Al, Mg, Fe or Zn.**
Distribution	The **steady-state volume of distribution** is approximately 40 L, an amount almost equal to the total amount of water contained in the body. The binding of delafloxacin to plasma proteins is approximately **84%;**
Metabolism	Minimally metabolised by **CYP450**, it is directly glucuronated. Glucuronation is predominantly mediated by UGT1A1, UGT1A3 and UGT2B15.
Elimination	After a single IV/oral dose, **65% of the radioactivity is excreted in the urine** and 28% in the faeces. Higher PK variability was observed in patients with severe hepatic impairment, and total exposure was increased approximately 40% compared with controls.

The half-life of oral delafloxacin is approximately **14 hours**
The half-life of delafloxacin IV is approximately **10 hours**
Exhibits concentration-dependent antibacterial effects and the fAUC24/MIC ratio is the main pharmacodynamic (PD) determinant of efficacy.

Parameter	Delafloxacin IV (300 mg, every 12 h)	Delafloxacin PO (450 mg, every 12 h)	Levofloxacin PO (750 mg, every 24 h)	Ciprofloxacin PO (500 mg, every 12 h)	Moxifloxacin PO (400 mg, every 12 h)
V_d (l)	35–48		100	84–189[a]	119–189[a]
C_{max} (mg/l)	9.29	7.45	8.6	3.0	4.5
fC_{max} (mg/l)	1.49	1.19	5.3–6.5	1.8–2.4	2.25–3.15
$AUC_{0-\tau}$ (mg h/l)	30.8	23.4	90.7	13.7	48
$fAUC_{0-\tau}$ (mg h/l)	4.93	3.74	56.2–68.9	8.2–11.0	24–33.6
AUC_{24} (mg h/l)	61.6	46.8	90.7	27.4	48
$fAUC_{24}$ (mg h/l)	9.86	7.48	56.2–68.9	16.4–22.0	24–33.6
Protein binding	84%		24–38%	20–40%	30–50%
$T_{1/2}$ (h)	9.28±4.33	15.2±6.15	8.8	4–6	10–14
Elimination (urine:feces)	64.5%:28.4%[b]	50.2%:47.7%	87%:4%	57%:20–35%	20%:25%
Oral bioavailability	59%	58.8%	99%	70%	92%
Metabolism	Glucuronidation[c]		Limited?	Oxidation?	Sulfation, glucuronidation
ELF/plasma penetration ratio	13:1	na	2:1	2:1	6:1

Jorgensen SCJ, Infect Dis Ther. 2018 Jun;7(2):197-217. doi: 10.1007/s40121-018-0198-x.

RCP Delafloxacina

Overview

Delafloxacina

Indicazioni approvate	Negli adulti per il trattamento delle seguenti infezioni: • infezioni batteriche acute della cute e dei tessuti molli (ABSSSI) • polmonite acquisita in comunità (CAP) *quando si considera inappropriato l'uso di altri agenti antibatterici comunemente raccomandati per il trattamento iniziale di tali infezioni*
Indicazioni rimborsate	ABSSSI (con scheda di prescrizione AIFA)
Posologia	**EV: 300 mg ogni 12 h** **OS: 450 mg cpr per os ogni 12 ore** Se CrCl <30 ml/min il dosaggio deve essere ridotto a 200 mg per via endovenosa ogni 12 ore
Formulazioni	EV: confezioni da 10 flaconcini. Cpr:confezioni da 10 cpr
Modalità di preparazione EV	Delafloxacina deve essere ricostituito in condizioni asettiche, utilizzando 10,5 mL di destrosio 50 mg/mL (5%) soluzione iniettabile (D5W) o cloruro di sodio 9 mg/mL (0,9%) soluzione iniettabile per ciascun flaconcino da 300 mg.
Controindicazioni e precauzioni d'impiego	pazienti con storia di tendinopatie, miastenia gravis e neuropatie periferiche, anamnesi positiva per casi di aneurisma aortico e/o una dissezione dell'aorta

RCP Delafloxacina

Delafloxacin

Place in therapy

New Antibiotics for *Staphylococcus aureus* Infection: An Update from the World Association of Infectious Diseases and Immunological Disorders (WAidid) and the Italian Society of Anti-Infective Therapy (SITA)

