fortune Journals

Research Article

CARDIOLOGY AND CARDIOVASCULAR MEDICINE

ISSN: 2572-9292

Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review

Fernando Baires[1], Erin Arias[2], María José Díaz Ramos[3], Cesar Burgos[4], Guillermo Lopez[5], Juan S Llompart[6], Jana Radwanski[7], Tywaun Tillman[8], Fernando Valerio-Pascua[9], Anupamjeet Kaur Sekhon[10], Jarmanjeet Singh[11], Chetan Jinadatha[12], Miguel Sierra-Hoffman[13,*], Mark L Stevens[14]

Abstract

Historically, the conventional treatment for enterococcal endocarditis (EE) has been combination antibiotic therapy, as it has proven to be more effective than monotherapy. A novel approach using dual beta-lactam therapy, which combines ampicillin and ceftriaxone, emerged as an equally effective alternative to the traditional combination therapy using aminoglycosides. One key advantage of this regimen is that it avoids the nephrotoxicity associated with aminoglycosides, making it the first aminoglycoside-sparing combination. This innovative treatment approach has gained widespread acceptance worldwide.

The incidence of EE is rising, particularly among elderly individuals, those with comorbidities, and patients with healthcare-associated infections. It is now the leading cause of infective endocarditis in kidney transplant recipients and patients who have undergone transcatheter aortic valve implantation (TAVI). Additionally, it is the second most common cause of endocarditis in hemodialysis patients. Given these trends, it is important to explore alternative treatment options that do not involve the use of aminoglycosides.

In this report, we present a case of a renal transplant patient who developed Enterococcus faecalis endocarditis that was successfully treated with an aminoglycoside sparing regimen of ampicillin and daptomycin. This case highlights the potential effectiveness of this combination therapy and paves the way for future research into this innovative approach.

In conclusion, the treatment landscape for EE has evolved with the introduction of new aminoglycoside sparing combinations. Further research is needed to fully understand the potential benefits and limitations of these alternative therapies and to establish evidence-based guidelines for the management of EE.

Keywords: Endocarditis; Enterococcal; Daptomycin; Transplant; Ampicillin

Introduction

At the turn of the 21st century, multiple paradigm shifts occurred in various disciplines of medicine. Due to improved surgical techniques and anti-rejection therapies, solid organ transplantation (SOT) has become widely accepted as a first line therapeutic option for end-stage kidney, heart, and liver organ failure. As a result, overall survival in these patients improved substantially [1].

Affiliation:

[1]Universidad Nacional Autónoma de Honduras, Tegucigalpa, Honduras

[2]Universidad Latina de Costa Rica powered by Arizona State University, San Jose, Costa Rica

[3]Universidad de Ciencias Médicas, San José, Costa Rica

[4]Instituto Nacional Cardiopulmonar El Tórax, Tegucigalpa, Honduras

[5]Facultad de Ciencias Médicas, Universidad de Cuenca. Cuenca, Ecuador

[6]Baylor University Department of Biology in the College of Arts and Sciences, Waco, TX, USA

[7]Citizens Medical Center, Victoria, TX, USA

[8]Citizens Medical Center, Victoria, TX, USA

[9]Department of Critical Care, Hospital CEMESA, San Pedro Sula, Cortés, Honduras

[10]Sleep Medicine, Kaiser Permanente, Fontana, CA, USA

[11]Department of Cardiovascular Medicine, University of California Riverside, CA, USA

[12]School of Medicine, Texas A&M University, Bryan, TX, USA

[13]Research and Infectious Disease Department, Texas A&M College of Medicine, Detar Family Medicine Residency Program, Victoria, TX, USA

[14]Research Department, Texas A&M College of Medicine, Detar Family Medicine Residency Program, Victoria, TX, USA

***Corresponding authors:**

Miguel Sierra-Hoffman, Research and Infectious Disease Department, Texas A&M College of Medicine, Detar Family Medicine Residency Program, Victoria, TX, USA.

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 338-346.

