Case report

A rationale for combination ampicillin and daptomycin in renal transplant patients with enterococcal infective endocarditis

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ABSTRACT

Treatment of enterococcal endocarditis in patients with history of renal transplantation is complicated. Treatment failure and/or drug toxicities are not uncommon. Treatment with ampicillin and daptomycin in a renal transplant patient has been rarely reported. Here we report a patient who was successfully treated with this novel combination.

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Introduction

Enterococcal endocarditis is a serious cause of morbidity and mortality and is the second most common cause of nosocomial endocarditis. In patients with a history of solid organ transplant, specifically kidney transplant recipients, treatment failure and/or drug toxicities are not uncommon. The combination of ampicillin and ceftriaxone is recognized as aminoglycoside sparing regimen for Enterococcus faecalis (E. faecalis) infectious endocarditis (IE) but with a wider therapeutic window and equivalent treatment success. Early clinical experience suggests ampicillin and daptomycin may provide an additional aminoglycoside sparing regimen with equivalent treatment success for E. faecalis and Enterococcus faecium (E. faecium) with the potential benefit of reduced toxicity. We report the successful treatment of E. faecalis IE with ampicillin and daptomycin in a renal transplant patient.

Case report

A 68-year-old Hispanic female, status post deceased donor kidney transplant (DDKT) eleven years prior presented with fever. The patient’s anti-rejection therapy included oral tacrolimus 0.5 ml twice a day as well as oral prednisone 5 mg daily. Her baseline serum creatinine ranged from 0.7 to 1 mg/dl since the transplantation. Days prior to the current admission, patient was diagnosed with urinary tract infection and was treated with ciprofloxacin with no noted improvement. She was then reevaluated by the referring facility for fever where blood cultures were drawn. Empiric cefepine, vancomycin and fluconazole were initiated while awaiting culture results. Two of two blood cultures were notable for gram positive cocci. E. faecalis was later confirmed. The isolate was susceptible to ampicillin (MIC < 2), vancomycin (MIC 2), gentamicin synergy (MIC < 500), and daptomycin (MIC 1). A transthoracic echocardiogram (TTE) was performed and was notable for an abnormal appearing aortic valve. A transesophageal echocardiogram (TEE) subsequently confirmed a vegetation measuring 0.7 cm. Daptomycin (6 mg/kg/day) was initiated in addition to ampicillin (2 gm IV every 4 h). Baseline creatine phosphokinas (CPK) was obtained in addition to thrice weekly monitoring of the blood cell count (CBC) and serum creatinine. Monitoring was continued over the next 6 weeks of therapy.

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Antibiotic therapy was discontinued at day 42 and a repeat blood culture collected 24h post-treatment were negative. During treatment, the patient’s baseline serum creatinine remained stable, without evidence of acute kidney injury or nephrotoxicity. The patient reported no other side effects. The only abnormal laboratory value noted over this time was an increase in the patient’s serum glucose, which was considered unrelated to antibiotic treatment. The patient was released from the hospital with no additional treatment. She has been followed for twelve months post-antibiotic therapy and remains symptom-free without cardiac complications or renal graft dysfunction (Fig. 1).

Discussion

Patients who undergo a solid organ transplantation have a high rate of complication with a bacteremic episode, when compared to the general population especially with staphylococci and enterococci [1]. Enterococcus species have evolved to become a very important pathogen causing endocarditis in renal transplant patients [2]. Further, over the last few decades it has become the 2nd most common pathogen in the subgroup of healthcare-acquired bacterial endocarditis, second only to Staphylococcus aureus [3].