Drug Class	Cephalosporins	Lipopeptides	Lipoglycopeptides	Oxazolidinones		Tetracyclines	Fluoroquinolones	
Drug Name	**Ceftobiprole**	**Ceftaroline**	**Telavancin**	**Dalbavancin**	**Oritavancin**	**Tedizolid**	**Omadacycline**	**Delafloxacin**
In vitro activity	MSSA, MRSA, CoNS, *streptococci*, penicillin-R *S. pneumoniae* and *E. faecalis* Gram-negative pathogens including *Pseudomonas aeruginosa*	MSSA, MRSA, hVISA, VISA, VRSA and DAP-non susceptible *S. aureus*, CoNS, *streptococci* penicillin-R *S. pneumoniae* Gram-negative pathogens excluding *Pseudomonas aeruginosa*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, *E. faecFalis*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB* Stable in the presence of ESBLs
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Protein synthesis	Protein synthesis	DNA replication
Type of activity	Bactericidal	Bactericidal	Bactericidal	Bactericidal	Bactericidal	Bacteriostatic	Bacteriostatic	Bactericidal
Half-life (h) - **Oral bioavailability (%)**	2–3	2–3	8	192–336	393	10 - 91	17–21 - 34.5	8 - 58.8
Doses, frequency and duration	IV: 500 mg over 2 h t.i.d.	IV: 600 mg over 60 min b.i.d./t.i.d. in severe infections	IV: 10 mg/kg q.d.	IV single-dose regimen 1500 mg over 30 min For sequential use: 1500 mg on day 1 and 1000/ 1500 mg every 2 weeks	IV single-dose regimen: 1200 mg over 3 h For sequential use: 1200 day 1 and then 800/1200 mg once week	Oral: 200 mg IV: 200 mg over 1 h q.d.	Oral: loading dose 450 mg, then 300 mg IV: loading dose 200 mg, then 100 mg over 30 min q.d.	Oral: 450 mg IV: 300 zmg over 1 h b.i.d.
Protein Binding (%) Excretion	16 Faeces: 6% Urine: 88%	20 Faeces: 6% Urine: 88%	90 Faeces: <1% Urine: <76%	93–98 Faeces: 20% Urine: 45%	85 Not metabolized	70–90 If oral: Faeces: 82% Urine: 18%	20 If oral: Faeces: N/A Urine: 27% If IV: Faeces: 81% Urine: 15%	84 If oral: Faeces: 28% Urine: 65% If IV: Faeces: 48% Urine: 50%
Doses adjustments not required for	CrCL > 50 mL/min	CrCL > 50 mL/min	CrCL > 50 mL/min	CrCL > 30 mL/min	Renal impairment, hepatic impairment	Hepatic dysfunction, renal dysfunction	Hepatic impairment, renal impairment	Body weight, hepatic impairment, mild-to-moderate renal impairment
FDA or EMA approval (Year and indications)	Not approved by the FDA 2009 ABSSSI, CAP, HAP	2010 ABSSSI, CAP	2009, ABSSSI, HAP, VAP	2014, ABSSSI	2014, ABSSSI	2014, ABSSSI	2018 ABSSSI, CAP	2017 and 2019, ABSSSI, CAP
Paediatrics Therapeutic indication	No data	Yes	No data	Yes	No data	Yes >12 years	Not approved	Not approved
Future directions and points of clinical interest	VAP	Primary SAB, complicated SAB secondary to non-ABSSSI causes (IE, OSM, or non-responsive to first line therapy)		OSM; prosthetic infection including IE, CLABSI, OPAT regimens	OSM; prosthetic infection including IE, CLABSI, OPAT regimens	OSM; HAP, or VAP due to MRSA Especially if resistant or intolerant to linezolid	HAP, biliary infections and OSM to allow early hospital discharge	HAP, MRSA OSM

- The advent of new oxazolidinones and cyclic lipopeptides, has increased therapeutic options for MDR Gram-positive pathogens, but new treatments for those pathogens are still required to keep up with the anticipated evolution of resistance.
- Sixteen products in the current pipeline show activity against one or more Gram-positive priority pathogens.
- Among them are two new antibiotic classes, and seven of the products are biological agents (monoclonal antibodies and endolysins).