Received: July 26, 2024
Accepted: August 02, 2024
Published: August 13, 2024

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

There were more than 948,252 SOT procedures done between 2001 and 2023 in the United States [1]. Renal transplantation is being performed worldwide and has become the standard of care in patients progressing to end-stage renal disease (ESRD) in preference to any form of renal replacement therapy. By the end of 2023, a total of 558,675 patients have had a functioning transplanted kidney in the US [2].

SOT patients are permanently at risk for many potential complications, not only in the immediate post-transplant stage but extending throughout their lifetime. Infections are always a threat given the long-term immunosuppressed state that results from anti-rejection medications. Petros Ioannou et al. [1] confirmed this observation in a comprehensive contemporary review, which found that renal transplant recipients have a significantly higher risk of infective endocarditis (IE) than other SOT patients. An extensive search of the published data showed that the leading organisms were gram-positive in 57.4% of the cases, and among them, Enterococci were the leading cause in 26.1% of the cases [1].

Of all the enterococcal species, *Enterococcus faecalis* is the most common causative organism in endocarditis, being responsible for 90% of all cases in the general population; this distribution is similar in the renal transplant population [3].

EE requires prompt identification and timely implementation of effective combination antibiotic therapy to eradicate the infection and avoid damage to the transplanted kidney. Additionally, early diagnosis and prompt initiation of antibiotic therapy will help avoid such potential complications as cardiac valve replacement and even death. Twentieth-century antibiotic practices have brought forth the current era of multidrug resistance, thus there is an urgent need to seek alternative therapeutic options. As a result, the most recent international guidelines have included new regimens for treating EE [4,5]. These regimens are both first and second-line therapies that spare the use of aminoglycosides. The most utilized aminoglycoside sparing combination is ampicillin and ceftriaxone for *E. faecalis* This combination has proven equivalent to ampicillin and gentamicin in treatment outcomes without the concomitant renal and ototoxicity of the aminoglycosides [6].

In 2012, the first reported success of the combination of ampicillin and daptomycin provided a novel experience with aminoglycoside sparing agents [7]. Subsequently, in 2015, a cohort of five chronic kidney disease (CKD) patients so treated supported this regimen's efficacy for managing *E. faecalis* endocarditis [8]. However, when first used, this combination was met with a challenge in a kidney transplant patient in 2018 [9]. Following this series of cases, a retrospective study of 35 patients treated with ampicillin and daptomycin was presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2020 [10]. This is to date the largest cohort, spanning three countries with all subspecies of Enterococcus, including *Enterococcus faecium*. This was the largest registry ever compiled in the literature, with results spanning the last decade.

This accumulated clinical experience supports the utilization of another promising aminoglycoside sparing regimen. We present a second case of a kidney transplant patient with *E. faecalis* endocarditis treated successfully with this combination. This manuscript reports this second case and reviews our experience using this combination.

Case Report

The patient is a 45-year-old African American female who worked as a correctional officer with a history of lupus-associated nephropathy requiring hemodialysis until a first renal transplant in 2012 and then a second renal transplant in 2017. Additional comorbidities included hypertension, diabetes mellitus, and construction of arteriovenous shunt. The patient had had anaphylaxis to levofloxacin. Current medications included tacrolimus 3 mg by mouth twice daily and prednisone 5 mg by mouth once daily; she reported being compliant with her home medications. She was in her usual state of health until presenting on 2022 to the emergency department (ED) with a two-day history of diarrhea. The diarrhea was not described as bloody nor associated with vomiting nor abdominal pain. She denied recent travel, contact with sick individuals, nor recent antibiotic use. The review of systems was positive for fever, muscle aches, nasal congestion, and headache. Vital signs at the time of consultation showed a blood pressure of 140/75, a heart rateo f 112, and an oral temperature of 100.9 F. The initial cardiac examination was unremarkable; specifically, there were no murmurs. Examination of the lungs and abdomen was unremarkable as well.

A complete workup, including blood cultures, was performed. The Chest X-Ray report described cardiomegaly with mild bibasilar pulmonary opacities, shown in Figure 1.

