

Update on the Spectrum of CEM-102 (Fusidic Acid [FA]) Against Contemporary Wildtype (WT) Bacterial Species Including Mutational Resistance (R) Analysis, and Synergy Testing

P. R. Rhomberg, R. E. Mendes, H. K. Becker, K. A. Fedler, H. S. Sader, R. N. Jones
JMI Laboratories, North Liberty, IA, USA

Background:

FA is a steroidal antimicrobial agent with focused Gram-positive activity (skin and skin structure infections) which acts by preventing bacterial protein synthesis via interacting with elongation factor G.

Methods:

A collection of 114 WT isolates (>80 species) was used to define the contemporary limits of FA spectrum against Gram-positive (GP) and -negative (GN) species. CLSI broth microdilution (BMD) and anaerobic agar dilution (AD) methods were performed. Modifications of standard test methods included adding 10% human serum, adjusting the medium pH to 5, 6, and 8 and synergy was assessed by the checkerboard method. Mutational rates to R were determined at 4X, 8X and 16X MIC.

Results:

Against GP FA MIC values ranged from 0.06-32 µg/ml with greatest potency against *S. aureus*, *Corynebacterium* spp. and *M. luteus* (MIC results 0.25, ≤0.12 and ≤0.5 µg/ml, respectively). Enterococci and streptococci were less susceptible (S; MIC ranges of 2-8 and 16-32 µg/ml, respectively). FA activity against GN species was limited (all MIC values ≥2 µg/ml) except for *E. brevis*, *M. catarrhalis* and *N. meningitidis* (MICs, 0.12-0.5 µg/ml). A 4-fold increase in FA MIC results was observed when 10% serum was added. Decreasing medium pH to 5.0-6.0 negated the protein binding effects. Among the 8 combinations tested, gentamicin (GEN) and rifampin (RIF) showed the greatest enhanced activity combined with FA (No antagonism). Single-step mutational rates ranged from 1.2×10^{-6} for 4XMIC to 9.8×10^{-8} for 16XMIC.

Conclusions:

FA demonstrated potent GP activity, especially against the staphylococci. A more limited activity was observed against GN species isolates. Added serum proteins adversely influenced MIC values; however lower media pH like seen at infection sites decreased negative protein binding effects. FA in vitro activity was most improved when combined with RIF.

| FA/co-drug | Synergy | | | | | |
|-------------------|----------|---------|----------|-------------|------------|---------------|
| | Complete | Partial | Additive | Indifferent | Antagonism | Indeterminate |
| Rifampin | 0 | 5 | 1 | 0 | 0 | 0 |
| Levofloxacin | 0 | 0 | 0 | 4 | 0 | 2 |
| Gentamicin | 1 | 1 | 3 | 1 | 0 | 0 |
| Oxacillin | 0 | 1 | 1 | 3 | 0 | 1 |
| Vancomycin | 0 | 0 | 2 | 4 | 0 | 0 |
| All agents tested | 1 | 7 | 9 | 24 | 0 | 7 |