# E-101, a novel first in class topical anti-infective, maintains a high degree of potency *in vitro* against problematic resistant clinical pathogens (ESKAPE pathogens)

# Poster No. P 1144

## ABSTRACT

**Objective:** E-101, a topical anti-infective which utilizes myeloperoxidase (MPO) for the generation of reactive oxygen species to kill bacteria, is being developed for the prevention of surgical site infections. Infections caused by antibiotic resistant pathogens have become common and are increasingly difficult to treat. This study evaluates the activity of E-101 against highly resistant "ESKAPE" pathogens (vancomycin resistant E. faecium [VRE], methicillin resistant S. aureus [MRSA], extended spectrum b-lactamase [ESBL]/carbapenemase producing K. pneumoniae, multi-drug resistant [MDR] A. baumannii and *P. aeruginosa*, and AmpC cephalosporinase producing *E. cloacae*).

Methods: E-101 activity was evaluated using a modified broth microdilution method based on CLSI M7. Modifications included serial dilution of enzyme (MPO) and inocula delivery in solution containing enzyme substrate. E-101 MICs represent mg/L of MPO. Comparators (currently marketed agents and phenotypic markers) were tested in accordance with CLSI M7 and M100. 103 non-duplicate clinical isolates were selected based on resistance phenotype for evaluation to include the "ESKAPE" phenotypes noted above.

**Results:** Against VRE, E-101 had an MIC50/MIC90 of 0.06/0.12 mg/L. Against S. aureus consisting of linezolid resistant isolates, daptomycin non-susceptible isolates, hospital and community acquired MRSA, VISA, and VRSA, E-101 had an MIC50/MIC90 of <0.008/0.015 mg/L with MICs not exceeding 0.06 mg/L. E-101 had an MIC50 and MIC90 0.12 mg/L against ESBL E. coli, ESBL K. pneumoniae, and KPC K. pneumoniae, with an MIC50 and MIC90 of 0.06 mg/L against *E. cloacae/C. freundii* with derepressed AmpC. Against MDR *P.* aeruginosa, E-101 had an MIC50/MIC90 of 0.03/0.06 mg/L, with an MIC50 and MIC90 of 0.03 mg/L against MDR A. baumannii. E-101 activity against this subset of purely resistant isolates was equivalent to that observed for E-101 during recent surveillance where isolates with these phenotypes were infrequently or not encountered.

Conclusions: E-101 was potent in vitro against ESKAPE pathogens, which constitute clinically important pathogens with problematic resistance (multi-drug resistance, emerging resistance to commonly utilized agents). This attribute highlights the utility of E-101 for the treatment of surgical site infections where resistant organisms are likely to be encountered, and potential for the treatment of other superficial infections caused by resistant organisms.

# BACKGROUND

 E-101 is a novel myeloperoxidase (MPO)-mediated antimicrobial. Once activated, E-101 generates combustive oxidative products which damage bacterial cells if MPO, halide and a source of

hydrogen peroxide are present (Figure 1)

•E-101 is currently undergoing clinical development for the prevention of surgical site infections in Europe and the US

•"ESKAPE" pathogens (Boucher et al, CID 2009;48:1) include pathogens with problematic resistance:

- •*E. faecium* (VRE)
- •*S. aureus* (MRSA and MDR)
- •*K. pneumoniae* (ESBL, KPC)
- •A. baumannii (MDR)
- •*P. aeruginosa* (MDR)
- •*E. cloacae* (AmpC)

•This study evaluates the *in vitro* activity of E-101 against "ESKAPE" pathogens, including those with emerging resistances

## METHODS

•Clinical isolates included those pre-selected for a particular resistance phenotype based on test history and genetically characterized isolates were selected from both the Eurofins and NARSA repositories (Table 1).

