

# Ability of CEM-102 (Fusidic Acid), Linezolid, Daptomycin to Select Resistant *S.aureus* Mutants at Steady-state Serum Levels

Abstract E-1557

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## Background:

We tested the ability of CEM-102 (sodium fusidate), an established antistaphylococcal drug, to select for resistant clones of 8 methicillin-resistant and 1 methicillin-susceptible *S. aureus* strains of varying resistance phenotypes compared to linezolid and daptomycin using starting concentrations equivalent to each drug's steady-state plasma concentration and different conditions.

## Methods:

The 8 MRSA were 3 CA-MRSA, 2 HA-MRSA, 1 hVISA, 1 VISA, 1 VRSA. In initial 12 h selections, each drug at steady-state concentration (CEM-102, 80 µg/mL; linezolid, 6.4 µg/mL; daptomycin, 6.7 µg/mL): was tested against 0.5 or 2.0 McFarland of inoculum in Mueller-Hinton broth (MHB) or MHB + 4 g/L human albumin and pH 6.5, with Ca<sup>2+</sup> for daptomycin. Ten serial 12 h passages were done at MIC equal to steady-state concentration for each drug in MHB or MHB + 4 g/L human albumin, pH 6.5. Two-fold dilutions above and two below steady-state concentration were included. Combinations in all tests were in duplicate.

## Results:

In the initial 12 h resistance selection in presence of steady-state concentration of each of the 3 agents, no mutants were selected by any drug on any medium. Serial passages at the steady-state plasma concentration on all *S. aureus* tested with CEM-102 did not yield mutants in MHB. Passage on CEM-102 in MHB with albumin (pH 6.5) yielded one, stable CEM-102 resistant mutant, originating from the VRSA strain in one of three independent experiments after six transfers. The resistance mechanism in this clone was a mutation (H457Y) in the EF-G protein encoded by *fusA*. Serial passages at steady-state concentration of daptomycin and linezolid did not yield mutants in all medium/strains combinations tested.

## Conclusions:

Under steady-state conditions, CEM-102, daptomycin, and linezolid did not (except for CEM-102 with a VRSA in 1 of three experiments) select for resistant mutants of *S. aureus* isolates. These data indicate that increased doses of CEM-102 prevent mutant selection by CEM-102.