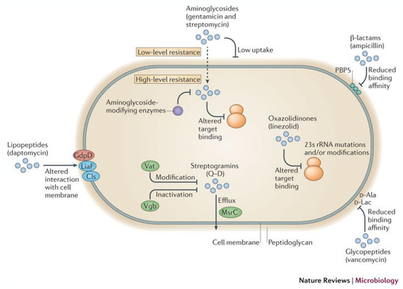
Together We Stand, Divided We Fall. A Successful In-Vitro Story of Failing Beta-Lactams in Combination with Daptomycin, and the Activity of Eravacycline in Vancomycin-Resistant Enterococcus faecium.

LoongFi Ho, MLS; Daniel Navas, MLS; Jose Alexander, MD; Angela Charles, MLS

AdventHealth Orlando
Jose.alexander@adventhealth.com

Background

Enterococcus faecium are predominantly inhabitants of the gastrointestinal tract. However, they can cause a variety of infections, such as urinary tract infection, intra-abdominal infection, bacteremia, or endocarditis. Vancomycin-resistant (VRE) E. faecium are becoming increasingly common in hospital settings, with reduced treatment options available to the patient even beyond vancomycin (VAN). In our institution, up to 50% of *E. faecium* are VRE. In this prospective study, we compared the synergy activity of daptomycin (DAP) in combination with ceftaroline (CFTL), ceftriaxone (CRO), ertapenem (ERT), and imipenem (IMP). Individually, we also evaluated eravacycline (ERA) potency.



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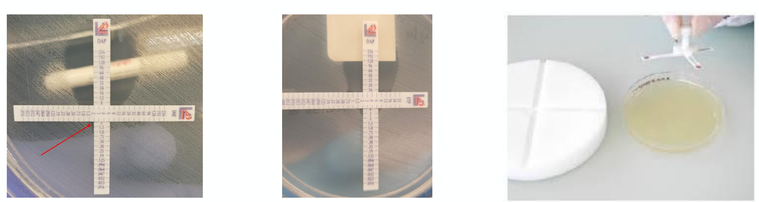
Arias, C., Murray, B. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol 10, 266–278 (2012). https://doi.org/10.1038/nrmicro2761

Methods

A total of 60 clinical isolates of *E. faecium* VRE were collected across AdventHealth Central Florida Division, from multiple sources including urine (n=24), blood (n=9), body fluid (n=11), wounds (n=6), surgical (n=7) and tissue (n=3). Antimicrobial susceptibility testing for VAN was performed using the VITEK®2 AST-GP75 card (bioMerieux, Inc.) while identification was done by MALDI-TOF (bioMerieux, Inc.). DAP, CFTL, CRO, ERT, IMP and ERA susceptibility were individually tested by gradient strips (Liofilchem®). Synergistic activity was performed via cross-method technique using the MTS™ Synergy Application System (Liofilchem®). DPT was crossed at MIC 4µg/mL with the MIC of CFTL, CRO, ERTP and IMP at ≤2µg/mL at <4 µg/mL, <2 µg/mL and <2 µg/mL respectively.



Images. *Synergy results and Liofilchem® MTS™ Synergy Application System*

Results

78% (n=46) were susceptible dose dependent (MIC <4 µg/mL) to DPT, with a MIC50/90, of 4/8 µg /mL and a range of 0.5 to 16 µg/mL. All isolates had a MIC >256µg/mL for CFTL, CRO, ERT and IMP. The combination of DPT + CFTL demonstrated the highest synergistic activity with 23.3% (n=14), followed by DPT + CRO 21.7% (n=13). DPT + ERT showed a 17.7% (n=10) synergistic activity, while DPT + IMP showed the least synergistic activity with 8.3% (n=5). No antagonism was observed with any of the combinations. ERA MIC50/90 was 0.032/0.047 µg /mL, with a range of 0.012 to 1 µg/mL, while ERA demonstrated a 98% inhibitory activity (MIC <0.06 µg/mL), one isolate was observed with an MIC of 1 µg/mL.

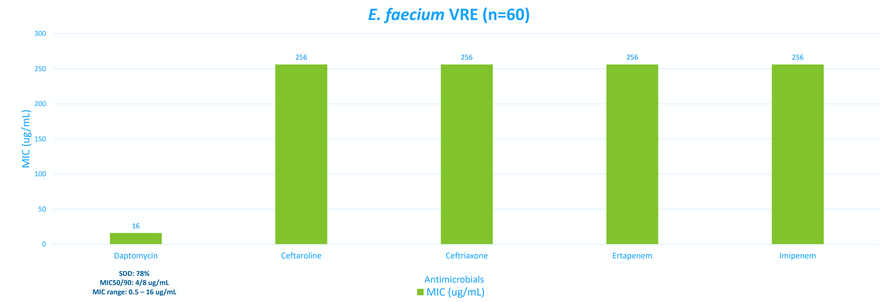


Table 1. *In-vitro activity of each individual agent*

Conclusion

DPT + CFTL demonstrated the highest in-vitro synergistic activity in 23.3% of all VRE isolates, while DPT + IMP had the lowest activity. 98% of the isolates were susceptible to ERA, confirming the low resistance prevalence of this 3rd generation tetracycline. A combined therapy of DPT plus CFTL and ERA, could be a reasonable therapeutic approach for severe infection caused by *E. faecium* VRE.

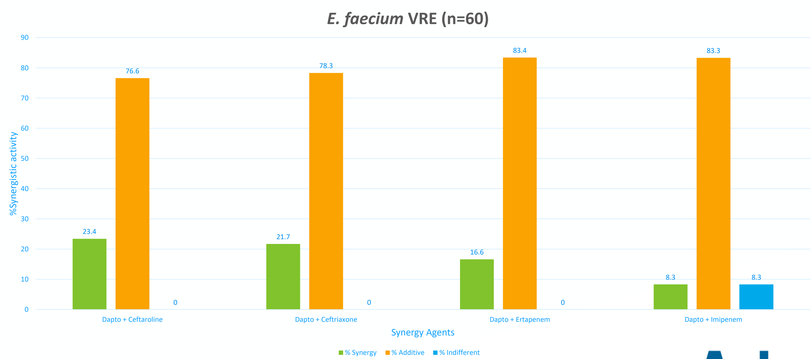


Table 2. *Synergistic activity between different β-lactams and daptomycin*

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