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Update on Fusidic Acid (CEM-102) Tested against *Neisseria gonorrhoeae* and *Chlamydia trachomatis*▽

Sexually transmitted diseases (STDs), including urethritis caused by gonococcus and *Chlamydia trachomatis*, are of increasing public health importance (1, 3, 6, 7, 9). The common occurrence of coinfections and the emergence of antimicrobial resistance of both pathogens emphasize the need for a single broadly active drug for management of these STDs (2, 3, 7, 9, 11–13). Penicillins and other beta-lactam agents effective against susceptible gonococci are ineffective against chlamydia. However, fluoroquinolones and macrolides provide broad coverage for both pathogens, but the emergence of gonococcal resistance within these classes limits their utility (2, 3, 9, 11–13). Early descriptions of the *in vitro* spectrum of activity of fusidic acid indicated the susceptibility of a limited number of *Neisseria gonorrhoeae* isolates (MIC range of 0.40 to 0.89 μg/ml) (8). This report examines the *in vitro* susceptibility of recent isolates of *N. gonorrhoeae* and *C. trachomatis* to fusidic acid (CEM-102; sodium fusidate), a potential alternative therapy for use in this clinical setting.

Thirty-five clinical isolates of *N. gonorrhoeae* collected in the United States, Asia, and European medical centers since 2005 were tested using reference agar dilution methods per the Clinical and Laboratory Standards Institute (CLSI) M07-A8 (4) and M100-S20 (5) documents. Five strains were penicillinase positive, and all gonococci were identified to the species level by at least two laboratories, including a reference, central laboratory (JMI Laboratories, North Liberty, IA). Resistance phenotypes were determined by agar dilution test results, followed by the use of confirmatory techniques as required by CLSI M100-S20 criteria (5). The quality control (QC) ranges and interpretive criteria for comparator compounds were as published by the CLSI (5). The tested QC strains included *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *N. gonorrhoeae* ATCC 49226, with all results being within established limits.

The activities of fusidic acid and five comparators tested against *N. gonorrhoeae* are shown in Table 1. The resistance rates for this organism collection were as follows (each pair of values represents the CLSI and EUCAST criteria, respectively): for penicillin, 45.7 and 45.7%; for tetracycline, 34.3 and 34.3%; for ciprofloxacin, 20.0 and 48.6%; for ceftriaxone, no criteria and 0.0%; and for azithromycin, no criteria and 5.7%. The MIC_{90} of fusidic acid against these *N. gonorrhoeae* isolates was only 1 μg/ml. According to the MIC_{50} (0.5-μg/ml) results, fusidic acid was 2-fold more active than penicillin and tetracycline (MIC_{50}, 1 μg/ml) but slightly less potent than azithromycin (MIC_{50}, 0.25 μg/ml). Fusidic acid was active against all strains of *N. gonorrhoeae* tested at ≤2 μg/ml.

Ten isolates of *C. trachomatis*, including standard isolates from the ATCC (E-BOUR, F-IC-CAL3, C-HAR32, J-UW-36, L2434, D-UW-57kx, and B-HAR-36) and recent clinical isolates N18 (cervical), N19 (cervical), and 7015 (infant eye), were selected for study. Susceptibility testing was performed with cell culture by use of HEp-2 cells (13) at State University of New York, Downstate Medical Center (Brooklyn, NY).

The activity of fusidic acid against *C. trachomatis* was compared with those of azithromycin, clarithromycin, telithromycin, and doxycycline (Table 2). The MIC range of fusidic acid against *C. trachomatis* was 0.12 to 0.5 μg/ml, with identical fusidic acid MBC_{90} and MIC_{90} values for this organism of 0.5 μg/ml. The MIC_{90} values for azithromycin, clarithromycin, telithromycin, and doxycycline were 0.12, 0.06, 0.06, and 0.06 μg/ml, respectively, each 2- to 4-fold lower than that for fusidic acid.

These *in vitro* testing data suggest that fusidic acid may be considered an alternative treatment for multidrug-resistant *N. gonorrhoeae* strains and could provide an advantage for treatment of STD as a single agent targeting both gonococcus and *C. trachomatis* (1, 3, 7, 9). The pharmacokinetics of fusidic acid has recently been modeled to define safe high-dose regimens designed to attenuate selection of resistance that was reported for doses originally approved for clinical use in Europe and Australia as well as to maximize potency versus cutaneous infection pathogens such as *Staphylococcus aureus* (10, 14). These modified dosing schedules achieve fusidic acid trough plasma levels of ca. 80 μg/ml, representing 40- to 160-fold-greater concentrations than the highest *N. gonorrhoeae* or *C. trachomatis* MIC result found in this report (8, 10, 14). However, fusidic acid urinary tract concentrations are limited. Further investigations of fusidic acid are needed to determine its potential role for STDs caused by these two pathogens.

TABLE 1. Activity of fusidic acid and five comparator agents tested against a comprehensive resistant challenge collection of 35 contemporary *N. gonorrhoeae* isolates

Antimicrobial	No. of occurrences at indicated MIC (μg/ml)											% for S isolates/% for R isolates[a]
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4	
Fusidic acid						12	17	5	1			−/− (−/−)
Azithromycin				1	15	12	5	1	1			−/− (80.0/5.7)
Ceftriaxone	18	6	6	3	2							100.0/− (100.0/0.0)
Ciprofloxacin	16	2			5	3	2	1	1		5	51.4/20.0 (51.4/48.6)
Penicillin		1	4	3		2	4	5	6	4	6	22.9/45.7 (22.9/45.7)
Tetracycline					6	2	8	7	7	1	4	22.9/34.3 (45.7/34.3)

[a] Values representing CLSI criteria (5) for S (susceptible) and R (resistant) isolates are shown outside parentheses. Values representing EUCAST criteria (http://www.eucast.org/clinical_breakpoints/) are shown in parentheses. "−" indicates no interpretive criteria.

TABLE 2. Activity of fusidic acid and four comparator agents tested against 10 *C. trachomatis* strains

Antimicrobial	MIC (μg/ml)[a]		MBC (μg/ml)[b]	
	Range	MIC_{90}	Range	MBC_{90}
Fusidic acid	0.12–0.5	0.5	0.12–0.5	0.5
Azithromycin	0.015–0.12	0.12	0.015–0.12	0.12
Clarithromycin	0.015–0.12	0.06	0.015–0.12	0.06
Telithromycin	0.015–0.25	0.06	0.015–0.25	0.06
Doxycycline	0.015–0.06	0.06	0.015–0.06	0.06

[a] The MIC is defined as the lowest antimicrobial concentration at which no intracellular inclusions were observed.

[b] The minimum bactericidal concentration (MBC) was defined as the lowest antimicrobial concentration that results in no observable inclusions after passage in cell culture.

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