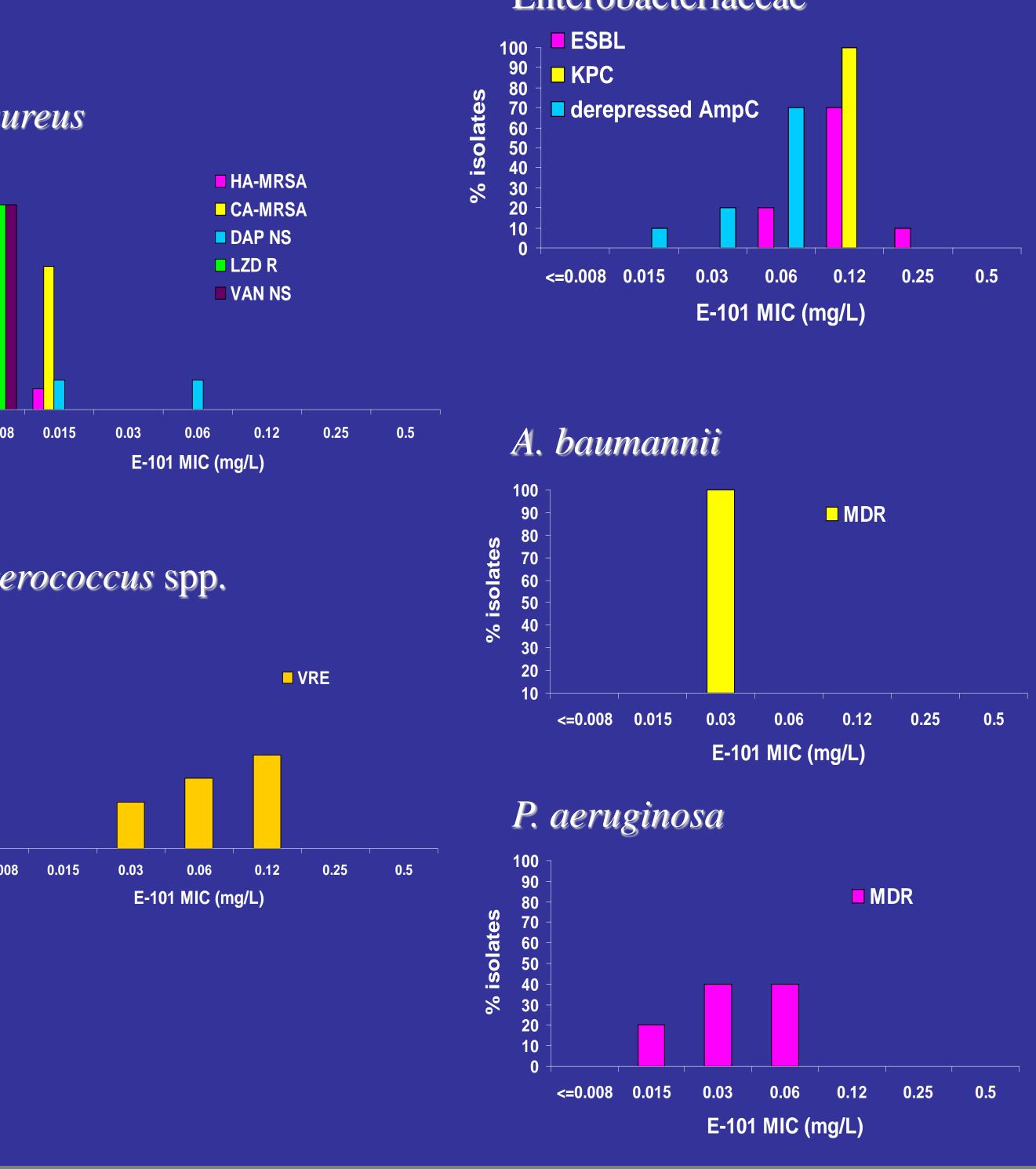
•Susceptibility of isolates to E-101 was determined using a modified broth microdilution method based on CLSI M7 guidelines. Modifications included diluting E-101 enzyme solution containing MPO in 2x cation-adjusted Mueller-Hinton broth in the panel, and delivering the inoculum at 2x final concentration in 2x substrate solution to achieve a final concentration of 1x E-101, 1x substrate solution, and 5 x 105 CFU/mL. Immediately postinoculation, E-101 begins to generate reactive oxygen species. MICs are reported based on mg/L MPO in E-101.

