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Contemporary Antimicrobial Activity of CEM-102 (Fusidic Acid [FA]) Against Canadian Isolates of Staphylococci and Streptococci (2001-2006)

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Amended Abstract

Background: FA is a steroidal antimicrobial agent utilized against Gram-positive (GP) pathogens with a mode of action that prevents bacterial protein synthesis. FA has been used worldwide (not USA) as an effective treatment for skin and skin structure infections as well as bone and joint infections.

Methods: To determine a contemporary susceptibility (S) spectrum pattern, 153 GP isolates (123 *S. aureus,* 15 coagulase-negative staphylococci [CoNS] and 15 *S. pyogenes* [SPYO]) were collected from 5 Canadian medical centers between 2001 and 2006. Reference broth microdilution (BMD) S testing was performed by CLSI M07-A8, 2009 methods for FA and 13 comparator antimicrobials.

Results: FA MIC results for *S. aureus* had MIC_{50} and MIC_{90} values of 0.12 µg/ml for the 2001-2002 and 2003-2004 time periods, however, for 2005-2006 the MIC_{90} increased to ≥2 µg/ml. Applying an international breakpoint from literature reviews at ≤1 µg/ml (S) and ≥2 µg/ml (R), the *S. aureus* isolates showed a small increase in the R rate over time (5.0-12.2%), not confirmed by 2007-2008 results (ICAAC abstract, 2009). The overall *S. aureus* population had a MIC_{90} of 0.25 µg/ml and R rate of 8.1%. Some comparator agents showed higher R rates that remained stable over the period tested, with highest R noted for erythromycin (ERY, 52.0%), ciprofloxacin (43.9%), and clindamycin (CLI, 28.5%). CoNS isolates had FA MIC_{50} and MIC_{90} values at 0.12 and 16 µg/ml, respectively. SPYO isolates were only moderately S to FA with all values at 4 or 8 µg/ml. Among the comparator agents, ERY had a R rate of 20.0% and CLI at 13.3% for SPYO.

	No. inhibited at MIC (µg/ml) of:							
S. aureus (years tested)	≤0.03	0.06	0.12	0.25	0.5	1	≥2	% at ≤1[a]
2001-2002	-	8	29	1	-	-	2	95.0
2003-2004	-	6	33	-	-	-	3	92.9
2005-2006	-	2	32	2	-	-	5	87.8

a. 7.0% R for 2007-2008.

Conclusions: FA demonstrated potent activity against Canadian staphylococci isolates with a low overall R rate (8.1%) among *S. aureus*, even though FA has been used clinically for more than two decades. CoNS isolates had a greater R rate than *S. aureus*. FA had a narrow range of MIC results (4-8 µg/ml) and was less active against SPYO.

Introduction

Gram-positive cocci are common causes of serious infections and multidrug resistance is a therapeutic challenge throughout the world. The global emergence of methicillin (oxacillin)-resistant *S. aureus* (MRSA), glycopeptide-resistant enterococci, streptococci resistant to penicillin and macrolides, and the more recent emergence of MRSA strains with reduced vancomycin susceptibility further reduce treatment options.

Fusidic acid (also known as CEM-102) is a steroidal antimicrobial agent utilized against Gram-positive pathogens with a mode of action that prevents bacterial protein synthesis. Fusidic acid has been used worldwide (not United States [USA]) as an effective treatment of skin and skin structure infections (SSSI) as well as bone and joint infections. Fusidic acid has been used in Europe and Australia since 1962 and in Canada since 1986-87; however, this compound has not been licensed in the USA.

We summarized the results for fusidic acid among three groups of Gram-positive strains collected in Canada from 2001-2008. Studies compared the activity of fusidic acid and comparator anti-staphylococcal agents against clinical isolates of *S. aureus*, coagulase-negative staphylococci (CoNS) and *Streptococcus pyogenes* (SPYO) obtained from patients with SSSI or bloodstream infections (BSI).

Materials and Methods

Isolates. A total of 253 non-duplicate clinical isolates of *S. aureus* (223 strains), CoNS (15 strains) and SPYO (15 strains) were collected from 5 Canadian hospitals between 2001 and 2008.

