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Activity of Fusidic Acid against Recent Clinical Isolates of Staphylococci Collected from United States Hospitals in 2016 as Part of the SENTRY Antimicrobial Surveillance Program D SHORTRIDGE, JM STREIT, PR RHOMBERG, RK FLAMM JMI Laboratories, North Liberty, Iowa, USA

Amended Abstract

Introduction: Fusidic acid (FA) is being studied in the United States as a targeted treatment for acute bacterial skin and skin structure infection and other infections caused by gram-positive pathogens. This study used 1,378 staphylococci isolates collected from 38 US hospitals in 2016 as part of the SENTRY Antimicrobial Surveillance Program.

Methods: Tested isolates from skin and skin structure infections and bloodstream infections were composed of 1,064 Staphylococcus aureus (SA) and 314 coagulase-negative staphylococci (CoNS). A central monitoring laboratory (JMI Laboratories) used the CLSI broth microdilution method to determine susceptibilities to FA and comparators. Other agents tested included vancomycin (VAN), daptomycin (DAP), clindamycin (CLN), trimethoprim-sulfamethoxazole (T-S) and linezolid (LZD). Interpretive criteria used for FA were EUCAST (2016), and CLSI (2016) criteria were used for the other comparators.

Results: FA and comparator susceptibilities (S) are shown in the table. For SA that included methicillin-resistant SA (MRSA), 99.9% had FA MICs ≤1.0 µg/mL, the EUCAST breakpoint for staphylococci. Against CoNS, 94.9% had FA MICs \leq 1.0 µg/mL. For MR-CoNS, 93.2% had MICs ≤1.0 µg/mL compared to CLN and T-S, which had 52.2% S and 51.2%S, respectively, with CLSI breakpoints

Conclusions: Against staphylococci, FA was among the most active oral agents and had activity for SA similar to VAN, DAP, and LZD. These data show that FA is a potent agent against SA in the US and support its continued development to treat staphylococcal infections.

MIC_{50/90} (µg/mL) and % susceptibility of FA and comparators

No.	FA ^a	VAN ^b	DAP ^b	CLNb	T-S [♭]	LZD ^b
1,064	0.12/0.12 (99.9)	0.5/1.0 (100.0)	0.25/0.5 (100.0)	≤0.25/>2 (85.5)	≤0.5/≤0.5 (98.0)	1.0/1.0 (100.0)
451	0.06/0.12 (100.0)	0.5/1.0 (100.0)	0.25/0.5 (100.0)	≤0.25/>2 (70.7)	≤0.5/≤0.5 (96.7)	0.5/1.0 (100.0)
314	0.12/0.12 (94.9)	1.0/2.0 (100.0)	0.25/0.5 (100.0)	≤0.25/>2 (65.6)	≤0.5/>4 (63.7)	0.5/1.0 (96.8)
207	0.12/0.12 (93.2)	1.0/2.0 (100.0)	0.25/0.5 (100.0)	≤0.25/>2 (52.2)	2.0/>4 (51.2)	0.5/1.0 (95.2)
	No. 1,064 451 314 207	No.FAa1,0640.12/0.12 (99.9)4510.06/0.12 (100.0)3140.12/0.12 (94.9)2070.12/0.12 (93.2)	No.FAaVANb $1,064$ $0.12/0.12$ (99.9) $0.5/1.0$ (100.0) 451 $0.06/0.12$ (100.0) $0.5/1.0$ (100.0) 314 $0.12/0.12$ (94.9) $1.0/2.0$ (100.0) 207 $0.12/0.12$ (93.2) $1.0/2.0$ (100.0)	No.FAaVANbDAPb $1,064$ $0.12/0.12$ $(99.9)0.5/1.0(100.0)0.25/0.5(100.0)4510.06/0.12(100.0)0.5/1.0(100.0)0.25/0.5(100.0)3140.12/0.12(94.9)1.0/2.0(100.0)0.25/0.5(100.0)2070.12/0.12(93.2)1.0/2.0(100.0)0.25/0.5(100.0)$	No.FAaVANbDAPbCLNb $1,064$ $0.12/0.12$ $0.5/1.0$ $0.25/0.5$ $<0.25/>2$ 451 $0.06/0.12$ $0.5/1.0$ $0.25/0.5$ $<0.25/>2$ 100.0 $0.5/1.0$ $0.25/0.5$ $<0.25/>2$ 314 $0.12/0.12$ $1.0/2.0$ $0.25/0.5$ $<0.25/>2$ 207 $0.12/0.12$ $1.0/2.0$ $0.25/0.5$ $<0.25/>2$ (93.2) $1.0/2.0$ $0.25/0.5$ $<0.25/>2$ (100.0) $1.0/2.0$ (100.0) $<0.25/0.5$	No.FAaVANbDAPbCLNbT-Sb $1,064$ $0.12/0.12$ $(99.9)0.5/1.0(100.0)0.25/0.5(100.0)0.25/2(85.5)0.5/20.5(98.0)4510.06/0.12(100.0)0.5/1.0(100.0)0.25/0.5(100.0)0.25/2(70.7)0.5/20.5(96.7)3140.12/0.12(94.9)1.0/2.0(100.0)0.25/0.5(100.0)0.25/25(65.6)0.5/24(63.7)2070.12/0.12(93.2)1.0/2.0(100.0)0.25/0.5(100.0)0.25/25(52.2)2.0/24(51.2)$

