ERTAPENEM AND CEFAZOLIN SALVAGE THERAPY FOR ENDOCARDITIS WITH PERSISTENT METHICILLIN-SUSCEPTIBLE STAPHYLOCOCCUS AUREUS BACTERAEMIA
A SINGLE CENTRE CASE SERIES

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Introduction:
- Methicillin-sensitive Staphylococcus aureus (MSSA) is a major cause of bacteraemia and is associated with significant morbidity and mortality. 1
- MSSA remains one of the most common causative organisms of native and prosthetic valve endocarditis. 2
- The mainstay of antimicrobial therapy for MSSA endocarditis is prompt initiation of an appropriate anti-staphylococcal beta-lactam antibiotic (oxacillin, nafcillin, flucloxacillin, cefazolin). 2
- In high inoculum infections of MSSA endocarditis, where treatment failure is associated with catastrophic clinical outcomes, there remains little guidance in the management of cases refractory to standard treatment.
- Combination antimicrobial therapy with cefazolin and ertapenem has shown promise with evidence of in vitro synergy as well as observational evidence of successful in vivo treatment of persistent MSSA bacteraemia. 2, 3

Case Series:
- We report three cases of MSSA endocarditis with persistent bacteraemia despite greater than 5 days of appropriate anti-staphylococcal beta-lactam antibiotic therapy (see table 1).
- In each case, culture clearance was achieved within 24 hours of initiation of combination therapy with ertapenem and cefazolin.
- An acute kidney injury was observed in one case (Case 2) in the setting of combination therapy with cessation of ertapenem at day ten as a result and continuation of cefazolin monotherapy.
- No other adverse effects were observed.
- Follow-up is ongoing; however, no recrudescence of endocarditis was noted at three months in any case.

Table 1: Summary of case series of infective endocarditis with persistent MSSA bacteraemia treated with combination ertapenem and cefazolin

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Antimicrobials (days)</th>
<th>Days pre E/C BC +ve</th>
<th>Days post E/C BC +ve</th>
<th>Heart Valve</th>
<th>Septic Sequelae</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>M</td>
<td>Gentamicin (1) Vancomycin (3) Cefazolin (10) ertapenem (14) Flucloxacillin (14)</td>
<td>12</td>
<td>0</td>
<td>Native Tricuspid and Pulmonary Valves</td>
<td>Bilateral empyema Septic arthritis of right hip</td>
<td>Intravenous drug use, chronic back pain</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>M</td>
<td>Flucloxacillin (7) Cefazolin (28) Eratapen (14) Flucloxacillin (14)</td>
<td>7</td>
<td>0</td>
<td>Native Tricuspid Valve</td>
<td>Multilevel vertebral osteomyelitis (cervical and lumbar) L psoas abscess</td>
<td>Metastatic melanoma, gout, psoriasis</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>Flucloxacillin (10) Cefazolin (42) Eratapen (7)</td>
<td>11</td>
<td>0</td>
<td>Bioprosthetic Aortic Valve</td>
<td>Bilateral cerebral parieto-occipital septic emboli</td>
<td>Severe asthma, ischaemic heart disease with CABG, HF-REF, Atrial fibrillation, Type 2 diabetes mellitus, hypertension, pulmonary embolism</td>
</tr>
</tbody>
</table>

Discussion:
- This series demonstrated rapid culture clearance of persistent MSSA bacteraemia in the setting of endocarditis with the use of combination antimicrobial therapy with ertapenem and cefazolin.
- This finding is consistent with reports from other small observational studies and case series around the world. 1, 4
- The true underlying mechanism by which this combination exerts its striking in vivo effects is unknown. However, there have been a number of proposed hypotheses including increased production of IL-18, increased binding of complementary penicillin binding protein (PBP) targets and potential impacts on quorum sensing within biofilms. 1, 4
- Our cases demonstrate that combination ertapenem and cefazolin antimicrobial therapy can successfully treat refractory high inoculum, biofilm associated MSSA endocarditis.
- Further prospective study of this combination against standard of care is warranted to support its use more widely and to better understand the mechanism by which it acts.

References