CEM-102 (Fusidic Acid) In Vitro Activity and Evaluation of Molecular Resistance Mechanisms Among European Gram-positive Isolates (2008-2009)

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Amended Abstract

Objectives: To evaluate the activity of fusidic acid (FA) among Gram-positive bacteria collected in European medical centres in the 2008-2009 period and to analyze the prevalence of FA resistance (R) mechanisms among staphylococci (2008).

Methods: A total of 7,504 strains collected from 29 European (EU) medical sites located in 13 countries were susceptibility (S) tested by CLSI reference broth microdilution against FA and comparator agents. 336 *Staphylococcus* spp. (2008 only) displaying FA MIC at ≥2 mg/L were tested for the presence of *fusB*, *fusC* and *fusD* and mutations on *fusA* and *fusE* (FA primary and secondary active site).

Results: FA was very active against all staphylococci displaying a MIC_{50} of 0.12 mg/L regardless of methicillin-resistant (MR) profile. Applying EUCAST breakpoints (none available for CLSI), 90.7% of *S. aureus* (SA) strains were S to FA, with lower rates observed among MRSA (77.9%). Coagulase-negative staphylococci (CoNS) demonstrated 36.7% R against FA (14/867 *S. saprophyticus* with intrinsically elevated FA MIC). MRCoNS displayed 40.5% of FA-R. FA demonstrated moderate activity against enterococci and streptococci, with MIC_{50} values for beta-haemolytic, group A, B and viridians group streptococci, *S. pneumoniae* and enterococci ranging from 4 to >8 mg/L. Among 336 staphylococci (FA MIC, ≥2 mg/L), the presence of acquired FA-R genes was detected in 64.9% of the strains (36.6% *fusB* and 28.3% *fusC*). *fusB* and *fusC* rates among FA-R strains were 10.1 and 16.9% for SA and 26.5 and 11.3% for CoNS, respectively. *fusA* mutations were detected in 56 of 62 FA-R SA, most common being aminoacid alterations on position 461 (Leu to Lys/Ser). One SA showed a mutation on *fusE* (Q140L). Ireland and Greece showed the highest SA FA-R rates with high prevalence of L461K *fusA* mutation (clinical outbreaks). Low staphylococci FA-R rates (1.4-3.1%) were observed in Israel, Italy, Poland, Spain and Sweden.

	MIC (mg/L)		EUCAST[a]
Organism (no. tested)	50%	90%	S%/R%
S. aureus (3,898)	0.12	0.5	90.7/9.3
MSSA (2,894)	0.12	0.25	95.1/4.9
MRSA (1,004)	0.12	>8	77.9/22.1
CoNS (867)	0.12	>8	63.3/36.7
MSCoNS (176)	0.12	8	78.4/21.6
MRCoNS (691)	0.25	>8	59.5/40.5
β-haemolytic Streptococci (374)	8	>8	-/-
Group A Streptococci (137)	4	8	-/-
Group B Streptococci (160)	8	>8	-/-
Viridans Group Streptococci (167)	>8	>8	-/-
S. pneumoniae (930)	8	>8	-/-
Enterococcus spp. (1,268)	4	4	-/-

a. "-" no interpretative criteria have been established.

Conclusions: FA appears to be a valuable alternative to other anti-MRSA oral agents in the treatment of serious staphylococci infections. Despite the long term of FA clinical use in European countries, staphylococci R rates are still remarkably low except in clonal occurrences in a minority of institutions.

Introduction

Fusidic acid (CEM-102) is an antimicrobial agent isolated from *Fusidium coccineum* that has been used in clinical practice in Europe since the early 1960s for the treatment of skin and skin structure infections (SSSI) as well as bone and joint infections, caused by indicated Gram-positive organisms. Only limited contemporary understanding of fusidic acid resistance at genetic, epidemiological and clinical levels is available, and prescribing practices are mostly based on outmoded data obtained from studies with small numbers of patients.

Fusidic acid binds to elongation factor G (EF-G) preventing its release from the ribosome and thus, stalling protein synthesis. For several years, mutations on *fusA*, the gene encoding EF-G was postulated to be the primary cause of resistance against this antimicrobial agent, although strains carrying these mutations were predominantly laboratory mutants that were exposed to this compound. Plasmid-mediated resistance has also been described and genes encoding proteins that play a protective role on EF-G have more recently been identified. The genes encoding these proteins are known as *fusB*, *fusC* and *fusD*, the latter identified to cause intrinsic fusidic acid resistance in *Staphylococcus saprophyticus*. Novel dosing regimens to maximize pharmacodynamic features and minimize the selection of resistant mutants have been designed achieving at least 80 mg/L concentrations of fusidic acid at trough.