•Isolates were concurrently tested against relevant comparators in accordance with CLSI M7

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| ABLE 1. Evaluated ESKAPE pathogens  | pathogens  | Activity profile of  |            | against cvalu  |   |   |               |
|---|--|--|------------|--|---|---|---------------|
|   |  |  |            |  | MIC (mg                                     | ./! \                                     |               |
| aureus (N=44)   |  | Dhanatura  |            |  |   |   |               |
| 10 hospital-acquired MRSA (HA-MRSA) <sup>1</sup>  | Organism   | Phenotype  | N          | range  | mode  | MIC <sub>50</sub>                         | MIC           |
| 1 USA600 (MDR US HA-MRSA clone)   | S. aureus  | overall  | 44         | <=0.008-0.06   | <=0.008                                     | <=0.008                                   | 0.01          |
| 9 USA100 (prevalent US HA-MRSA clone)   |  | HA-MRSA<br>CA-MRSA   | 10<br>10   | <=0.008-0.015<br><=0.008-0.015   | <=0.008<br>0.015                            | <=0.008<br>0.015                          | <=0.0<br>0.01 |
| 10 community-acquired MRSA (CA-MRSA) <sup>1</sup>   |  | DAP NS   | 7          | <=0.008-0.013  | <=0.008                                     | NA  | NA            |
| 10 USA300 (prevalent US CA-MRSA clone)  |  | LZD R  | 9          | <=0.008-0.015  | <=0.008                                     | NA  | NA            |
|   |  | VAN NS   | 11         | <=0.008-<=0.008  | <=0.008                                     | <=0.008                                   | <=0.0         |
| 7 daptomycin non-susceptible (DaptoNS) isolates   |  |  |            |  |   |   |               |
| 9 linezolid resistant (LZD R) isolates  | Enterococcus spp.  | VRE  | 9          | 0.03-0.12  | 0.12  | NA  | NA            |
| 8 vancomycin non-susceptible (VAN NS) isolates  | Enterobacteriaceae   | overall  | 30         | 0.015-0.25   | 0.12  | 0.12                                      | 0.1           |
| 3 vancomycin resistant (VRSA)   | Enterobacternaceae   | ESBL   | 10         | 0.06-0.25  | 0.12  | 0.12                                      | 0.1           |
| 5 vancomycin intermediate (VISA)  |  | KPC  | 10         | 0.12-0.12  | 0.12  | 0.12                                      | 0.1           |
|   |  | derepressed AmpC   | 10         | 0.015-0.06   | 0.06  | 0.06                                      | 0.0           |
| nterococcus spp. (n=9)  |  |  |            |  |   |   |               |
| 5 <i>E. faecalis</i> (vancomycin resistant)   | A. baumannii   | MDR  | 10         | 0.03-0.03  | 0.03  | 0.03                                      | 0.0           |
| 4 <i>E. faecium</i> (vancomycin resistant)  | P. aeruginosa  | MDR  | 10         | 0.015-0.06   | 0.03  | 0.03                                      | 0.0           |
|   |  |  | 10         | 0.013-0.00   | 0.05  | 0.03                                      | 0.0           |
| atorobactoriacoao enn (N=30)  |  |  |            |  |   |   |               |
| nterobacteriaceae spp. (N=30)   |  |  |            |  |   |   |               |
| 10 ESBL phenotype confirmed <sup>2</sup>  |  |  |            |  |   |   |               |
| 5 E. coli   |  |  |            |  |   |   |               |
| 5 K. pneumoniae   | FIGURE 2. E  | -101 MIC distrib   | utions     | against ESKA   | PE path                                     | ogens b                                   | y             |
| 10 KPC positive <i>K. pneumoniae</i> <sup>3</sup>   | phenotype  |  |            |  |   |   |               |
| 10 derepressed AmpC <sup>4</sup>  |  |  |            | Enterobac  | teriacea                                    | ae  |               |
| 5 Citrobacter spp.  |  |  |            | 100 ┐  |   |   |               |
|   |  |  |            |  |   |   |               |
| <u> </u>  |  |  |            | 90 - <b>KPC</b>  |   |   |               |
| 5 Enterobacter spp.   | Contraction  |  |            |  | ed AmnC                                     |   |               |
|   | S. aureus  |  |            |  | ed AmpC                                     |   |               |
| 5 Enterobacter spp.<br>DR <sup>5</sup> P. aeruginosa (N=10)   | S. aureus  |  |            |  | ed AmpC                                     |   |               |
|   |  |  |            | 80       -         70       -         60       -         60       -         50       -         40       -         30       -   | ed AmpC                                     |   |               |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)   | 100 -<br>90 -  | CA-MRSA  |            | 80 -<br>70 -<br>60 -<br>50 -<br>40 -   | ed AmpC                                     |   |               |
