Activity of Fusidic Acid Tested Against Contemporary *Staphylococcus aureus* Collected from United States Hospitals

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Abstract

Background: Fusidic acid (FA) is an established anti-staphylococcal agent used in clinical practice in Europe, Australia and Canada for at least three decades. FA is currently under clinical development for therapy of acute bacterial skin and skin-structure infections (ABSSSI) in the USA. This study assessed the activities of FA and comparators tested against *S. aureus* isolates.

Methods: *S. aureus* (7,340) were collected from 51 institutions distributed within all USA census regions in 2008 – 2009. Identification was performed by standard algorithms and Vitek 2. Isolates were tested for susceptibility (S) by CLSI methods (M07-A8 and M100-S20). *S. aureus* were analyzed based on resistance (R) patterns. A pan-R pattern was defined as *S. aureus* exhibiting a R phenotype to at least 5 antimicrobial classes (projected breakpoint).

Results: Isolates were mainly from bacteremia (46.0%), SSSI (31.5%) and respiratory tract infections (16.6%). Overall, FA inhibited 99.6% of tested *S. aureus* at ≤1 µg/mL. FA ($MIC_{50/90}$, 0.12/0.25 µg/mL) and tigecycline (TG; $MIC_{50/90}$, 0.12/0.25 µg/mL; 100.0% S) showed equivalent activity against *S. aureus*, while FA was two- to 16-fold more active than daptomycin (DA; $MIC_{50/90}$, 0.25/0.5 µg/mL; 99.9% S), vancomycin (VA; $MIC_{50/90}$, 1/1 µg/mL; 100.0% S) and linezolid (LZ; $MIC_{50/90}$, 2/2 µg/mL; 99.9% S). Gentamicin (97.9% S), tetracycline (95.5% S) and trimethoprim/sulfamethoxazole (98.6% S) also exhibited coverage against nearly all *S. aureus*. FA had consistent modal MIC and MIC_{50} values (0.12 µg/mL) across all R subsets. Only FA (MIC_{90}, 0.25 µg/mL), TG (MIC_{90}, 0.25 µg/mL), DA (MIC_{90}, 0.5 µg/mL), VA (MIC_{90}, 1 µg/mL) and LZ (MIC_{90}, 2 µg/mL) sustained potency against strains with pan-R patterns.

Conclusion: FA demonstrated potent activity against this current collection of *S. aureus* from USA hospitals. FA activity was comparable to TG, which were at least two-fold more active than other agents with similar clinical indications.

Organism/ Resistance pattern[a] (no. tested/% of total)	Number (cumulative %) inhibited at MIC (µg/mL)							
	≤0.06	0.12	0.25	0.5	1	2	4	8
All *S. aureus* (7,340/100.0)	1070(14.6)	**5327(87.2)**[b]	826(98.4)	70(99.4)	20(99.6)	10(99.8)	9(99.9)	8(100.0)
2008 *S. aureus* (3,962/54.0)	397(10.0)	**3066(87.4)**	434(98.4)	48(99.6)	5(99.7)	3(99.8)	3(99.8)	6(100.0)
2009 *S. aureus* (3,378/46.0)	673(19.9)	**2261(86.9)**	392(98.5)	22(99.1)	15(99.6)	7(99.8)	6(99.9)	2(100.0)
MRSA (3,877/52.8)	493(12.7)	**2884(87.1)**	435(98.3)	38(99.3)	15(99.7)	8(99.9)	3(>99.9)	1(100.0)
MSSA (3,463/47.2)	577(16.7)	**2443(87.2)**	391(98.5)	32(99.4)	5(99.6)	2(99.6)	6(99.8)	7(100.0)
OX, ER, CP (1,364/18.6)	149(10.9)	**1017(85.5)**	184(99.0)	9(99.6)	3(99.9)	2(100.0)	–	–
OX, ER, CL, CP (1,156/15.7)	97(8.4)	**859(82.7)**	168(97.2)	20(99.0)	7(99.6)	4(99.9)	1(100.0)	–
OX, ER (751/10.2)	141(18.8)	**574(95.2)**	27(98.8)	3(99.2)	4(99.7)	0(99.7)	2(100.0)	–
ER (729/10.0)	115(15.8)	**523(87.5)**	83(98.9)	5(99.6)	1(99.7)	1(99.9)	1(99.9)	1(100.0)
ER, CP (177/2.4)	27(15.3)	**125(85.9)**	20(97.2)	2(98.3)	2(99.4)	1(100.0)	–	–
OX, CL, CP (137/1.9)	23(16.8)	**104(92.7)**	7(97.8)	2(99.3)	0(99.3)	0(99.3)	0(99.3)	1(100.0)
ER, CL, CP (112/1.5)	12(10.7)	**83(84.8)**	16(99.1)	1(100.0)	–	–	–	–
Pan-R (170/2.4)	31(18.2)	**116(86.5)**	22(99.4)	22(99.0)	0(99.0)	1(100.0)	–	–