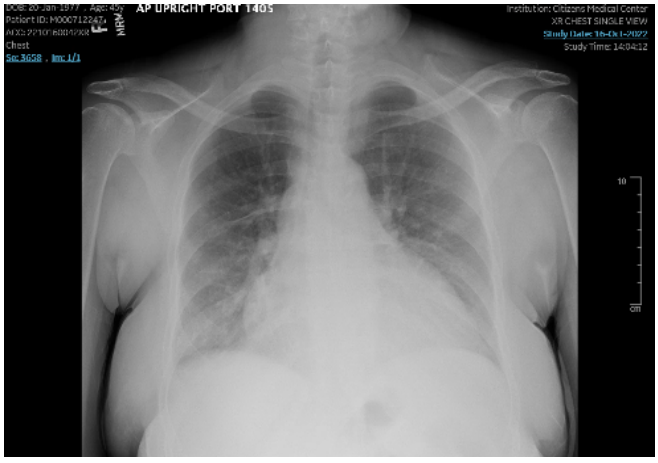

Figure 1: Cardiomegaly with mild bibasilar pulmonary opacities on Chest X-Ray.

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

An abdominal computed tomography (CT) scan revealed no acute abdominopelvic abnormalities. The Complete Blood Count showed a white blood cell (WBC) count of 11,560 cells/mm^3 (range: 4,800- 10,800), neutrophils 79.6% (range: 50- 75%), and lymphocytes 8.10% (range: 20- 40%). Hemoglobin level was 13.2 g/dl (range 11.5- 16.0), and platelet count was mildly decreased at 129,000 per cubic mm (range: 130,000 – 400,000). A complete metabolic panel revealed increases in both blood urea nitrogen and creatinine levels at 36 mg/dl (range: 7-20) and 2.81 mg/dl (range: 0.57-1.11), respectively. Urinalysis showed increased urine WBC of 6-10 (range: 0-2) and the presence of red blood cells and 2+ proteinuria, COVID-19 test was negative. Table 1 shows detailed laboratory values during the patient's hospitalization. At that point she was felt to be stable, and was discharged from the ED with oral cephalexin 500 mg every 6 hours by mouth for seven days due to a suspected urinary tract infection and acute viral rhinitis with frontal sinusitis.

Table 1: Lab values during patient stay.

Lab Values During Patient Stay							
Day of Treatment	**SCr**	**GFR**	**BUN**	**CPK**	**Na**	**K+**	**Urine Protein**
Day 1	2.27	28	28	135	138	4.5	2+
Day 2	1.7	39	22		143	4.3	
Day 3	1.61	42	21		142	4.6	
Day 4	1.74	38	19	62	145	4.2	
Day 5	1.85	36	18		140	4.3	
Day 7	1.8	37	16	55	142	3.9	
Day 9	1.93	34	18		141	4.7	
Day 10	2.13	30	18	66	138	5.4	
Day 12	2.32	27	19		137	4.7	
Day 13	1.98						
Day 14	1.84	36	20	56	141	4.5	
Day 15	1.89	35	21		141	4.9	
Day 16	1.74	38	23	41	141	4.8	
Day 18	2.11	31	23		141	4.7	
Day 20	1.86	35	19	70	142	4.3	
Day 23	1.93	34	22	70	140	4.6	
Day 25	2.22	29	24		142	4.3	
Day 27	1.87	35	26	39	139	4.6	
Day 30	1.86	35	25	35	143	4.3	
Day 34	1.97	33	29	46	143	4.8	
Day 37	1.97	33	29	64	142	4.2	
Day 41	1.88	35	28	66	142	4.5	
Day 43	1.83	36	28	65	142	4.4	

A day later, the patient was asked to return to the ED due to a positive blood culture for *E. faecalis* that was collected from her right arm. The patient was admitted to the hospital and started on intravenous vancomycin 1.25 g. On admission, a transthoracic echocardiogram was performed as shown in Figure 2, which revealed aortic sclerosis and trace mitral regurgitation.

