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

Matthew Eustace[1,2], Robert Horvath [1,2,3].
1. Infection Management Services, The Prince Charles Hospital, Brisbane, Queensland, Australia.
2. Faculty of Medicine, University of Queensland, Herston, Australia.
3. Pathology Queensland, Brisbane, Australia.

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.[1]
- 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.

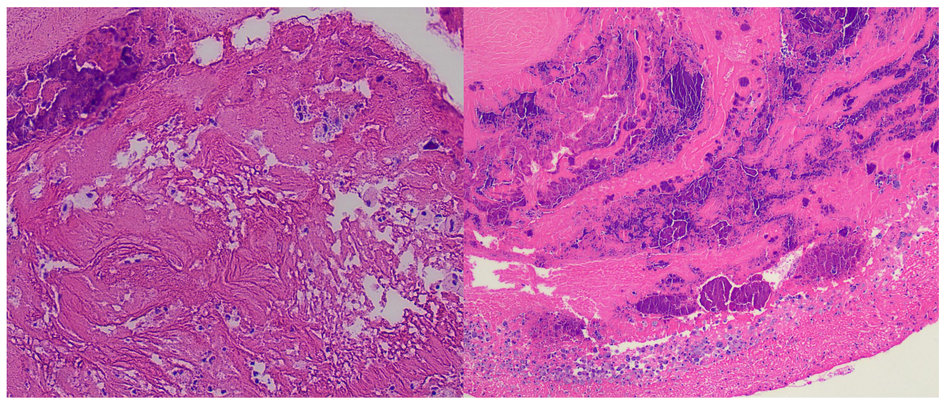

Figure 1: Sections of tricuspid valve of Case 1. Haematoxylin and eosin staining demonstrating extensive inflammatory fibrinous exudate with acute on chronic inflammation and scattered histiocytes.

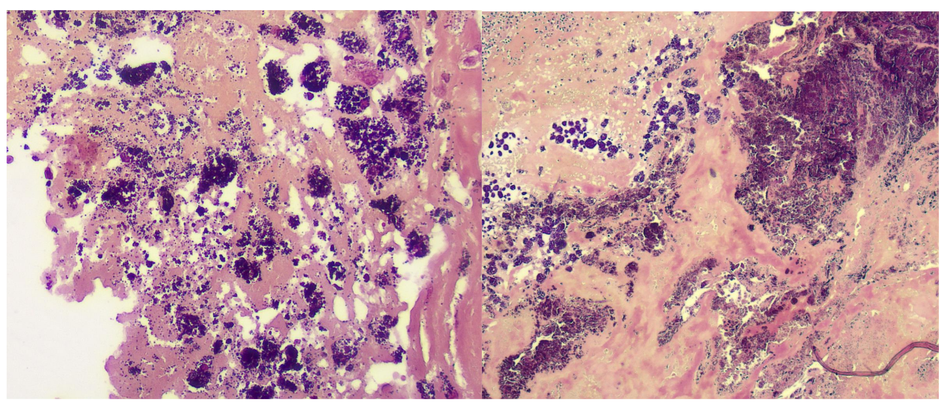

Figure 3: Gram stain of section of tricuspid valve of Case 1 demonstrating gram-positive cocci.

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

Case	Age	Gender	Antimicrobials (days)	Days pre E/C BC +ve	Days post E/C BC +ve	Heart Valve	Septic Sequelae	Comorbidities
1	28	M	Gentamicin (1) Vancomycin (3) Flucloxacillin (10) Cefazolin (28) Ertapenem (14) Flucloxacillin (14)	12	0	Native Tricuspid and Pulmonary Valves	Bilateral empyema Septic arthritis of right hip	Intravenous drug use, chronic back pain
2	67	M	Flucloxacillin (7) Cefazolin (7) Ertapenem (7) Flucloxacillin (35)	7	0	Native Tricuspid Valve	Multilevel vertebral osteomyelitis (cervical and lumbosacral), L) psoas abscess	Metastatic melanoma, gout, psoriasis
3	66	M	Flucloxacillin (10) Cefazolin (42) Ertapenem (7)	11	0	Bioprosthetic Aortic Valve	Bilateral cerebral parieto-occipital septic emboli	Severe asthma, ischaemic heart disease with CABG, HFrEF, Atrial fibrillation, Type 2 diabetes mellitus, hypertension, pulmonary embolism

E/C = Ertapenem + cefazolin

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-1β, 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

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