a. Most prevalent resistance patterns noted among *S. aureus*. MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*. CL, clindamycin; CP, ciprofloxacin; ER, erythromycin; and OX, oxacillin. Pan-R = pan resistance phenotype (resistance to at least 5 antimicrobial classes). Criteria for susceptibility were those published by CLSI (M100-S20, 2010). Intermediate and resistant results grouped as resistant.
b. Modal MIC and MIC_{50} values are bold, while MIC_{90} results are underlined.

Introduction

Fusidic acid was first isolated in 1962 from *Fusidium coccineum*. This antimicrobial agent interacts with elongation factor G (EF-G), preventing its release from the ribosome and thereby inhibiting bacterial protein synthesis. Resistance to fusidic acid is primarily considered to be caused by mutations on the EF-G-encoding gene; however, acquired fusidic acid resistance mechanisms have also been described in clinical strains. These mobile genes, named *fusB* and *fusC*, can be chromosomal- or plasmid-mediated and were shown to protect EF-G from binding with fusidic acid molecules.

Fusidic acid has been used in Europe and Australia since the 1960's and in Canada since 1980; however this compound has not been licensed by the United States (USA) Food and Drug Administration (FDA); and it is not currently available for prescription in the USA. This belated introduction of fusidic acid into this country may now be viewed as positive in that it provides an additional antistaphylococcal agent with low toxicity and a unique mechanism of action that is devoid of cross resistance to other classes of antibacterials (including methicillin-resistant *Staphylococcus aureus* [MRSA]). Furthermore, the extensive foreign experience with fusidic acid in the treatment of serious staphylococcal infections over the past four decades provides a wealth of information about optimal use, particularly with regards to the implementation of dosing/delivery strategies to delay or avoid the development of resistance.

In this study, we evaluated the activity of fusidic acid against *S. aureus* isolates collected in USA medical centers during 2008 and 2009. Isolates were categorized according to different resistance patterns and mechanisms of resistance were evaluated for those strains showing elevated fusidic acid MIC results (≥2 µg/mL).

Materials and Methods

Bacterial strains. A total of 7,340 *S. aureus* strains collected during 2008 and 2009 in 51 USA hospitals, located in the nine Census Regions were analyzed as part of the SENTRY Antimicrobial Surveillance Program. These isolates were collected from bloodstream, respiratory tract, and skin and skin-structure infections (SSSI), according to defined protocols. Only one isolate per patient from documented infections were included. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux, Hazelwood, MO) or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. Isolates were susceptibility tested by a reference broth microdilution procedure as described by the Clinical and Laboratory Standards Institute (CLSI; 2009) using validated microdilution panels manufactured by TREK Diagnostics (Cleveland, OH, USA). Categorical interpretations for all antimicrobials were those found in M100-S20-U and quality control (QC) was performed using *Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212. All QC results were within specified ranges as published in CLSI documents. For fusidic acid, the interpretive susceptibility criteria of the EUCAST group (2010) were applied at ≤1 µg/mL.

Detection of fusidic acid resistance mechanisms. All strains displaying fusidic acid MIC at ≥2 µg/mL were tested for the presence of acquired *fusB*, *fusC* and *fusD* in a multiplex PCR approach. Detection of *fusD* (intrinsic of *S. saprophyticus*) was included in this reaction to detect strains that were incorrectly identified as other staphylococcal species.

Constitutive genes *fusA* and *fusE* were amplified and sequenced using Extensor Hi-fidelity Master Mix (ABGene, Sussex, United Kingdom) as well as custom and previously described oligonucleotides. Sequencing was performed in five and two reactions, respectively. The nucleotide sequences and deduced amino acid sequences were analyzed using the Lasergene software package (DNASTAR, Madison, WI) and compared with sequences available through the internet using BLAST (http://www.ncbi.nlm.nih.gov/blast/).