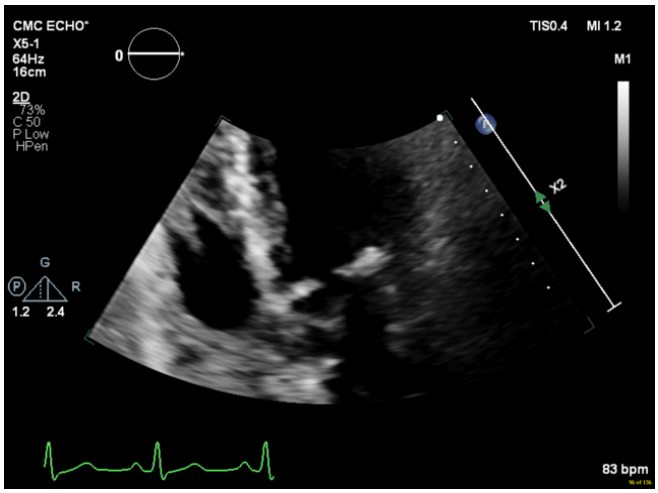

Figure 2: Transthoracic ECHO apical 4-chamber view demonstrating nonspecific thickening of the mitral valve and annular apparatus).

Endocarditis could not be ruled out, which prompted stopping vancomycin and initiating antibiotic coverage with ampicillin/sulbactam 3 g every 12 hours intravenously (at that time, plain Ampicillin was unavailable but was substituted two weeks later). The physical examination was positive for a systolic murmur in the right parasternal border and a systolic murmur in the left fifth intercostal space. Axillary and inguinal lymph nodes were palpable, and lower extremity trace edema was present. During her hospital stay there were 6 blood cultures drawn, of which only 2 were positive for *E. faecalis*. Note that the patient was started on antimicrobial therapy after the first positive blood culture. Two days after consultation, the patient underwent a transesophageal echocardiogram, which confirmed the presence of a 0.7 × 0.6 cm vegetation attached to the posterior leaflet annulus of the mitral valve as shown in Figure 3.

The multidisciplinary team, guided by Infectious Disease specialists, recommended that the main goal was to treat the infection without causing any further worsening of her renal function. A regimen consisting of daptomycin 6 mg/kg IV with ampicillin/sulbactam 3g IV was initiated. For the remaining four weeks of treatment, ampicillin was given at 1 g IV q 8h, and was adjusted to the glomerular filtration rate (GFR). If the GFR was greater than 30 ml/min/1.73m^2, the patient was to receive daptomycin every 24 hours and ampicillin every 12 hours. A six-week duration of treatment was recommended. Heart valve replacement was not needed during the treatment.

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

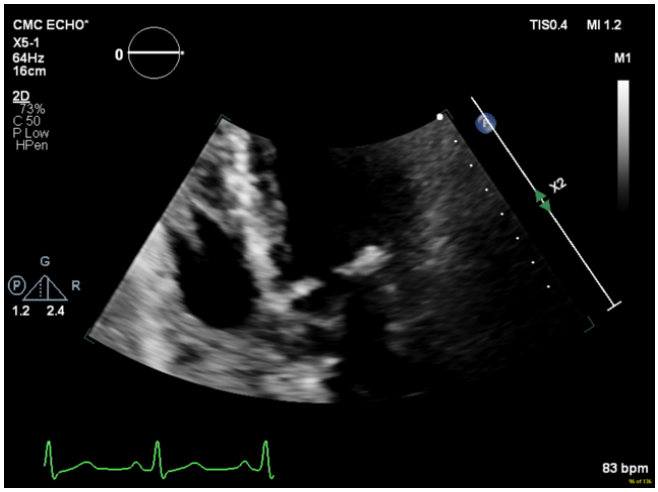

Figure 3: Vegetation on a 2D ECHO. Trans-esophageal echo at mid-esophageal commissural view (61 degrees) demonstrates a 0.7 × 0.6 cm vegetation (arrow) on the atrial aspect of the anterior mitral leaflet.

