

Capability of CEM-101 to Select for Resistant Pneumococcal and Group A Streptococcal Clones by Multistep Resistance Selection.

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Background:

CEM-101 (CEM) is a new fluoroketolide 2 to 4-fold more active than telithromycin (TEL) against macrolide R pneumococci. We tested ability of CEM, azithromycin (AZI), clarithromycin (CLA), TEL, clindamycin (CLI) to select R clones in 8 pneumo. strains of varying resistotypes.

Methods:

1 strain each was tested: macrol S, *erm(B)*, *mef(A)*, *ermB + mefA*, *erm(A)*, L4, L22, and 23S rRNA mutations. CLSI macrodilution tested MICs. Serial passages were daily in MHB + 5% lysed horse blood at subinh. drug conc., with each subseq. passage an inoculum from the tube 1-2 dilutions < MIC that matched turbidity of growth control. Daily passages were done until MIC increased >4-fold (min. 14, max. 50 passages). R clones were subcultured 10x in drug-free medium to test stability of selected R. Identity between parents and R clones was confirmed by PFGE and macrolide R phenotypes identified by PCR/sequencing.

Results:

Parental MICs ($\mu\text{g/ml}$) were: CEM, 0.004-1; AZI, 0.03-8; CLA, 0.016-16; TEL, 0.004-0.5; CLI, 0.016-1 (4 strains with AZI, 2 CLA, 2 CLI MICs $\geq 64 \mu\text{g/ml}$ not tested). CEM MICs increased after 14-43 days in all 8 strains tested. For 7 strains, MICs rose from 0.004-0.03 $\mu\text{g/ml}$ (parents) \rightarrow 0.06-0.5 $\mu\text{g/ml}$ (R clones) in 14-43 days. For the 8th strain, containing *erm(B) + mef(A)*, MICs rose from 1 $\mu\text{g/ml}$ (parent) \rightarrow 32 $\mu\text{g/ml}$ (R clone) in 18 days with no changes in L4, L22, 23S rRNA. AZI had R clones after 14-29 days in 3/4 strains with MICs rising from 0.03-2 $\mu\text{g/ml}$ (parents) \rightarrow 0.5->64 $\mu\text{g/ml}$ (R clones). CLA had R clones after 14-49 days in 5/6 strains with MICs rising from 0.03-16 $\mu\text{g/ml}$ (parents) \rightarrow 16->64 $\mu\text{g/ml}$ (R clones). TEL had R clones after 14-38 days in 5 clones of 8 tested with MIC rising from 0.004-0.5 $\mu\text{g/ml}$ (parents) to 0.06->64 $\mu\text{g/ml}$ (R clones). CLI had R clones after 14-43 days in 2/5 strains with MICs rising from 0.03-0.06 $\mu\text{g/ml}$ (parents) \rightarrow 0.25->64 $\mu\text{g/ml}$ (R clones).

Conclusions:

CEM had clones with higher MICs in all 8 strains, but 7 of 8 strains had clones with CEM MICs $\leq 0.5 \mu\text{g/ml}$ and in only 1 *erm(B) + mef(A)* strain with parental MIC=1 $\mu\text{g/ml}$ was a R clone with an MIC=32 $\mu\text{g/ml}$ found.