

## Delafloxacin Activity against *Staphylococcus aureus* with Reduced Susceptibility or Resistance to Methicillin, Vancomycin, Daptomycin or Linezolid

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### Introduction

- Delafloxacin (ABT 492) is a new fluoroquinolone that is available in both oral and parenteral formulations.
- Delafloxacin has been approved by the Food and Drug Administration (FDA) for the management of acute bacterial skin and skin structure infections.
- Delafloxacin's *in vitro* activity and favorable clinical response against MRSA infections distinguishes it from other fluoroquinolones.
- This research focused on evaluating delafloxacin's activity against MRSA strains including blood isolates and isolates with reduced susceptibility or resistance to daptomycin, vancomycin, linezolid, and levofloxacin.
- We also evaluated activity based upon SCC *mec* typing.

### Materials

- A collection of 183 isolates were selected for *in vitro* testing.
- Vancomycin resistant *S. aureus* (VRSA)(n=15), vancomycin intermediate *S. aureus* (VISA) (n=31), linezolid resistant *S. aureus* (LRSA) (n=4) and, heteroresistant VISA (hVISA) (n=1), were obtained from the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) program (now known as BEI Resources).
- Two LRSA isolates were obtained from Robinson Memorial Center in Ohio. The remaining samples were isolates from Ascension-St. John Hospital.

### Methods

- The minimal inhibitory concentration (MIC) of delafloxacin (DFX), levofloxacin (LEV), vancomycin (VAN), daptomycin (DAP), ceftaroline (CPT) and linezolid (LZD) were determined by broth microdilution testing using cation-adjusted Mueller Hinton broth.
- All testing was performed per CLSI guidelines and all plates were prepared in house. All plates were inoculated with approximately  $5 \times 10^8$  CFU/ml of each isolate and incubated at 35°C for 18 to 24 hours.
- S. aureus* ATCC 29213 was used to monitor quality control for all the agents. MICs were read visually as the lowest drug concentration well with no visible bacterial growth.
- FDA breakpoints were used to determine delafloxacin susceptibility and CLSI breakpoints were used to determine susceptibility for all the other agents.
- Minimal bactericidal concentrations (MBC) were also determined, following CLSI guidelines. All testing was performed in triplicate.
- Staphylococcal cassette chromosome *mec* element (SCC) types were determined by a multiplex PCR method (Zhang et al. 2005, JCM43:5026-5033). Isolates that were non-typeable with the multiplex PCR were analyzed using primers identified by Okuma (2002, JCM 46:2155-2161)

### Antibiotic Breakpoints:

- S = Susceptible
- I = Intermediate
- SDD = Susceptible-dose dependent
- R = Resistant
- NS = Non-susceptible

Antibiotic	S ≤	I =	R ≥
Delafloxacin	S ≤ 0.25	I = 0.5	R ≥ 1.0
Levofloxacin	S ≤ 1.0	I = 2.0	R ≥ 4.0
Vancomycin	S ≤ 2.0	I = 4.0 - 8.0	R ≥ 16.0
Daptomycin	S ≤ 1.0	NS ≥ 1.0	
Ceftaroline	S ≤ 1.0	SDD = 2.0 - 4.0	R ≥ 8.0
Linezolid	S ≤ 4.0		R ≥ 8.0

### Results

**Table 1: MRSA results of blood isolates (n=110) collected at Ascension St. John Hospital**

Isolate and Agent	MIC						MBC		
	Range	MIC	MIC	% S	% I	% R	Range	MBC <sub>50</sub>	MBC <sub>90</sub>
<b>2016-2018 MRSA</b>									
Delafloxacin	0.004-->4.0	0.25	1	68%	14%	18%	0.004-->4.0	0.5	2
Levofloxacin	0.25-->16	4	>16	38%	0%	62%	0.25-->16	8	>16
Vancomycin	0.5--4.0	1	1	99%	1%	0%	0.5--4.0	1	2
Daptomycin	0.25--4.0	0.5	1	96%	NS= 4%		0.25--4	0.5	1
Ceftaroline	0.25--2.0	0.5	1	99%	SDD= 1%	0%	0.25--2.0	0.5	1
Linezolid	1.0--4.0	2	2	100%	0%	0%	8-->8.0	>8.0	>8.0

**Table 2a: MIC results of blood isolates (n=64) identified as SCC type IVA**

Isolate and Agent	MIC			% S	% I	% R
	Range	MIC	MIC			
<b>SCC IVA (2016-2018)</b>						
Delafloxacin	0.008-0.5	0.25	0.25	94%	6%	0%
Levofloxacin	0.25-8.0	4	8	44%	0%	56%

**Table 2b: MIC results of blood isolates (n=16) identified as SCC type IVB**

Isolate and Agent	MIC			% S	% I	% R
	Range	MIC	MIC			
<b>SCC IVB (2016-2018)</b>						
Delafloxacin	0.004-2.0	0.008	0.008	88%	0%	12%
Levofloxacin	0.25->16	0.25	1	88%	0%	12%

**Table 2c: MIC results of blood isolates (n=30) identified as SCC type IIA**

Isolate and Agent	MIC			% S	% I	% R
	Range	MIC	MIC			
<b>SCC IIA (2016-2018)</b>						
Delafloxacin	0.25-->4.0	1	1	3%	37%	60%
Levofloxacin	4-->16	>16	>16	0%	0%	100%