During her hospitalization, the patient's blood work began to improve, showing a decrease in her WBC and an improvement in creatinine levels, down to 1.83 mg/dl. Eight days after onset of symptoms, the patient was transferred to a skilled nursing unit to continue intravenous treatment as recommended. Six weeks later, the patient was discharged from the skilled nursing unit in stable and improved condition, having experienced a full recovery. At a six-month follow-up, blood cultures were negative. The patient was alive and doing well, with baseline renal function returning a year later.

Discussion

Globally, the adoption of Solid Organ Transplantation (SOT) as first-line therapy for end-stage organ failure has not come without its share of complications. EE poses a substantial risk to renal transplant patients, and multiple factors must be considered given the grave nature of this infection. Such factors include addressing multidrug-resistant organisms, antibiotic therapy-related toxicity, and preserving the transplanted organ. Additional considerations include salvaging an affected cardiac valve and avoiding the need for a valve replacement. Ampicillin and gentamicin have historically been the standard of care as first-line treatment for many years until the aminoglycoside sparing regimen of ampicillin and ceftriaxone showed non-inferiority in clinical studies.

Gram-positive bacteria comprise more than eighty percent of the pathogens responsible for native and prosthetic valve IE [11]. Historically, Enterococcus has been the third most common infectious agent when considered under the original classification of acute, subacute, and chronic IE. This format is intended to group the different types of IE based on the clinical pathophysiological presentation and, therefore, helps to accurately predict the infecting organism. More recently, a novel approach has proposed implementing a more practical system based on the population studied, including categories of community-acquired, nosocomial, non-nosocomial healthcare-associated, IV drug users, prosthetic valves, pacemakers, and defibrillators [12]. Using this scheme, Enterococcus becomes a common cause of IE in the hospital and nosocomial environments, second only to staphylococcus.

Enterococcus is the third leading agent of IE worldwide, accounting for nearly ten percent of the cases [13]. Moreover, *Enterococci* are the top causative agents of endocarditis in Transcatheter Aortic Valve Implantation (TAVI) patients [14] and the second leading cause of prosthetic valve endocarditis in hemodialysis-dependent patients [3,15]. *E. faecalis* is the most common subspecies identified, responsible for 90% of the cases [16]. *E. faecium* accounts for far fewer cases but is associated with hospital-acquired infections and is known for its ability to develop more robust antibiotic resistance. New data has shown the gap is closing between *E. faecium* and *E. faecalis* bacteremia, with a ratio of 1:1.8, respectively [17]. The increasing antibiotic resistance shown by enterococcus species has highlighted the importance of gaining newer insights on different treatment options, as discussed by Nappi *et al*. [18].

A landmark study that broke decades of the longstanding tradition of including aminoglycosides in any combination of therapy conducted by Fernandez-Hidalgo *et al*. [6] showed the non-inferiority of ampicillin and ceftriaxone compared to ampicillin plus gentamicin for treating *E. faecalis* IE [6]. The median length of treatment was six weeks in both groups. Clinical outcomes were not significantly different in either group, except for the development of renal failure, which was significantly less frequent in the ampicillin plus ceftriaxone group. With ampicillin plus ceftriaxone, the clinical cure rate was 71.4 %. The success rate after three months was 67.4%, with a relapse rate of 5% and a 1-year mortality of 23.3%. These results were based on a large cohort, together with a smaller study with overlapping results by Pericàs et al. [15,16] that was published later, and led to both the American Heart Association and European Society of Cardiology guidelines to include ampicillin plus ceftriaxone as a first-line treatment option for *E. faecalis*, and the preferred choice for high-level aminoglycoside resistant (HLAR) strains [4,19,20]. Another newer option is a two-week shortened gentamicin course within the beta-lactam plus gentamicin therapeutic combination. This is supported by non-inferiority and more extensive safety data shown in a Danish study [21]. Although considered a breakthrough, these results and guidelines met with some criticism.

Beganovic et al. [21] published an excellent review of 30 years of literature regarding Enterococcal endocarditis. This review emphasizes that combination therapy remains the ideal approach to reduce the significant rates of morbidity and

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

mortality observed in the past. The authors stress that critical steps are needed to encourage more research regarding this infection. In one of their conclusions, they highlight that the double beta-lactam therapy, ampicillin, and ceftriaxone combination is a more desirable strategy which spares aminoglycosides. while leaving the door open in the future for potential aminoglycoside sparing regimens. We refer the reader to the manuscript for complete details [22].