In this study, we evaluated the activity of fusidic acid against 7,504 Gram-positive strains collected during 2008 and 2009 from European countries. Additionally, mechanisms of fusidic acid resistance were evaluated among 336 staphylococcal strains collected in 2008.

Materials and Methods

Bacterial isolates. A total of 7,504 Gram-positive isolates collected from 29 European medical sites from 13 countries were analyzed in the SENTRY Antimicrobial Surveillance Program. Only one isolate per patient from documented infections were included in this prevalence design study. Isolates were collected from bloodstream, respiratory tract and skin structures infections (SSSI) according to a common protocol. Species identification was confirmed by standard biochemical tests, the Vitek System (bioMerieux, Hazelwood, MO) or 16S rRNA sequencing, when necessary.

Antimicrobial susceptibility testing. All strains were tested for antimicrobial susceptibility using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI M07-A8). Cation-adjusted Mueller-Hinton broth was used in validated panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Categorical interpretations for all antimicrobials were those found in M100-S20 and quality control (QC) was performed using *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within specified ranges as published in CLSI documents.

Detection of fusidic acid resistance mechanisms. Among 443 staphylococcal strains from 2008 displaying fusidic acid MIC at ≥2 mg/L, 336 (not related to outbreaks in specific institutions) were tested for the presence of *fusB*, *fusC* and *fusD* via a multiplex PCR approach.

Strains presenting negative results for *fusB*, *fusC* and *fusD*, and/or showing highly elevated fusidic acid MIC values (≥512 mg/L) were evaluated for detection of mutations in *fusA* or *fusE*. Amplification was performed with specific primers and amplicons were sequenced in five and two reactions, respectively. The nucleotide sequences and deduced amino acid sequences were analyzed using the Lasergene software package (DNASTAR, Madison, Wisconsin, USA) and compared with sequences available through the internet using BLAST (http://www.ncbi.nlm.nih.gov/blast/).

Results

- Overall, 90.7% of the *S. aureus* strains were susceptible to fusidic acid using current EUCAST breakpoint (1 mg/L; Table 1).
- Fusidic acid resistance rates were higher among MRSA when compared to MSSA strains (22.1% and 4.9%, respectively).
- Other orally administered antimicrobial agents providing good coverage against all *S. aureus* were: tetracycline, clindamycin and levofloxacin with susceptibility rates of 90.9, 88.7 and 73.2%, respectively. All MSSA and MRSA strains were susceptible to linezolid (Table 1).
- Using the EUCAST breakpoint criteria, 63.3% of the coagulase-negative staphylococci (CoNS) strains were susceptible to fusidic acid. Oxacillin-resistant CoNS were more resistant to fusidic acid than oxacillin-susceptible strains (40.5 and 21.6%, respectively). Fourteen (1.6%) CoNS were *S. saprophyticus* displaying intrinsically elevated fusidic acid MIC values due to the presence of *fusD*.
- *S. pneumoniae* strains displayed more elevated fusidic acid MIC values (MIC_{50}, 8 mg/L; 80 mg/L trough level with novel loading dose regimen). Comparator agents showed good coverage of pneumococci strains, with the lowest susceptibility rates observed for erythromycin and penicillin (Table 1).
- Fusidic acid demonstrated moderate activity against β-haemolytic and viridians group streptococci with MIC values ranging from 2 to >8 mg/L.
- Fusidic acid activity against enterococci was moderate, and MIC_{50} and MIC_{90} values were at 4 mg/L. Linezolid showed comparable potency against these organisms, covering 99.8% of the strains.
- Acquired fusidic acid resistance genes, *fusB* and *fusC*, were detected in 64.9% (218/336) of tested fusidic acid resistant strains (Table 2).
- The gene *fusB* was more prevalent among the CoNS strains compared to *S. aureus* (26.5 versus 10.1%, respectively; Table 2), whereas *fusC* was similarly detected in both monitored staphylococcal groups (16.9% of CoNS and 11.3% of *S. aureus*). Both *fusB* and *fusC* generally confer low-level resistance (MICs, 4-16 mg/L).
- Mutations on *fusA* were only detected in 16.6% (56/336) of the 62 screened fusidic acid-resistant strains. The aminoacid alteration L461K was the most frequent mutation, being detected alone in 32 strains (MIC, ≥512 mg/L), followed by L461S (10 strains) H457Y (3), P404L (2), A376V (1), F441Y (1), V90A (1), V90I (2) and the combinations D189V/L430S, T387I/E449K, A70V/A160V/H457Y, V90I/H457Q/L461K (1 strain each; Table 2).
- One strain from Ireland harboured a mutation on *fusE*, encoding the alteration Q140L.
- Ireland and Greece exhibited the highest fusidic acid resistance levels among *S. aureus* with low rates of acquired resistance genes (Table 2). Strains from these countries displayed highly elevated MIC values (≥512 mg/L), presence of EF-G L461K alteration and proven clonal occurrences within hospitals were detected (data not shown).
- Low *S. aureus* fusidic acid resistance rates (1 to 3%) were observed in Germany, Israel, Italy, Poland, Spain and Sweden. Strains with modestly elevated fusidic acid MIC values (≤64 mg/L) showed a great diversity of acquired fusidic acid resistance mechanisms.
- Acquired fusidic acid resistance genes (*fusB* and *fusC*) were detected in the majority of fusidic acid-resistant strains from Belgium, France, Italy, Sweden, Switzerland, Turkey and United Kingdom (72.2 to 92.9% of strains classified as resistant) and were slightly less common in Germany, Spain and Israel (61.3 to 66.7% of strains classified as resistant; Table 2).