Results

- Among 7,340 *S. aureus* collected in USA medical centers, 46.0% were recovered from bloodstream infections, 31.5% from SSSI and 16.6% from respiratory tract infections.
- Fusidic acid inhibited 99.6% of the *S. aureus* at ≤1 µg/mL (EUCAST susceptibility breakpoint). Twenty-seven (0.4%) strains showed MIC values at ≥2 µg/mL.
- Fusidic acid was comparably active against *S. aureus* strains categorized into eight different resistance groups, including isolates resistant to five or more compounds (pan-resistant [pan-R] e.g., MIC_{50} at 0.12 µg/mL for all eight groups, Table 1). The most common groups included resistances to oxacillin, erythromycin, clindamycin, and the fluoroquinolones.
- Among the orally administered agents evaluated (linezolid, tetracycline and trimethoprim/sulfamethoxazole), fusidic acid (modal MIC_{50} at 0.12 µg/mL and MIC_{90} at ≤0.25 µg/mL) displayed activity comparable to linezolid (>99.3% coverage at 2 µg/mL for all *S. aureus*; see Table 1).
- Among the 27 fusidic acid non-susceptible strains detected, 15 (55.5%) harbored acquired genes, including three strains (11.1% of the non-susceptible strains) positive for *fusB* and 12 strains (44.4%) positive for *fusC*.
- Mutations on *fusA* were detected in four strains [14.8% of the 27 (0.4%) resistant strains], all MRSA. These isolates carried previously described mutations M453I (one strain), L461S (one strain) and P404L combined with A71V (two strains from the same medical site).
- A 21-amino acid deletion on *fusE* was detected in two genetically similar (clonal) USA300-like strains from the same hospital. These strains demonstrated slow growth in culture media, suggesting a fitness cost for these small colony variants.

Table 2. Resistance mechanisms to fusidic acid detected in *S. aureus* isolated in the United States (2008-2009).

Year (no.)	%MRSA	no. sites	No. by mechanism[a]			
			fusA	*fusB*	*fusC*	*fusE*
2008 (12)	33.3	7	M453I[b]	1	7	2[c]
2009 (14)	50.0	12	L461S, A71V+P404L(2)[d]	2	5	-
MRSA (11)	-	8	L461S, M453I, A71V+P404L(2)[d]	-	-	2[c]
MSSA (15)	-	11	-	3	12	-

a. *fusD* only observed in *S. saprophyticus*.
b. *fusA* mutation site.
c. Clonal occurrence of two strains in a Michigan hospital.
d. Clonal occurrence of two strains in an Oregon site.

Table 1. Antimicrobial activity of fusidic acid and comparator antimicrobial agents when tested against *Staphylococcus aureus* stratified by resistance patterns from USA medical centers (2008-2009).