**Table 3: Delafloxacin results from 55 (of 110) isolates tested with a levofloxacin MIC ≥ 8.0 mcg/ml.**

2016-2018 Isolates	MIC	≥ 8.0 mcg/ml			MBC				
		≤0.25	0.5	≥1.0					
<b>Isolate and Agent</b>									
Range	MIC	MIC	% S	% I	% R	Range	MBC	MBC	
LEV MIC ≥ 8.0									
Delafloxacin	0.25-->4.0	0.5	1	36.4%	27.2%	36.4%	0.25-->4.0	1	2

**Table 4a: Results from 40 (of 183) isolates identified as Daptomycin Non-susceptible**

Isolate and Agent	MIC						MBC		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	% S	% I	% R	Range	MBC <sub>50</sub>	MBC <sub>90</sub>
<b>DAP NS</b>									
Delafloxacin	0.008-->4	0.5	1	38%	30%	32%	0.008-->4.0	0.5	2
Levofloxacin	0.25-->16	>16	>16	15%	0%	85%	0.25-->16	>16	>16
Vancomycin	1.0--8.0	4	8	35%	65%	0%	1.0--8.0	4	8
Daptomycin	2.0--8.0	2	4	0%			2.0--16	2	4
Ceftaroline	0.25--1.0	0.5	1	100%	0%	0%	0.25--2.0	1	1
Linezolid	1.0--2.0	2	2	100%	0%	0%	4.0-->8.0	>8.0	>8.0

**Table 4b: Results from 35 (of 183) isolates identified as Vancomycin Intermediate**

Isolate and Agent	MIC						MBC		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	% S	% I	% R	Range	MBC <sub>50</sub>	MBC <sub>90</sub>
<b>VISA</b>									
Delafloxacin	0.008--1.0	0.5	1	40%	31%	29%	0.008--2.0	0.5	1
Levofloxacin	0.25-->16	16	>16	9%	0%	91%	0.25-->16	16	>16
Vancomycin	4.0--8.0	4	8	0%	100%	0%	4.0--8.0	4	8
Daptomycin	0.5--8.0	2	4	26%	NS=74%		1.0--16	2	4
Ceftaroline	0.25--1.0	0.5	1	100%	0%	0%	0.25--2.0	1	2
Linezolid	1.0--4.0	2	2	100%	0%	0%	4.0-->8.0	8	>8

**Table 4c: Results from 15 (of 183) isolates identified as Vancomycin Resistant**

Isolate and Agent	MIC						MBC		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	% S	% I	% R	Range	MBC <sub>50</sub>	MBC <sub>90</sub>
<b>VRSA</b>									
Delafloxacin	0.12--4.0	1	4	7%	40%	53%	0.12-->4.0	1	4
Levofloxacin	8.0-->16	>16	>16	0%	0%	100%	8.0-->16	>16	>16
Vancomycin	32-->64	>64	>64	0%	0%	100%	64-->64	>64	>64
Daptomycin	0.25--1.0	0.5	1	100%	NS=0%		0.25--1	0.5	1
Ceftaroline	0.25--1.0	0.5	1	100%	0%	0%	0.25--1	1	1
Linezolid	1.0--4.0	2	2	100%	0%	0%	4.0-->8.0	8	>8

**Table 4d: Results from 6 (of 183) isolates identified as Linezolid Resistant**

Isolate and Agent	MIC						MBC		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	% S	% I	% R	Range	MBC <sub>50</sub>	MBC <sub>90</sub>
<b>Linezolid Resistant</b>									
Delafloxacin	0.5-->4.0	0.5	0%	50%	50%	0%	1.0-->4.0	1	
Levofloxacin	16-->16	>16	0%	0%	100%	0%	16-->16	>16	
Vancomycin	1.0--2.0	1	100%	0%	0%	0%	1.0--2.0	1	
Daptomycin	0.5--1.0	0.5	100%	NS=0%			0.5--1.0	0.5	
Ceftaroline	0.5--1.0	1	100%	0%	0%	0%	1	1	
Linezolid	>8	>8	0%	0%	100%	0%	>8	>8	

### Conclusions

- Among SCC IVA strains delafloxacin demonstrated a high level of susceptibility (94%) compared to levofloxacin (44%). Both delafloxacin and levofloxacin demonstrated poor activity against the genotype SCC II with 3% and 0% susceptibility, respectively. Since the genotype SCC IVA is most often community-acquired one should anticipate that delafloxacin will be more active against *Staphylococcus aureus* arising in the community than in the hospital.
- Delafloxacin demonstrated some activity against DNSSA and VISA at 38% and 40% respectively. Delafloxacin is generally not active against VRSA and LRSA.
- When evaluating delafloxacin against isolates with levofloxacin MIC's ≥ 8 mcg/ml suggesting the presence of quinolone resistance-determining regions, delafloxacin was active against 36.4% of strains.
- In vitro* activity for delafloxacin will vary based upon resistance to other antimicrobial agents and genetic markers including the number of quinolone resistance-determining region mutations, thus necessitating the need for performance of susceptibility testing to assist in clinical decision making.