Table 1. Antimicrobial activity (MIC in mg/L) of fusidic acid (CEM-102) and comparator antimicrobial agents when tested against Gram-positive strains collected during 2008-2009 in European medical centres.

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (3,989)				
Fusidic Acid (CEM-102)	0.12	0.5	- / -	90.7 / 9.3
Oxacillin	0.5	>2	74.2 / 25.8	74.2 / 25.8
Erythromycin	≤0.25	>2	70.7 / 28.0	71.8 / 28.0
Clindamycin	≤0.25	>2	88.7 / 11.0	88.0 / 11.3
Linezolid	2	2	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	16	74.2 / 25.8	- / 25.8
Tetracycline	≤2	≤2	90.9 / 8.5	90.6 / 9.4
Levofloxacin	≤0.5	>4	73.2 / 26.2	73.2 / 26.2
MSSA (2,894)				
Fusidic Acid (CEM-102)	0.12	0.25	- / -	95.1 / 4.9
Oxacillin	0.5	1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	83.9 / 14.7	85.0 / 14.7
Clindamycin	≤0.25	≤0.25	97.7 / 2.2	97.2 / 2.3
Linezolid	2	2	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	99.9 / 0.1	- / 0.0
Tetracycline	≤2	≤2	94.3 / 5.2	93.9 / 6.1
Levofloxacin	≤0.5	≤0.5	94.0 / 5.5	94.0 / 5.5
MRSA (1,004)				
Fusidic Acid (CEM-102)	0.12	>8	- / -	77.9 / 22.1
Oxacillin	>2	>2	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	32.7 / 66.1	33.7 / 66.1
Clindamycin	≤0.25	>2	62.8 / 36.6	61.8 / 37.2
Linezolid	2	2	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	16	>16	0.0 / 100.0	0.0 / 100.0
Tetracycline	≤2	>8	81.3 / 17.9	81.0 / 19.0
Levofloxacin	>4	>4	13.3 / 85.9	13.3 / 85.9
CoNS (876)				
Fusidic Acid (CEM-102)	0.12	>8	- / -	63.3 / 36.7
Oxacillin	>2	>2	20.3 / 79.7	20.3 / 79.7
Erythromycin	>2	>2	35.8 / 63.7	36.0 / 63.7
Clindamycin	≤0.25	>2	68.2 / 30.0	65.3 / 31.8
Linezolid	1	1	99.7 / -	99.7 / 0.3
Amoxicillin/clavulanate	2	>16	20.3 / 79.7	- / 79.7
Tetracycline	≤2	>8	84.8 / 13.6	79.0 / 21.0
Levofloxacin	4	>4	43.7 / 53.5	43.7 / 53.5
MS (176)				
Fusidic Acid (CEM-102)	0.12	8	- / -	78.4 / 21.6
Oxacillin	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	65.3 / 34.1	65.3 / 34.1
Clindamycin	≤0.25	≤0.25	94.3 / 4.5	93.2 / 5.7
Linezolid	1	1	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	100.0 / 0.0	- / 0.0
Tetracycline	≤2	4	90.3 / 8.0	87.5 / 12.5
Levofloxacin	≤0.5	≤0.5	91.5 / 8.5	91.5 / 8.5
MR (691)				
Fusidic Acid (CEM-102)	0.25	>8	- / -	59.5 / 40.5
Oxacillin	>2	>2	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	28.2 / 71.2	28.5 / 71.2
Clindamycin	≤0.25	>2	61.5 / 36.5	58.2 / 38.5
Linezolid	1	1	99.6 / -	99.6 / 0.4
Amoxicillin/clavulanate	2	>16	0.0 / 100.0	0.0 / 100.0