^ª EUCAST (2016) [♭] CLSI (2016)

Introduction

- Fusidic acid (CEM-102) is a steroidal antibiotic that possesses a well-characterized potency against gram-positive bacteria such as staphylococci, including methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative staphylococcal species (CoNS)
- Europe has used fusidic acid (FA) for many years for acute therapy of skin and skin structure infections, and for long-term treatment of bone and joint infections.

- staphylococci

- when necessary
- (S) to FA and comparators
- (LZD)

- Figure
- breakpoint for staphylococci

• FA has never been used in the US and an oral formulation is currently being studied in clinical trials as a targeted treatment for acute bacterial skin and skin structure infections and other infections caused by

 Resistance rates for staphylococci to other commonly used outpatient therapies such as cephalexin, trimethoprim-sulfamethoxazole (T-S) and clindamycin (CLN) are increasing in the US

• In this study, FA and comparators were tested against 1,378 staphylococci isolates collected from 38 US hospitals in 2016 as part of the SENTRY Antimicrobial Surveillance Program

Materials and Methods

• A total of 1,378 non-duplicated staphylococci isolates were collected prospectively from 38 US medical centers

 Tested isolates from skin and skin structure infections and bloodstream infections were composed of 1,064 Staphylococcus aureus (SA) and 314 coagulase-negative staphylococci (CoNS)

 Submitting laboratories identified isolates, and JMI Laboratories confirmed isolate identification by using standard techniques that included biochemical tests, matrix-assisted laser desorption ionizationtime of flight mass spectrometry (MALDI-TOF), and DNA sequencing,

The CLSI broth microdilution method was used to determine susceptibilities

- Other agents tested included: vancomycin (VAN), daptomycin (DAP), clindamycin (CLN), trimethoprim-sulfamethoxazole (T-S) and linezolid

- EUCAST (2017) interpretive criteria were used for FA (S \leq 1 and R >1 mg/L), and CLSI (2017) criteria were used for other comparators

Results

• FA and comparators susceptibilities are shown in Table 1

• FA MIC distributions for MRSA, methicillin-susceptible SA (MSSA), MR-CoNS and methicillin-susceptible CoNS (MS-CoNS) are shown in