Although enterococcal species is one of the most common causes of enterococcal IE in the renal transplanted population, individual cases have been rarely reported in literature with only 5 published cases found in the English literature [4–6]. Of the five cases, 3 were male and 2 were female (all adults) with a median age of 46 years (Table 1). Enterococcal endocarditis occurred within the first 6 months post transplantation in all five previously reported cases. Enterococcus were also found to be vancomycin resistant (VRE) in 60% (3/5) of the cases (2 cases were E. faecium, and one was E. faecalis). The E. faecium were also found to be resistant to ampicillin-sulbactam (1/5), ciprofloxacin (1/5), and ampicillin 1/5. E. faecalis was found to have high-level resistance to gentamicin (Table 1). Initial treatment failure occurred in 4/5 (80%). Only 1/5 was treated successfully with the initial antimicrobial regimen with ampicillin+gentamicin. Of the five patients two (40%), needed valve replacement surgery to secure a successful outcome. One patient had dose adjustments due to side effects another developed myalgias, hyponatremia, and increasing creatine secondary to quinupristin/dalfopristin (Q/D); Another patient failed combination therapy of Q/D plus doxycycline (lab reported susceptibility to these antimicrobials) after initial therapy consisting of ampicillin + gentamicin but eventually achieved a positive outcome with linezolid monotherapy. Linezolid had to be discontinued due to thrombocytopenia. Another patient with E. faecium IE failed combination therapy with doxycycline and chloramphenicol despite proven susceptibilities also. Patient also failed a 6-week course of ampicillin-gentamicin combination despite proven synergy; another patient failed ampicillin monotherapy with a susceptible strain. Only one patient with E. faecalis (VRE) was cured with initial regimen of ampicillin and gentamicin without side effects. Creatinine levels increased in 3/5 (60%); two reported the use of an aminoglycoside as initial antimicrobial option.

The need for combination therapy to obtain microbiological eradication and cure have been recognized since the early 50’s. Multiple combinations have been advocated for enterococcal endocarditis including ampicillin and gentamicin, most recently ceftriaxone plus ampicillin [8]. Ampicillin plus daptomycin has also been proven successful in a small cohort of 5 patients in which all had abnormal renal function [9].

Our patient with renal transplantation and multiple comorbidities developed enterococcus IE 11 years after her transplant surgery. Renal function was stable for more than 10 years; therefore, the challenge was to obtain a complete eradication of the infection without affecting the transplanted organ. We selected ampicillin and daptomycin combination therapy in our case to achieve both definitive cure of the infection without risking renal failure as well as the fact that the treating physician (MSH) had prior success with such a regimen in non-transplant patients [9].

Daptomycin is a cyclic lipopeptide that has proven to have in vitro activity against enterococci with an MIC for E faecalis and E faecium of 4 and 1 mg/l respectively [10]. Clinical cure rates of 87% with bacteremia have been achieved when daptomycin is used as monotherapy [10]. Clinical cures have been achieved with linezolid monotherapy also [7]. Even in the presence of proven antimicrobial resistance to other antibiotics, the combination of ampicillin with daptomycin has shown to have a synergistic benefit [11]. Sakoulas et al. investigated the synergistic properties of ampicillin and daptomycin in VRE. From in vitro studies, they postulated that exposure to ampicillin induced a sizable reduction in net positive surface charge on the organism that was associated with an increased surface binding of daptomycin [11]. This proposed mechanism of synergy influenced antibiotic selection for our patient along with authors prior experience.

![Fig. 1](image_url)

Fig. 1. Transesophageal ECHO with long (A) and short (B) axis views of the aortic valve. Vegetations are present on the right coronary cusp (red arrow) and non-coronary cusp (blue arrow).
| Case No./ Reference | Age / Gender | Initial and Final Creatinine (mg/dL) | Subspecies | Prior Antimicrobials | Final Therapy | Surgery | Outcome | Comments |
|---------------------|--------------|-------------------------------------|-------------|---------------------|---------------|---------|---------|----------|
| 1 (Paterson DL, [4]) | 60 / F       | NM                                  | Enterococcus faecalis | Ampicillin plus gentamicin (6 week course) | same as initial | Side effects none | no      | alive     | 1. Needed Ampicillin desensitization Prior to treatment 2. VR none |
| 2 (Pourreza-Gholi F, [5]) | 28 / F       | I: 1.46 F: 2.0                      | NM          | Empirical (not specified) | Vancomycin    | none    | Aortic and mitral valve replacement | alive     |
| 3 (Pourreza-Gholi F, [5]) | 22 / M       | I:2.0 F:2.18                       | NM          | Ampicillin 2 g / day | Vancomycin    | none    | Aortic valve replacement | alive     |
| 4 (Thompson R, [6]) | 56 / M       | F: 4.9                              | Enterococcus faecium | 1. vancomycin 1 g / day; empirically follow 2. chloramphenicol plus doxycycline follow 3. Ampicillin plus gentamicin (54 days) day 82: bacteremia recurred: amp plus gentamicin was restarted follow 4. Q/D (960 mg/8 hr) plus amp 1. Q/D 7.5 mg/kg every 8 hr plus am/sulfactam followed 2. Q/D plus doxycycline | myalgias | none | alive | VR, resistant to am-p-sulbactam and ciprofloxacin; susceptible to chloramphenicol and doxycycline; gentamicin inhibitory at 120 mg/ml; FIC index 0.8 for gentamicin and ampicillin suggesting synergy (patient fail a 6 week course) |
| 5 (Archuleta S, [7]) | 64 / M       | NM                                  | Enterococcus faecium | Linezolid 600 mg daily (6 weeks) | trombocytopenia | none | alive | VR(MIC >16ug/ml, ampicillin resistant (MIC >8ug/ml; susceptible to Q/D (MIC >1ug/ml)) none |
| 6 ** | 68 / F       | I: .73 F: .79                       | Enterococcus faecalis | 1. Ampicillin 2 G IV q/4 h; Daptomycin 6 mg/kg q/d for 6 weeks | none | none | none | alive |