Tetracycline	≤2	>8	83.4 / 15.1	76.8 / 23.2
Levofloxacin	4	>4	31.5 / 65.0	31.5 / 65.0
β-haemolytic streptococci (374)				
Fusidic Acid (CEM-102)	8	>8	- / -	- / -
Penicillin	≤0.015	0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	80.5 / 18.2	80.5 / 18.2
Clindamycin	≤0.25	≤0.25	90.3 / 8.8	91.2 / 8.8
Linezolid	1	1	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	- / -	100.0 / 0.0
Tetracycline	≤2	>8	55.1 / 42.8	55.1 / 44.9
Levofloxacin	≤0.5	1	100.0 / 0.0	94.7 / 0.0
Group A streptococci (137)				
Fusidic Acid (CEM-102)	4	8	- / -	- / -
Penicillin	≤0.015	≤0.015	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	≤0.25	92.0 / 6.6	92.0 / 6.6
Clindamycin	≤0.25	≤0.25	97.8 / 2.2	97.8 / 2.2
Linezolid	1	1	100.0 / -	100.0 / 0.0
Imipenem	≤1	≤1	- / -	100.0 / 0.0
Amoxicillin/clavulanate	≤2	≤2	90.5 / 8.0	90.5 / 9.5
Tetracycline	≤0.5	2	100.0 / 0.0	89.1 / 0.0
Levofloxacin	4	8	- / -	- / -
Group B streptococci (160)				
Fusidic Acid (CEM-102)	8	>8	- / -	- / -
Penicillin	0.06	0.06	100.0 / -	100.0 / 0.0
Erythromycin	≤0.25	>2	71.3 / 27.5	71.3 / 27.5
Clindamycin	≤0.25	>2	83.6 / 15.1	84.9 / 15.1
Linezolid	1	1	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	- / -	100.0 / 0.0
Tetracycline	>8	>8	23.8 / 75.6	23.8 / 76.3
Levofloxacin	≤0.5	1	100.0 / 0.0	98.1 / 0.0
Viridans group streptococci (167)				
Fusidic Acid (CEM-102)	>8	>8	- / -	- / -
Penicillin	0.06	1	77.2 / 6.0	84.4 / 6.0
Erythromycin	≤0.25	>2	63.5 / 33.5	- / -
Clindamycin	≤0.25	≤0.25	91.6 / 7.8	92.2 / 7.8
Linezolid	1	1	100.0 / -	- / -
Amoxicillin/clavulanate	≤1	2	- / -	84.4 / 6.0
Tetracycline	≤2	>8	65.9 / 30.5	- / -
Levofloxacin	1	2	98.2 / 1.2	- / -
S. pneumoniae (930)				
Fusidic Acid (CEM-102)	8	>8	- / -	- / -
Penicillin[b]	≤0.03	2	94.1 / 0.1	- / -
Penicillin[c]	≤0.03	2	72.7 / 16.3	72.7 / 5.9
Erythromycin	≤0.25	>2	70.5 / 29.2	70.5 / 29.2
Clindamycin	≤0.25	>2	79.6 / 19.8	80.2 / 19.8
Linezolid	1	1	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	2	94.1 / 3.4	- / -
Tetracycline	≤2	>8	74.8 / 24.7	74.8 / 25.2
Levofloxacin	1	1	98.1 / 1.5	98.1 / 1.9
Trimethoprim/sulfamethoxazole	≤0.5	>2	75.1 / 15.1	82.0 / 15.1
Enterococcus spp. (1,268)				
Fusidic Acid (CEM-102)	4	4	- / -	- / -
Ampicillin	2	>16	64.8 / 35.2	64.5 / 35.2
Vancomycin	1	>16	86.8 / 12.5	86.8 / 12.5
Linezolid	1	2	99.8 / 0.2	99.8 / 0.2
Gentamicin (HL)	≤500	>1000	68.7 / 31.3	- / -
Streptomycin (HL)	≤1000	>2000	54.0 / 46.0	- / -
Levofloxacin	>4	>4	47.7 / 50.4	- / -