|   | 100<br>90<br>80<br>80<br>70  |  |            | 80       -   |   |   |               |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter</i> spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction   | 100<br>90<br>80<br>80<br>70  | □ CA-MRSA<br>■ DAP NS  |            | 80       -         70       -         60       -         50       -         40       -         30       -         20       -   | 0.03 0.(                                    |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter</i> spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>ceftazidime/cefotaxime MIC when combined with clavulanic acid  | 100<br>90<br>80<br>70<br>60<br>50<br>40  | <ul> <li>CA-MRSA</li> <li>DAP NS</li> <li>LZD R</li> </ul>                                 |            | 80       -   |   |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter</i> spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>teftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR   | 100<br>90<br>80<br>70<br>80<br>80<br>70<br>-<br>80<br>-<br>80<br>-<br>80<br>-<br>80<br>-<br>8  | <ul> <li>CA-MRSA</li> <li>DAP NS</li> <li>LZD R</li> </ul>                                 |            | 80       -   | 0.03 0.(                                    |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter spp.</i> (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>beftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)  | 100<br>90<br>80<br>70<br>60<br>60<br>60<br>70<br>40  | <ul> <li>CA-MRSA</li> <li>DAP NS</li> <li>LZD R</li> </ul>                                 |            | 80       -   | 0.03 0.(                                    |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter</i> spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>teftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR   | 100<br>90<br>80<br>70<br>60<br>50<br>40<br>30<br>20<br>10<br>0   | <ul> <li>CA-MRSA</li> <li>DAP NS</li> <li>LZD R</li> <li>VAN NS</li> </ul>                 |            | 80       70       Image: Construction of the second  | 0.03 0.0<br>E-101 MI                        |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter spp.</i> (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>beftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)  | 100<br>90<br>80<br>70<br>60<br>50<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>40<br>30<br>20<br>10<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25                                   |            | 80       -   | 0.03 0.0<br>E-101 MI                        |   | 0.25          |
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| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter spp.</i> (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>beftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)  | 100<br>90<br>80<br>70<br>60<br>50<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>0<br>40<br>30<br>20<br>10<br>40<br>30<br>20<br>10<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40<br>40  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25                                   |            | $ \begin{array}{c} 80 \\ 70 \\ 60 \\ 50 \\ 40 \\ 20 \\ 10 \\ 0 \end{array} $ $= 0.008  0.015$ A. bauman $A. bauman 100 \\ 90 \\ 0 \end{bmatrix}$   | 0.03 0.0<br>E-101 MI                        |   | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter spp.</i> (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>beftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)  |  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0.03 0.0<br>E-101 MI                        | C (mg/L)                                  | 0.25          |
| DR <sup>5</sup> <i>P. aeruginosa</i> (N=10)<br>DR <sup>5</sup> <i>Acinetobacter spp.</i> (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing - >two-fold reduction<br>beftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes   |  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | <b>Set of a set of a se</b> | 0.03 0.0<br>E-101 MI                        | C (mg/L)                                  | 0.25          |
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| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>motypically positive per CLSI M100 in prior testing - >two-fold reduction<br>seftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive   |  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | <b>Set of a set of a se</b> | 0.03 0.0<br>E-101 MI                        | C (mg/L)                                  | 0.25          |
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| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>motypically positive per CLSI M100 in prior testing - >two-fold reduction<br>seftazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive   | <b>Enterococcus</b>  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0.03 0.0<br>E-101 MI                        | C (mg/L)                                  |               |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>motypically positive per CLSI M100 in prior testing ->two-fold reduction<br>testazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive<br>oxygen species from MPO; mechanism of  | 100<br>90<br>80<br>70<br>60<br>50<br>40<br>30<br>20<br>10<br>0<br>20<br>10<br>0<br>20<br>10<br>0<br>20<br>10<br>0<br>20<br>10<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0   | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0.03 0.0<br>E-101 MI                        | C (mg/L)<br>MDR                           | 0.25          |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>vs HA MRSA designations based on USA type reported in NARSA repository<br>motypically positive per CLSI M100 in prior testing ->two-fold reduction<br>testazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>enotypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive<br>oxygen species from MPO; mechanism of  | 100<br>90<br>80<br>70<br>60<br>50<br>40<br>30<br>20<br>10<br>0<br>50<br>40<br>30<br>20<br>10<br>0<br>50<br>40<br>30<br>20<br>10<br>0<br>50<br>40<br>30<br>20<br>10<br>0<br>50<br>40<br>30<br>20<br>10<br>0<br>50<br>40<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>50<br>10<br>0<br>10<br>0<br>10<br>0<br>15<br>0<br>0<br>15<br>0<br>15<br>0<br>15<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10<br>10   | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0.03 0.0<br>E-101 MI                        | C (mg/L)                                  |               |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>Vs HA MRSA designations based on USA type reported in NARSA repository<br>notypically positive per CLSI M100 in prior testing - >two-fold reduction<br>detazidime/cefotaxime MIC when combined with clavulanic acid<br>sitive for KPC-2/KPC-3 by PCR<br>notypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes  | $ \frac{100}{90} \\ \frac{80}{50} \\ \frac{100}{20} \\ \frac{20}{10} \\ \frac$   | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            |  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR                           |               |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DL <sup>5</sup> Acinetobacter spp. (N=10)<br>W HAMRSA designations based on USA type reported in NARSA repository<br>photypically positive per CLSI M100 in prior testing - >two-fold reducion<br>eftazidime/cefotaxime MIC when combined with clavulanic acid<br>strue for KPC-2/KPC-3 by PCR<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59;<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive<br>oxygen species from MPO; mechanism of<br>action of E-101<br>Diverging Cluconolactore<br>Glucose Oxidase  | 100       90 <t< td=""><td>CA-MRSA<br/>DAP NS<br/>LZD R<br/>VAN NS<br/>3 0.06 0.12 0.25<br/>E-101 MIC (mg/L)</td><td></td><td><math display="block"> \begin{array}{cccccccccccccccccccccccccccccccccccc</math></td><td>0.03 0.0<br/>E-101 MI<br/>5 0.03 0<br/>E-101 M</td><td>C (mg/L)<br/>MDR</td><td></td></t<>  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)               |            | $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR                           |               |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DS 4 AGS 4 designations based on USA type reported in NARSA repository<br>motypically positive per CLSI M100 in prior testing - >two-fold reduction<br>seftazidime/cefotaxime MIC when combined with clavulanic acid<br>strue for KPC-2/KPC-3 by PCB<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59)<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>MIGURE 1. Generation of reactive<br>oxygen species from MPC9; mechanism of<br>action of E-101<br>DECED   | 100       90 <t< td=""><td>CA-MRSA<br/>DAP NS<br/>LZD R<br/>VAN NS<br/>3 0.06 0.12 0.25<br/>E-101 MIC (mg/L)<br/>VRE</td><td></td><td></td><td>0.03 0.0<br/>E-101 MI<br/>5 0.03 0<br/>E-101 M</td><td>C (mg/L)<br/>MDR</td><td></td></t<>  | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)<br>VRE        |            |  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR                           |               |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>VS HA MRSA designations based on USA type reported in NARSA repository<br>enotypically positive per CLSI M100 in prior testing ->two-fold reduction<br>intradime/cefotaxime MIC when combined with clavulanic acid<br>istive for KPC-2/KPC-3 by PCR<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59;<br>R based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive<br>oxygen species from MIPO; mechanism of<br>action of E-101<br>Divergence oxidase  | <b>Enterococcus</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>S</b> | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)<br>VRE        | <b>0.5</b> |  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR                           | 0.25          |
| DR <sup>5</sup> P. aeruginosa (N=10)<br>DR <sup>5</sup> Acinetobacter spp. (N=10)<br>VS HA MRSA designations based on USA type reported in NARSA repositors<br>brotypically positive per CLSI M100 in prior testing ->two-fold reduction<br>detaidime/cefotaxime MIC when combined with clavulanic acid<br>bitwe for KPC-2/KPC-3 by PCR<br>motypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>inhibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S50;<br>R based on prior testing; resistance to > 3 different antimicrobial classes  | <b>Enterococcus</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>S</b> | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)<br>VRE<br>VRE | <b>0.5</b> |  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR<br>0.06 0.12<br>IC (mg/L) | 0.25          |
| R <sup>5</sup> P. aeruginosa (N=10)<br>R <sup>5</sup> Acinetobacter spp. (N=10)<br>s HA MRSA designations based on USA type reported in NARSA repository<br>otypically positive per CLSI M100 in prior testing -> two-fold reduction<br>trazidime/cefotaxime MIC when combined with clavulanic acid<br>ive for KPC-2/KPC-3 by PCR<br>otypically positive based on prior testing (cefoxitinR, ceftazidimeR/cefotaximeR<br>hibited by clavulanic acid, carbapenem susceptible; Livermore, JAC 2001;48:S59;<br>based on prior testing; resistance to > 3 different antimicrobial classes<br>FIGURE 1. Generation of reactive<br>oxygen species from MPO; mechanism of<br>action of E-101<br>Successe Oxidase<br>Output of the state of the s | <b>Enterococcus</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>Solution</b><br><b>S</b> | CA-MRSA<br>DAP NS<br>LZD R<br>VAN NS<br>3 0.06 0.12 0.25<br>E-101 MIC (mg/L)<br>VRE<br>VRE | <b>0.5</b> |  | 0.03 0.0<br>E-101 MI<br>5 0.03 0<br>E-101 M | C (mg/L)<br>MDR<br>0.06 0.12<br>IC (mg/L) | 0.25          |
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# RESULTS