NM, not mention, VR, vancomycin resistant, Gm, gentamicin, Amp, ampicillin, HLR, High level resistance, Q/D, Quinupristin/dalfupristin.
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Daptomycin and ampicillin may be a preferred initial choice for treatment of enterococcal endocarditis particularly when renal dysfunction or renal transplantation are present. The choice of first-line treatment clearly depends on indication and bacterial expectations, patient preferences and allergies, past treatment experiences, side effect profiles as well as availability, dispensing regulations and cost. In conclusion an individualized approach to antibiotic selection is preferred but when renal dysfunction or renal transplantation coexist with enterococcal endocarditis the combination of daptomycin and ampicillin could be considered as an alternative to standard first line therapy.

### Competing Interests/Funding

None.

### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Author statement

All authors have reviewed and participated in the manuscript preparation. MSH, VV, TT cared for the patient and provided the case report. MTC, OAI performed the literature search and construction of table. MTC, MSH, AH, RF, RW, CJ helped with discussion, formatting, references, and submission.
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References

[1] Berenger B.M., Doucette K, Smith SW. Epidemiology and risks factors for nosocomial bloodstream infections in solid organ transplants over a 10-year period. Trans Inf Dis 2016;18(2):183–90.
[2] Moshkani Farahani M, Rostami Z, Einollahi B, et al. Infective endocarditis after renal transplantation. Neuphrourol Mon 2014;6:e12326.
[3] Pericas JM, Cervera C, del Rio A, et al. Enterococcal endocarditis revisited. Future Microbiol 2015;10(7):1215–40.
[4] Paterson DI, Dominguez EA, Chang F, Snydman DR, Singh N. Infective endocarditis in solid organ transplant recipients. Clin Infect Dis 1998;26 (3):589–94.
[5] Pour-reza-Gholi F, Farrokhi F, Einollahi B, Nemati E. Successful treatment of infective endocarditis in four kidney transplant recipients. Iran J Kidney Dis 2007;1(1):43–5.
[6] Thompson R, Lavin B, Talbot G. Endocarditis due to vancomycin-resistant Enterococcus faecium in an immunocompromised patient: cure by administering combination therapy with quinupristin/dalfopristin and high-dose ampicillin. South Med J 2005;98(8):818–20.
[7] Archuleta S, Murphy B, Keller MJ. Successful treatment of vancomycin-resistant Enterococcus aecium endocarditis with linezolid in a renal transplant recipient with human immunodeficiency virus infection. Transpl Infect Dis 2004;6(3):117–9.
[8] Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating Enterococcus faecalis infective endocarditis. Clin Infect Dis 2013;56(9):1261–8.
[9] Sierra-Hoffman M, Iznasho O, Lamp KC, Mohr JF, Wino RE. Daptomycin and ampicillin combination for treatment of Enterococcus faecalis endocarditis. Infect Dis Clin Pract (Baltim Md) 2015;23(4):198–201.
[10] Cantón R, Ruiz-Garbajosa P, Chaves RI, Johnson AP. A potential role for daptomycin in enterococcal infections: what is the evidence? J Antimicrob Chemother 2010;65(6):1126–36.
[11] Sakoulas G, Bayern AS, Poglino J, et al. Ampicillin enhances daptomycin, Cationic host defense peptide-mediated killing of ampicillin, vancomycin-resistant Enterococcus faecium. Antimicrob Agents Chemother 2012;56 (2):838–44.