Organism group/ Resistance pattern Antimicrobial agent (no. strains)[a]	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
Staphylococcus aureus (All; 7,340)					
Fusidic acid	0.12	0.25	≤0.06 – 8	- / -	99.6 / 0.4
Linezolid	2	2	≤0.06 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	≤2	≤2 – >8	95.5 / 3.8	94.5 / 5.5
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.6 / 1.4	98.6 / 1.4
Daptomycin	0.25	0.5	≤0.06 – 4	99.9 / -	99.9 / 0.1
Tigecycline[c]	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
2008 (3,962)					
Fusidic acid	0.12	0.25	≤0.015 – 8	- / -	99.7 / 0.3
Linezolid	2	2	0.25 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	≤2	≤2 – >8	95.5 / 3.9	94.8 / 5.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5 / 1.5	98.5 / 1.5
Daptomycin	0.25	0.5	≤0.06 – 4	99.8 / -	99.8 / 0.2
Tigecycline[c]	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
2009 (3,378)					
Fusidic acid	0.12	0.25	≤0.06 – 8	- / -	99.6 / 0.4
Linezolid	2	2	≤0.06 – >8	99.9 / 0.1	99.9 / 0.1
Tetracycline	≤2	≤2	≤2 – >8	95.4 / 3.7	94.2 / 5.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.6 / 1.4	98.6 / 1.4
Daptomycin	0.25	0.5	≤0.06 – 2	>99.9 / -	>99.9 / <0.1
Tigecycline[c]	0.12	0.25	≤0.03 – 1	>99.9 / -	>99.9 / <0.1
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
MRSA (3,877)					
Fusidic acid	0.12	0.25	≤0.06 – 8	- / -	99.7 / 0.3
Linezolid	2	2	0.25 – >8	99.8 / 0.2	99.8 / 0.2
Tetracycline	≤2	≤2	≤2 – >8	94.9 / 4.6	93.5 / 6.5
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.4 / 1.6	98.4 / 1.6
Daptomycin	0.25	0.5	≤0.06 – 4	99.7 / -	99.7 / 0.3
Tigecycline[c]	0.12	0.25	≤0.03 – 1	99.9 / -	99.9 / 0.1
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (3,463)					
Fusidic acid	0.12	0.25	≤0.06 – 8	- / -	99.6 / 0.4
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	96.1 / 2.9	95.6 / 4.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.7 / 1.3	98.7 / 1.3
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
ER + CP + OX-R (1,364)					
Fusidic acid	0.12	0.25	≤0.06 – 2	- / -	99.9 / 0.1
Linezolid	2	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	99.2 / 0.8
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
ER + CL + CP + OX-R (1,156)					
Fusidic acid	0.12	0.25	≤0.06 – 4	- / -	99.6 / 0.4
Linezolid	2	2	0.25 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	97.1 / 2.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
ER + OX-R (751)					
Fusidic acid	0.12	0.12	≤0.06 – 4	- / -	99.7 / 0.3
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	99.7 / 0.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	≤0.25	≤0.25	≤0.25 – 0.5	100.0 / 0.0	98.9 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Quinupristin/dalfopristin	0.5	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
ER-R (729)					
Fusidic acid	0.12	0.25	≤0.06 – 8	- / -	99.7 / 0.3
Linezolid	2	2	≤0.06 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	99.6 / 0.4
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
ER + CP-R (177)					
Fusidic acid	0.12	0.25	≤0.06 – 4	- / -	99.4 / 0.6
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	99.4 / 0.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
CL + CP + OX-R (137)					
Fusidic acid	0.12	0.12	≤0.06 – 8	- / -	99.3 / 0.7
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 4	100.0 / 0.0	99.3 / 0.7
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	0.06 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
ER + CL + CP-R (112)					
Fusidic acid	0.12	0.25	≤0.06 – 0.5	- / -	100.0 / 0.0
Linezolid	2	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	97.1 / 2.9	97.1 / 2.9
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Tigecycline[c]	0.12	0.25	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Pan-R (170)					
Fusidic acid	0.12	0.25	≤0.06 – 2	- / -	99.4 / 0.6
Linezolid	1	2	0.25 – >8	97.1 / 2.9	97.1 / 2.9
Tetracycline	8	>8	≤2 – >8	45.9 / 48.2	42.9 / 57.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	77.6 / 22.4	77.6 / 22.4
Daptomycin	0.25	0.5	≤0.06 – 4	95.3 / -	95.3 / 4.7
Tigecycline[c]	0.12	0.25	0.06 – 1	98.8 / -	98.8 / 1.2
Vancomycin	1	1	0.25 – 2	100.0 / 0.0	100.0 / 0.0

a. Most prevalent resistance patterns noted among *S. aureus*. MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*. CL, clindamycin; CP, ciprofloxacin; ER, erythromycin; and OX, oxacillin. Pan-R = pan resistance phenotype (resistance at least 5 antimicrobial classes).
b. Criteria as published by the CLSI [2010] and EUCAST [2010]. β-lactam susceptibility should be directed by the oxacillin test results.
c. USA-FDA breakpoints were applied [Tygacil Product Insert, 2005].

Conclusions

- Fusidic acid non-susceptible strains (0.4% overall) showed varying resistance mechanisms. Plasmid-mediated resistance genes, such as *fusB* and *fusC* can be co-selected by the use of antimicrobial agents other than fusidic acid.
- Although 99 to 100% of the resistant groups analyzed were susceptible to vancomycin, tigecycline, daptomycin, and linezolid according to CLSI interpretive criteria, fusidic acid was comparable or up to eight-fold more potent than these agents against these important multidrug-resistant (MDR) pathogens and is an agent that can be orally delivered.
- Fusidic acid exhibited potent activity against nearly all *S. aureus* (0.4% non-susceptible) similar to parenteral-only agents (daptomycin, tigecycline and vancomycin) and linezolid (modal MIC_{50} at 0.12 µg/mL and MIC_{90} at ≤0.25 µg/mL), emphasizing the usefulness of this antimicrobial agent to treat staphylococcal infections caused by MDR organisms in the USA.

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