Esposito, S.; Blasi, F.; Curtis, N.; Kaplan, S.; Lazzarotto, T.; Meschiari, M.; Mussini, C.; Peghin, M.; Rodrigo, C.; Vena, A.; et al. New Antibiotics for Staphylococcus aureus Infection: An Update from the World Association of Infectious Diseases and Immunological Disorders (WAidid) and the Italian Society of Anti-Infective Therapy (SITA). Antibiotics ***2023****,12,742.*

New-Generation Antibiotics for Treatment of Gram-Positive Infections: A *Review with Focus on Endocarditis and Osteomyelitis*

	Cephalosporins	Lipopeptides	Lipoglycopeptides			Oxazolidinones		Fluoroquinolones	Tetracyclines
	Ceftaroline	**Daptomycin**	**Telavancin**	**Dalbavancin**	**Oritavancin**	**Linezolid**	**Tedizolid**	**Delafloxacin**	**Omadacycline**
In vitro activity	MSSA, MRSA, CoNS, streptococci, some *Enterococcus faecalis* isolates	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, *E. faecalis*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*
No activity	*Enterococcus faecium*, VRE *vanA, vanB*		VRE *vanA*	VRE *vanA*				*E. faecium*, VRE *vanA, vanB*	
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Protein synthesis	Protein synthesis	DNA replication	Protein synthesis
FDA/EMA approved dosing regimen (for ABSSSI, unless otherwise mentioned)	600 mg b.i.d. IV	ABSSSI 4 mg/kg/day IVBSI/IE 6 mg/kg/day IV	10 mg/kg/day IV	1500 mg IV single doseAlternative: 1000 mg IV single dose at day 1, followed by 500 mg IV single dose at day 8	1200 mg IV single dose	600 mg b.i.d. IV / PO	200 mg q.d. IV / PO	300 mg b.i.d. IV OR450 mg b.i.d. PO	Loading dose: - IV: 200 mg q.d. on day 1 OR 100 mg b.i.d on day 1- PO (for ABSSSI only): 450 mg q.d. on day 1 and 2. Maintenance: - IV: 100 mg q.d. OR- PO: 300 mg q.d.

Bloem,A.;Bax,H.I.;Yusuf, E.; Verkaik, N.J. *J. Clin. Med.* **2021**, *10*, 1743.

THERAPEUTIC ADVANCES in
Infectious Disease

Case Report

'TAVR Infected Pseudomonas Endocarditis': a case report

Ther Adv Infect Dis

2022, Vol. 9: 1–8

DOI: 10.1177/20499361221138459

Francis Essien, Shane Patterson, Fernando Estrada, Timothy Wall, John Madden and Michael McGarvey

Abstract: *Pseudomonas aeruginosa* (*P. aeruginosa*) rarely causes infective endocarditis (IE), previously reported for approximately 3% of all patients with IE.[1] Most commonly, the infection occurs in intravenous drug users (IVDU) as right-sided endocarditis, noting presentations *of P. aeruginosa* IE without history of intravenous drug to be extremely rare, finding only a few cases reported in the literature. However there are increasing reports of cardiovascular implantable electronic device–related and prosthetic heart valve infections caused by this pathogen in non-IVDUs.[2] This report will focus on the clinical presentation, management, and outcome of *P. aeruginosa* endocarditis in an 89-year-old patient with a transcatheter aortic valve replacement (TAVR). Medical management was pursued due to the patient's underlying comorbidities. Long-term suppressive antibiotic therapy with delafloxacin was successful in maintaining negative blood cultures, despite an allergy to levofloxacin and ciprofloxacin.

Evaluation and Management of Diabetes-related Foot Infections

- DFI is common and can devastate patients' mobility, independence, and quality of life.
- Individuals with diabetes are prone to more frequent and severe infections, with many of these infections being polymicrobial (more frequently co-isolated: *Staphylococcus aureus* and *Pseudomonas aeruginosa)*.
- These patients are most likely to benefit from limb preservation efforts (high risk of decline in functional status with amputation)
- Modern RCTs of DFIs have used an IV-to-oral antibiotic switch strategy with IV durations as short as a median of 2 days, achieving high rates of cure.
- For At least 6-8 weeks of antibiotic therapy (OVIVA).
- But: worse outcomes with oral vs IV among patients with no defined pathogen
  & poorer outcomes with oral penicillin vs IV therapy.