For SA including MRSA, 99.9% had FA MICs ≤1.0 µg/mL, the EUCAST

One MSSA isolate was resistant (R) to FA with an MIC of 2.0 µg/mL

The highest MRSA MIC was 0.5 µg/mL

• For SA, 85.5% were S to CLN, and 70.7% of MRSA were S to CLN

98.0% of SA and 96.7% of MRSA were S to T-S

Organism/				EUCAST ^a			
antimicrobial agent (no. of							
isolates)	MIC ₅₀	MIC ₉₀	% S	%	%R	% S	%
Staphylococcus aureus (n=1,064)							
Fusidic acid	0.12	0.12				99.9	
Clindamycin	≤0.25	>2	85.5	0	14.5	85.4	0.1
Vancomycin	0.5	1	100	0	0	100	
Linezolid	1	1	100		0	100	
Tetracycline	≤0.5	≤0.5	97.4	0.4	2.3	95.1	1.3
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	98		2	98	0.3
Daptomycin	0.25	0.5	100			100	
MRSA (n=451)							
Fusidic acid	0.06	0.12				100	
Clindamycin	≤0.25	>2	70.7	0	29.3	70.7	0
Vancomycin	0.5	1	100	0	0	100	
Linezolid	0.5	1	100		0	100	
Tetracycline	≤0.5	≤0.5	97.3	0.2	2.4	94.7	2.4
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	96.7		3.3	96.7	0.4
Daptomycin	0.25	0.5	100			100	
Coagulase-negative staphylococcia (n	=314)						
Fusidic acid	0.12	0.12				94.9	
Clindamycin	≤0.25	>2	65.6	1.3	33.1	64.6	1
Vancomycin	1	2	100	0	0	100	
Linezolid	0.5	1	96.8		3.2	96.8	
Tetracycline	≤0.5	>8	84.7	0	15.3	83.1	1.3
Trimethoprim-sulfamethoxazole	≤0.5	>4	63.7		36.3	63.7	23.9
Daptomycin	0.25	0.5	100			100	
MR-CoNS ^b (n=207)							
Fusidic acid	0.12	0.12				93.2	
Clindamycin	≤0.25	>2	52.2	1.4	46.4	51.7	0.5
Vancomycin	1	2	100	0	0	100	
Linezolid	0.5	1	95.2		4.8	95.2	
Tetracycline	≤0.5	>8	79.2	0	20.8	77.8	1.4
Trimethoprim-sulfamethoxazole	2	>4	51.2		48.8	51.2	32.9
Daptomycin	0.25	0.5	100			100	

^a Organisms include: Staphylococcus capitis (19), S. cohnii (2), S. epidermidis (216), S. haemolyticus (13), S. hominis (43), S. lugdunensis (11), S. petrasii (1), S. pettenkoferi (5), S. schleiferi (2), S. warneri (2) ^b Organisms include: Staphylococcus capitis (3), S. cohnii (2), S. epidermidis (166), S. haemolyticus (10), S. hominis (21), S. lugdunensis (1), S. pettenkoferi (4)

- No isolates were R to VAN, DAP, or LZD
- Against CoNS, 94.9% had FA MICs of $\leq 1.0 \mu g/mL$ with 16 R isolates, using EUCAST breakpoints
- 14 MR-CoNS had MICs in the range of 2 to 8 µg/mL
- 2 MS-CoNS had MICs of 8 µg/mL
- 65.6% were S to CLN and 63.7% were S to T-S
- For MR-CoNS, 93.2% had FA MICs of ≤1.0 µg/mL compared to CLN and T-S, which had 52.2%S and 51.2%S, with CLSI breakpoints, respectively

Conclusions

- Against staphylococci, FA was among the most potent oral agents tested
- FA had activity for SA similar to VAN, DAP, and LZD
- Only 1.2% of staphylococci had FA MICs >1 µg/mL, suggesting that R to FA (based on EUCAST breakpoints) in the US is very low
- 1 SA and 16 CoNS had FA MICs >1 µg/mL (Figure 1)
- These data show that FA is a potent agent against SA in the US and support continued development to treat staphylococcal infections

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MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; MS-CoNS, methicillin-susceptible coagulase-negative staphylococci

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References

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%R

3.6

1.7

29.3

2.9

5.1

34.4

3.2

15.6

12.4

47.8

4.8

20.8

15.9



https://www.jmilabs.com/data/posters/ASMMicrobe17 -fusidic-acid.pdf

Figure 1 MIC distribution of fusidic acid for MRSA, MSSA, MR-CoNS, and MS-CoNS