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#### S. aureus

•E-101 maintained potent MICs (0.015 mg/L or less excluding one daptomycin non-susceptible isolate) overall against S. aureus, including those resistant to current anti-Gram positive agents

•E-101 was active against prevalent HA-MRSA and CA-MRSA clones

#### Enterococci

•E-101 maintained potency against vancomycin resistant enterococci, with MICs in the 0.03-0.12 mg/L range.

•E-101 MICs were 2-4 fold lower against vancomycin resistant *E. faecium* (0.03-0.06 mg/L) relative to vancomycin resistant *E. faecalis* (0.06-0.12) mg/L)

#### Enterobacteriacea

•Against various species and types of beta-lactamase producing Enterobacteriaceae, E-101 maintained potent MICs, including the recently emerged KPC producing K. pneumoniae.

#### A. baumannii

•E-101 had MICs of 0.03 mg/L against all evaluated multi-drug resistant A. baumannii isolates.

#### P. aeruginosa

•Against multi-drug resistant *P. aeruginosa*, E-101 was highly active with an  $MIC_{50}$  of 0.03 mg/L and an  $MIC_{90}$  of 0.06 mg/L.

# CONCLUSIONS

•The emergence and spread of resistance combined with the increasing prevalence of multi-drug resistance among ESKAPE pathogens has left relatively few effective therapeutic options for the treatment of drug resistant infections

•These developments highlight the need for new agents active against these resistant organisms (further illustrated by the recent emergence and spread of KPC and NDM-1 carbapenemases)

•E-101, currently undergoing evaluation for topical prevention of surgical infections, is a novel agent with multiple mechanisms of action that maintains its activity against ESKAPE pathogens with challenging resistance phenotypes

## ACKNOWLEDGEMENTS

This study was supported by a grant from Exoxemis, Inc.. Eurofins would also like to acknowledge Parveen Grover, Dinesh Shah, and Venkat Alluru for their work on this project.