Hyperglycemia potentiates increased *Staphylococcus aureus* virulence and resistance to growth inhibition by *Pseudomonas aeruginosa*

Nicolas W Cortes-Penfield, *Clinical Infectious Diseases*, Volume 77, Issue 3, 1 August 2023
Genito CJ, Darwitz BP, Microbiol Spectr. 2023 Nov 7:e0229923. doi: 10.1128/spectrum.02299-23.

Open Forum Infectious Diseases

PERSPECTIVES

Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV

Kusha Davar,[1] Devin Clark,[1] Robert M. Centor,[2] Fernando Dominguez,[1] Bassam Ghanem,[3] Rachael Lee,[4] Todd C. Lee,[5] Emily G. McDonald,[6] Matthew C. Phillips,[7,8] Parham Sendi,[9] and Brad Spellberg[1]

(1) the patient is clinically and hemodynamically stable;
(2) procedural source control ideally with clearance of bacteremia;
(3) the patient's gut is functioning and likely to absorb oral medications;
(4) a published regimen is available for the target pathogen

Table 2. Summary of Randomized Controlled Trials of Oral vs IV-Only Therapy

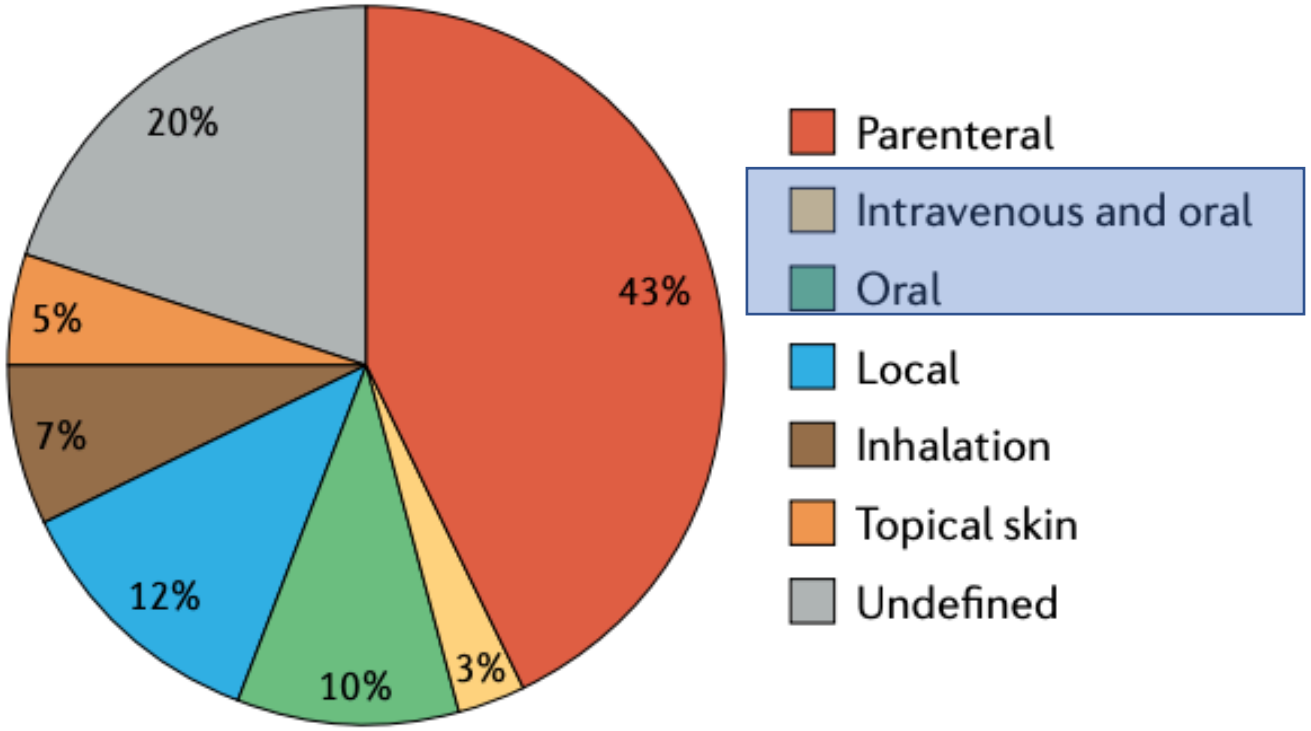
Diagnosis	No. of RCTs Demonstrating IV > Oral	No. of RCTs Demonstrating Oral ≥ IV	References
Osteomyelitis	0	9 (all equal)	[103–111]
Bacteremia	0	10 (8 equal, 2 superior cure for oral)	[109, 112–120]
Endocarditis	0	3 (2 equal, 1 superior mortality for oral)	[121–123]