Susceptibility test methods. All strains were tested by the reference broth microdilution method (CLSI M07-A8, 2009) using in-house prepared frozen-form and/or commercially prepared (TREK Diagnostics, Cleveland, Ohio, USA) validated panels in cation-adjusted Mueller-Hinton broth (with 2-5% lysed horse blood added for testing streptococci). Fusidic acid (CEM-102) reagent grade powder was obtained from Cempra Pharmaceuticals and the 13 comparator agents were obtained from the respective manufacturers or Sigma-Aldrich Inc. Interpretation of MIC results was in accordance with published CLSI criteria (CLSI M100-S19, 2009) as well as EUCAST (2009) breakpoints. Quality control (QC) strains utilized included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619.

Results

- Sampled *S. aureus* from Canada (2001-2008) generally had susceptible (MIC_{90}, 0.12 µg/ml) MIC values for fusidic acid. The EUCAST susceptibility rate at ≤1 µg/ml ranged from 87.8 to 95.0% (Table 1); average across all years at 92.4% (Table 2).
- Other agents with high susceptibility rates against *S. aureus* were: daptomycin (100.0%), doxycycline (95.5%), linezolid (100.0%), TMP/SMX (95.1%) and vancomycin (100.0%). The topical agent mupirocin was also very active (91.5% susceptible by CLSI criteria); see Table 2.
- Fusidic acid was active against a smaller collection of CoNS (MIC_{50}, 0.12 µg/ml; 60.0% susceptible); see Tables 1 and 3. However, fusidic acid was only moderately active (MIC range, 4-8 µg/ml) against *S. pyogenes* (Tables 1 and 4).
- Staphylococci not susceptible (MIC, ≥4 µg/ml) to fusidic acid were examined by molecular methods to determine the mechanism. Only six *S. aureus* were detected and the acquired resistance genes *fus*B and *fus*C were most common (five strains; 83.3%); see Figure 1. In 2007-2008, CoNS isolates were also examined for resistances and among the tested strains (10 total) the mechanisms were *fus*A (0), *fus*B (7), *fus*C (3) and *fus*D (0, data not shown).

Table 1. Fusidic acid (CEM-102) MIC frequency distribution for all Canadian isolates (253 strains) tested.

Organism/group (no. tested)	Occurrences at MIC (µg/ml): 0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16	% ≤1 µg/ml
S. aureus											
2001-2002 (40)	-	8	29	1	-	-	-	1	-	1	95.0
2003-2004 (42)	-	6	33	-	-	-	1	1	-	1	92.9
2005-2006 (41)	-	2	32	2	-	-	-	2	2	1	87.8
2007-2008 (100)	1	20	71	1	-	-	1	1	4	1	93.0
CoNS											
2001-2006 (15)	-	6	3	-	-	-	-	-	1	5	60.0
S. pyogenes											
2001-2006 (15)	-	-	-	-	-	-	-	11	4	-	0.0

Table 2. Antimicrobial activity of fusidic acid (CEM-102) and comparator agents when tested against *Staphylococcus aureus* (223 strains) isolated in Canada (2001-2008).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[b] %S / %R
Fusidic acid (CEM-102)	0.12	0.12	0.03 – 256	-[b] / -	92.4 / 7.6
Ciprofloxacin	0.5	>2	≤0.25 – >2	61.0 / 37.7	61.0 / 39.0
Clindamycin	≤0.25	>2	≤0.25 – >2	74.4 / 25.1	74.4 / 25.6
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Doxycycline	≤1	≤1	≤1 – >8	95.9 / 3.3	93.5 / 5.7
Erythromycin	0.5	>2	≤0.25 – >2	53.4 / 46.6	53.4 / 46.6
Gentamicin	≤2	8	≤2 – >8	89.7 / 9.4	48.9 / 11.2
Linezolid	2	2	0.5 – 2	100.0 / -	100.0 / 0.0
Mupirocin	≤4	≤4	≤4 – >256	91.5 / 4.5	- / -
Oxacillin	0.5	>2	≤0.25 – >2	57.8 / 42.2	57.8 / 42.2
Trim/sulfa[c]	0.06	0.25	≤0.03 – >4	95.1 / 4.9	95.1 / 3.3
Vancomycin	≤0.5	1	≤0.5 – >2	97.3 / 0.0	100.0 / 0.0

a. Criteria as published by the CLSI [2009] or the EUCAST group [2009].
b. - = no interpretative criteria published for this category.
c. Trimethoprim/sulfamethoxazole.