a. Criteria as published by the CLSI [2010] and EUCAST [2009].
b. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis) therapy'.
c. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V) therapy'.

Table 2. Fusidic acid (CEM-102) resistance mechanisms detected among 336 *Staphylococcus* spp. collected in European medical sites during 2008.

Location (no. overall SA[a]/CoNS)	*S. aureus* no. of R (%)[b]	*fusB*	*fusC*	CoNS no. of R (%)[b]	*fusB*	*fusC*	% Acquired FA-R[c] genes	*fusA* mutations (no. tested)	*fusE* mutations (no. tested)
All Countries (2,700/436)	288 (10.6)	34	57	155 (35.5)	89	38	64.9	(see below)	(see below)
Belgium (93/28)	6 (6.4)	-	1	12 (42.9)	8	4	72.2	1 V90I, 1 L461K (3)	- (2)
France (541/85)	35 (6.5)	2	16	42 (49.4)	28	6	74.3	1 V90A, 1 V90I, 1 A376 V, 1 P404L, 1 H457Y, 4 L461S, 1 T387I/E449K (10)	- (1)
Germany (453/70)	13 (2.8)	3	1	23 (32.9)	7	8	61.3	1 V90I, 1 H457Y, 1 L461K (3)	- (1)
Greece (242/4)	127 (52.4)	18	4	1 (25.0)	1	-	54.8	10 L461K (10)	NT[d]
Ireland (241/4)	48 (19.9)	3	3	2 (50.0)	1	-	15.6	17 L461K, 1 L461S, 1 D189V/L430S (21)	Q104L (6)
Israel (70/25)	2 (2.8)	-	-	7 (28.0)	5	1	66.7	1 L461S (1)	NT[d]
Italy (147/64)	4 (2.7)	1	4	14 (21.9)	8	4	85.0	1 L461S (1)	NT[d]
Poland (66/24)	1 (1.5)	-	-	3 (12.5)	-	1	50.0	1 L461S (1)	NT[d]
Spain (208/16)	3 (1.4)	-	1	4 (25.0)	1	2	66.7	- (1)	NT[d]
Sweden (163/24)	5 (3.0)	1	3	9 (37.5)	7	2	92.9	1 A70V/A160V/H457Y (1)	- (1)
Switzerland (59/19)	4 (6.7)	1	2	9 (47.4)	7	2	92.3	1 F441Y (2)	- (1)
Turkey (128/50)	8 (6.2)	1	3	16 (32.0)	9	6	82.6	1 H457Y, 1 V90I/H457Q/L461K (2)	NT[d]
UK (289/21)	34 (11.7)	4	19	10 (47.6)	7	2	74.4	1 P404L, 3 L461K, 2 L461S (6)	NT[d]

a. SA = *S. aureus*.
b. No. of R = represents the number of strains showing fusidic acid MIC values ≥2 mg/L.
c. FA-R = fusidic acid resistance.
d. NT= Not tested.

Conclusions

- Fusidic acid demonstrated sustained activity against *S. aureus*, including methicillin-resistant strains. MIC_{50} and MIC_{90} values were predominantly below the concentrations that can be achieved in vivo.
- Fusidic acid demonstrated moderate activity when tested against enterococci and streptococci with MICs generally below the trough levels achieved with the projected dosing regimen for CEM-102.
- Acquired fusidic acid resistance genes conferring low level resistance were more prevalent among fusidic acid non-susceptible European strains (65.1% of the fusidic acid resistant strains), contrasting to earlier reports that these genes were present among clonal isolates from restricted geographic areas or institutions.
- Isolates harbouring *fusA* mutations usually present with highly elevated fusidic acid MIC values (≥512 mg/L) and were commonly related to clonal dissemination. Additionally, these strains were usually collected in hospitals from Greece and Ireland.

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