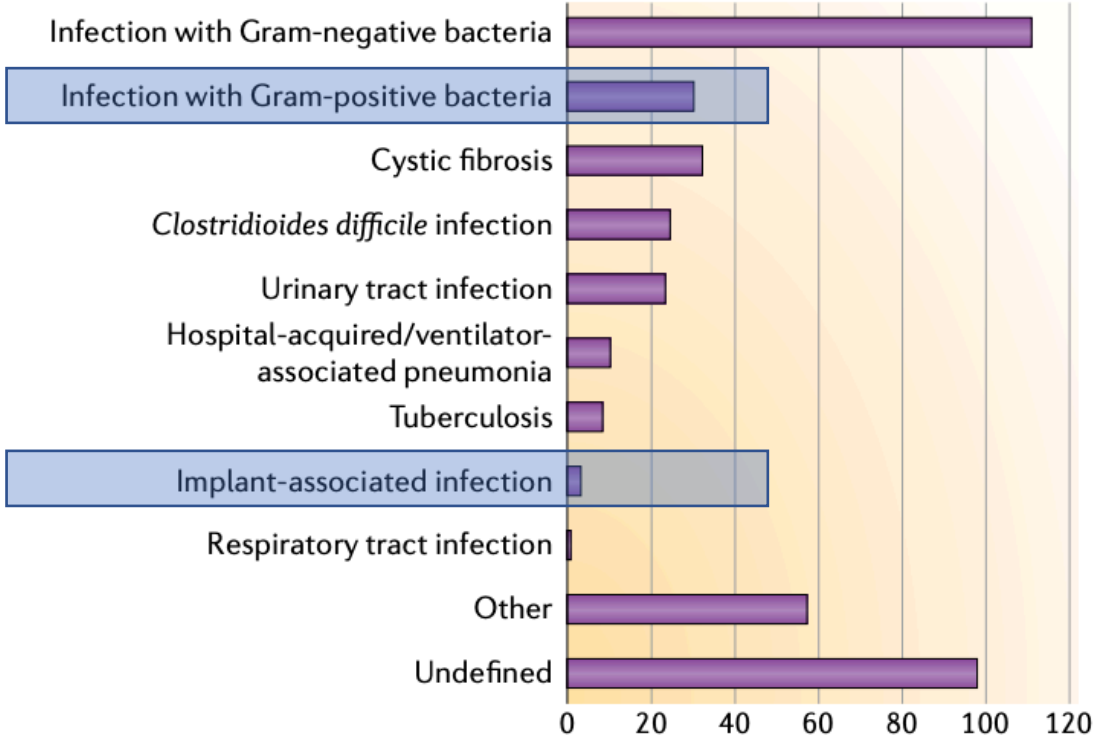
Abbreviations: IV, intravenous; RCT, randomized controlled trial.

With the shared goal of bettering patient care..
"Oral is the new IV" needs to be more than just a motto.
It is time to make that switch, both in our mind-set and in practice..

Davar K, et al. Open Forum Infect Dis. 2022 Dec 29;10(1):ofac706.
Clinical Microbiology and Infection 29 (2023) 1117e1119

Antibacterial approaches, development phase, indications and routes of administration in the preclinical pipeline





*Theuretzbacher, U., Outterson, K., Engel, A. et al. The global preclinical antibacterial pipeline. Nat Rev Microbiol **18**, 275–285 (2020).*

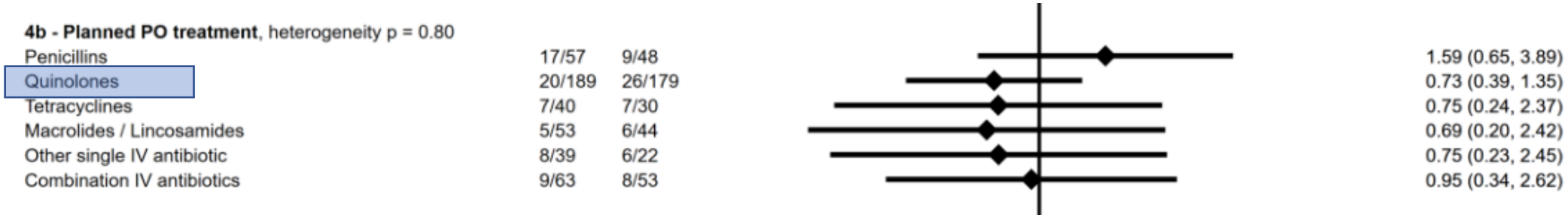
Are all antibiotics the same?