Table 3. Antimicrobial activity of fusidic acid (CEM-102) and comparator agents when tested against coagulase-negative staphylococci[a] (15 strains) isolated in Canada (2001-2006).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
Fusidic acid (CEM-102)	0.12	16	0.06 – 32	-[c] / -	60.0 / 40.0
Ciprofloxacin	>2	>2	≤0.25 – >2	40.0 / 60.0	40.0 / 60.0
Clindamycin	0.5	>8	≤0.06 – >8	53.3 / 46.7	46.7 / 46.7
Daptomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Doxycycline	≤1	≤1	≤1 – 4	100.0 / 0.0	93.3 / 6.7
Erythromycin	>8	>8	0.12 – >8	13.3 / 80.0	13.3 / 86.7
Gentamicin	2	>8	≤1 – >8	73.3 / 20.0	46.7 / 53.3
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
Mupirocin	≤4	>256	≤4 – >256	53.3 / 33.3	- / -
Oxacillin	>2	>2	≤0.25 – >2	20.0 / 80.0	20.0 / 80.0
Trim/sulfa[d]	1	>4	≤0.03 – >4	60.0 / 40.0	60.0 / 20.0
Vancomycin	1	2	0.5 – 2	100.0 / 0.0	100.0 / 0.0

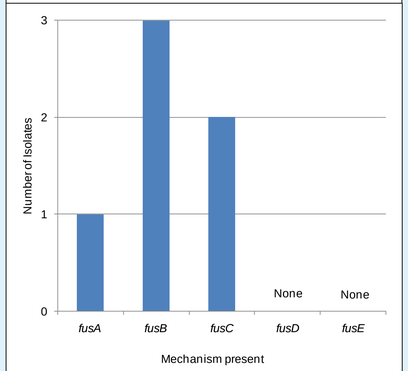
a. Includes: *Staphylococcus capitis* (2 strains), *S. epidermidis* (7 strains), *S. haemolyticus* (3 strains), *S. hominis* (1 strain), and *S. simulans* (2 strains).
b. Criteria as published by the CLSI [2009] or the EUCAST group [2009].
c. - = no interpretative criteria published for this category.
d. Trimethoprim/sulfamethoxazole.

Table 4. Antimicrobial activity of fusidic acid (CEM-102) and comparator agents when tested against *Streptococcus pyogenes* (15 strains) isolated in Canada (2001-2006).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[b] %S / %R
Fusidic acid (CEM-102)	4	8	4 – 8	-[b] / -	- / -
Ciprofloxacin	≤0.25	2	≤0.25 – >2	- / -	- / -
Clindamycin	≤0.06	>8	≤0.06 – >8	86.7 / 13.3	86.7 / 13.3
Daptomycin	0.12	0.12	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Doxycycline	≤1	≤1	≤1 – 8	- / -	93.3 / 6.7
Erythromycin	≤0.06	8	≤0.06 – 8	80.0 / 20.0	80.0 / 20.0
Gentamicin	8	>8	4 – >8	- / -	- / -
Linezolid	1	1	1	100.0 / -	100.0 / 0.0
Mupirocin	≤4	≤4	≤4	- / -	- / -
Penicillin	≤0.015	≤0.015	≤0.015	100.0 / -	100.0 / 0.0
Trim/sulfa[c]	0.06	0.25	0.06 – 0.25	- / -	100.0 / 0.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2009] or the EUCAST group [2009].
b. - = no interpretative criteria published for this category.
c. Trimethoprim/sulfamethoxazole.

Figure 1. Occurrence of resistance mechanisms among *S. aureus* isolates (2007-2008) with elevated fusidic acid (CEM-102) MIC values (≥4 µg/ml).



Conclusions

- Fusidic acid (CEM-102) exhibited potent activity (MIC_{90}, 0.12 µg/ml) against *S. aureus* and CoNS isolates from Canada, regardless of resistance to other classes of antimicrobial agents.
- Fusidic acid was generally 4- to 16-fold more potent than listed comparators against important MDR isolates among the staphylococci.
- No increasing trends in resistance rates were noted over an eight-year period (2001 – 2008), and resistances detected were dominated by acquired *fus*B and *fus*C gene types.
- Fusidic acid remains a potent agent against staphylococci that cause cutaneous infections and other infections in Canadian patients.

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