Group	**Antibiotics**
Group 1 Good oral bioavailability Oral dose = IV dose	Levo/Moxi Doxicyclin TMP/SMX Linezolid
Group 2 No-as-good oral bioavailability, *but* Oral dose >> IV dose	Ciprofloxacin **Delafloxacin**
Group 3 Good oral bioavailability Oral dose < IV dose	Amoxicillin Cefalexin Clindamycin
Group 4 No-as-good oral bioavailability Oral dose < IV dose	Ampicillin Cefuroxime Cloxacillin Cefixime

Adapted from: 2015 Can J Hosp Pharm, Béïque.

How should I switch to oral?

OVIVA trias: Forest plot of odds ratios (95% CI) for definitive treatment failure by subgroups (PO/IV)



Li HK, OVIVA Trial Collaborators. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019 Jan 31;380(5):425-436.

CHOICE OF ORAL ANTIBIOTICS from the POET trial

Methicillin resistant coagulase-negative staphylococci
1) Linezolid 0.6 g x 2 and fusidic acid
2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x2

Enterococcus faecalis:
1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
4) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Streptococci with a minimal inhibitory concentration for penicillin of ≥1 mg/L:
1) Linezolid 0,6 g x2 and rifampicin 0.6 g x 2
2) Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2
3) Moxifloxacin 0.4 g x 1 and clindamycin 06 g x3

Iversen K, N Engl J Med. 2019 Jan 31;380(5):415-424.

Oral switch for gram negative BSI: Post-randomisation antimicrobial therapy

Cephalosporin	44 (52%)	31 (35%)
Fluoroquinolone	2 (8%)	17 (19%)
Trimethoprim/sulfamethoxazole	1 (1%)	14 (16%)
Total duration of antimicrobial therapy	11 (8–14)	14 (11–16)

Ali S. Omrani, Clinical Microbiology and Infection, accepted 12 October 2023 https://doi.org/10.1016/ j.cmi.2023.10.014.

Are we ready for the change in the paradigm of antibiotic management?

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–3
https://doi.org/10.1093/eurheartj/ehad529

EDITORIAL
Valvular heart disease

A change in the paradigm of antibiotic management in infective endocarditis: are we ready?

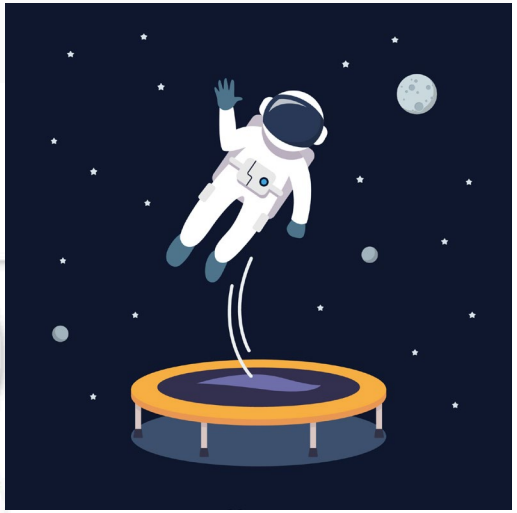
Nuria Fernández-Hidalgo [1,2,3]* **and Ignacio Ferreira-González** [2,4,5]

Antimicrobial Development and Drug Resistance (KC Claeys and J Smith, Section Editors)
Published: 31 October 2023

One Small Step (Down) for Antibiotics, One Giant Leap for Outpatient Therapy: The Role of Oral Antibiotics in Serious Bacterial Infections

Jessica K. Ortwine, Wenjing Wei, Norman S. Mang, Brenton C. Hall & Helen Ding

Current Infectious Disease Reports (2023) | Cite this article



Current options for completing antimicrobial treatment in most cases of IE due to gram-positive microorganisms

Acute phase of treatment
(includes surgery, if needed)

Hospitalization
IV antibiotics for 2-3 weeks

Consolidation phase of treatment

- **Continue hospitalization**
  IV antibiotics
- **Home**
  Conventional OPAT
- **Home**
  Switch to oral antibiotics
- **Home**
  Long-acting antibiotics

Clinical cases, real-life possible future purposes

O. ELENA 30/11/1981

»CAP escavata ascessualizzata da MSSA e sepsi da *Pseudomonas aeruginosa* e MSSA»

- Ricoverata in TIPO ricoverata per Insufficienza Multi-Organo nel contesto di severa polmonite bilaterale.
- Sottoposta a ventilazione non invasiva e successivamente a intubazione orotracheale (04/04-14/04),
- Impostata empiricamente terapia antibiotica inizialmente empirica con piperacillina/tazobactam + linezolid, successivamente meropenem (04/04-13/04) + oxacillina (dal 04/04 al 19/04), quest'ultima sospesa per sospetta reazione avversa (rash cutaneo).
- In data 20/04 per stabilità clinica veniva trasferita in Medicina dove iniziava nuovamente, su indicazione infettivologica, terapia antibiotica con cefepime (23/4) per persistenza di quadro febbrile, a fronte di un miglioramento del quadro clinico e laboratoristico.
- Reazione allergica anche a cefepime.
- **Quali opzioni terapeutiche alternativa al carbapenemico ev per allergia B-lattamici?**
- *Delafloxacina?*

K. IOANA 25/5/79

»CRBSI (Picc-relata) da MRSA e *Pseudomonas aeruginosa* »

- Attivata per pa oncologica in fase avanzata (prognosi a settembre di circa 1 anno) che entra in PS per iperpiressia associata ad ipotensione (90/50). Portatrice di PICC.
- Iniziata terapia con meropenem e vancomicina con buona risposta clinica MA
- Si esegue colloquio con il marito che sembra consapevole della severità del quadro clinico ed esprime il desiderio se le condizioni della moglie miglioreranno di tornare in Romania.
- **Quali opzioni terapeutiche alternativa per OPAT?**
- *Delafloxacina?*

B. ANGELA 18/03/1962

»SSI da MRSA e *Pseudomonas aeruginosa* in paziente sottoposta e quadrantectomia bilaterale»

- Esiti di quadrantectomia mammaria bilaterale esposore.
- A sinistra persiste deiscenza della ferita con necrosi della porzione superiore dell'areola. Si consegna l'esito dell'esame microbiologico: contaminazione da MRSA e Pseudomonas Aeruginosa.
- Si consigliava: Levofloxacina 750 mg cp, 1 cp al giorno per 6 giorni
- **Opzioni terapeutiche migliori per os?**
- *Delafloxacina?*

Sangue periferico es. colturale (flacone aerobio)

esito		vedi identificazione microbica
tempo di positivizzazione		0, 12:29
es. microscopico		Stafilococchi
identificazione microbica		sviluppo di :

Staphylococcus aureus

	SIR	MIC ug/ml
Cefoxitina screening	-	Neg
Oxacillina	S	*vedi nota*
Ceftarolina	S	0.25
Eritromicina	S	1
Clindamycin	S	0.25
Resistenza inducibile alla Clindamicina	-	Neg
Rifampicina	S	*vedi nota*
Levofloxacin	SE*	0.25
Trimetoprim - sulf.	S	*vedi nota*
Tetraciclina	S	*vedi nota*
Tigecycline	S	*vedi nota*
Gentamicina	S	*vedi nota*

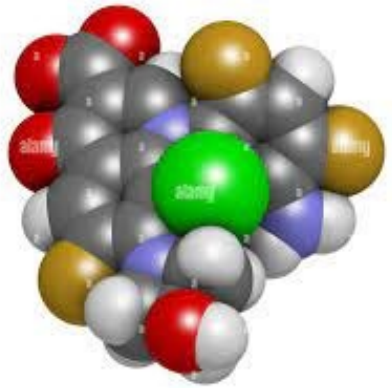
Sangue da CVC es. colturale (flacone anaerobio)

esito		vedi identificazione microbica	
tempo di positivizzazione		0, 18:35	gg, hh:mm
es. microscopico		Bacilli Gram negativi	
identificazione microbica		sviluppo di :	

Pseudomonas aeruginosa

	SIR	MIC ug/ml	Limite di sensibilità
Piperacillina - Tazob.	S	8	16
Cefotaxime	**R**	16	
Ceftazidime	S	2	8
Cefepime	S	2	8
Meropenem	S	0.5	2
Ciprofloxacina	S	0.25	0,5
Trimetoprim - sulf.	**R**	80	
Fosfomycin		<=16	
Tigecycline	**R**	>=8	
Gentamicina	S	2	4
Amikacina	S	4	8

Conclusions and future directions



Delafloxacin's, a new anionic FQ, has a chemical structure (**dual-targets**) that confers **major stability**, enhances the its **potency** and may reduce the **risk for selection of resistant** microbial strains

Delafloxacin showing potent antimicrobial activity against **gram-positive, gram-negative but also anaerobic** pathogens may allow for single-drug treatment of **polymicrobial infections**, such as decubitus ulcers, diabetic foot infections, osteomyelitis and intra-abdominal infections.

Delafloxacin also demonstrated higher concentrations **within the biofilms or abscesses** and high potency at the local acidic pH of the model. This model suggests that delafloxacin should be considered in further clinical trials evaluating infections related to biofilm formation such as **prosthetic infections.**

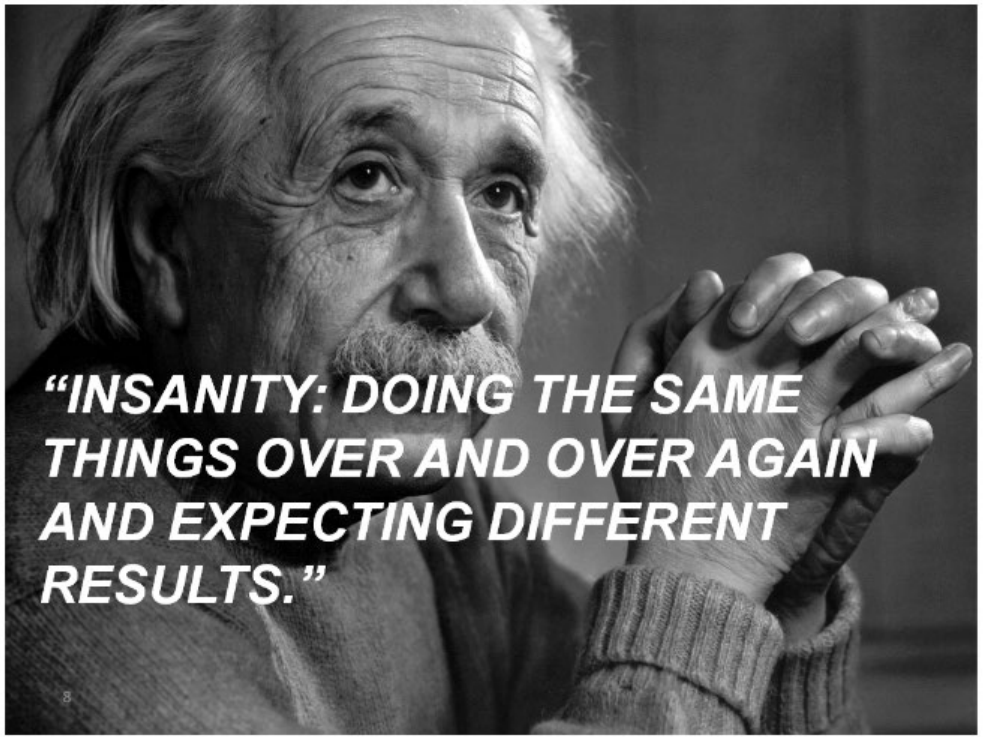
Among all the available antimicrobial agents, delafloxacin is the only one **available as both oral** and intravenous formulations with both **MRSA and P. aeruginosa** activity as of now.

Further clinical investigations will be necessary to determine whether delafloxacin exhibits a low **probability for selection of resistant mutants** in *S. aureus* as well as Gram-negative bacterial pathogens such as *P. aeruginosa*.

Additional clinical trials will help us to determine the clinical role for delafloxacin's use beyond the current FDA&EMA&AIFA approved indications.

Meschiari's Personal consideration

Thanks for your attention!



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