Koehler et al. [23] in a letter to the editor, wrote that the double beta-lactam combination is still up for debate. He raises reasonable concerns, such as potentially increasing the incidence of *Clostridium difficile* associated colitis and the emergence of gram-negative bacteria resistance [23].

Daptomycin is a cyclic lipopeptide antibiotic with bactericidal activity against many gram-positive bacteria, including Vancomycin-Resistant Enterococci (VRE) [24]. This antibiotic has an unusual mechanism of action, and when combined with ampicillin, results in unexpected synergy. The mechanism of this synergy has yet to be fully understood. However, this combination seems to enhance daptomycin's bactericidal activity [11], and its broad safety profile makes it especially appealing for patients with impaired renal function.

Thus far, the data regarding the use of daptomycin with ampicillin in clinical practice for IE consists mostly of case reports [9,25], as shown in Table 2. However, in a rabbit model, the authors recently compared the efficacy of combination therapy of daptomycin and ampicillin versus daptomycin monotherapy. Comparison was made against induced Daptomycin Non-Susceptible (DNS) strains in an experimental Enterococcal endocarditis model [26]. The study used a collection of *E. faecalis* strains from patients infected with IE and created an experimental endocarditis model using infected rabbits. In daptomycin-sensitive strains, the combination of daptomycin and ampicillin was significantly more effective than daptomycin alone. Daptomycin and ampicillin combination therapy was also similarly as effective as ampicillin and ceftriaxone therapy. The authors recommended that a daptomycin Minimum Inhibitory concentration (MIC) with the E-test be performed on all initial IE blood isolates to rule out DNS strains. If DNS strains were observed, it was recommended that the combination of daptomycin and ampicillin should be avoided, and ampicillin and ceftriaxone should be utilized instead due to inherent resistance.

Table 2: Kidney Transplant Patients with Infective Endocarditis due to E. Faecalis.

Case	Year	Country	Age (Sex)	Transplant organ	Time between transplant and IE development	Affected Valve(s) / type of endocarditis	Organism	Initial Therapy	Directed therapy	Outcome	Reference
1	1998	USA	60 (F)	Kidney	2 mo	Mitral / native	NM	Ampicillin; Gentamicin	Ampicillin; Gentamicin	Alive and well	[27]
2	2007	Iran	28 (F)	Kidney	6 mo	Mitraland Aortic/ native	E. faecalis	Vancomycin	Vancomycin; MVR; AVR	1 yr follow-up: Alive and Well	[28]
3	2007	Iran	22 (M)	Kidney	5 mo	Mitral, Aortic/ native	NM	Ampicillin 2G IV	Vancomycin and Amikacin added; AVR	3 mo follow-up: Alive and Well	[28]
4	2016	UK	77 (M)	Kidney	NM	mitral valve/ native	E. faecalis	Intravenous amoxicillin.	IV amoxicillin (6-week total duration), oral ciprofloxacin and intravitreal vancomycin and ceftriaxone.	Good recovery from his endocarditis, loss of vision in the affected eye.	[29]
5	2018	USA	68 (F)	Kidney	11 yr	Aortic	E. faecalis	Ampicillin 2G IV q/4hr; Daptomycin 6mg/kg q/d for 6 weeks	Ampicillin 2G IV q/4hr; Daptomycin 6mg/kg q/d for 6 weeks	6 mo follow-up: Alive and Well	[9]
6	2018	Portugal	50 (M)	Kidney	5 mo	Mitral and Aortic Valve /Native	E. faecalis	Vancomycin	Vancomycin and Surgery (Aortic and Mitral valve replacement.).	Alive	[30]
7	2020	China	60 (M)	Kidney	2 weeks	No described	E. faecalis	Sulfonamide (10 days).	Linezolid and piperacillin/ tazobactam for 7 days.	Death	[31]
8	2020	China	48 (M)	Kidney	1 week	No described	E. faecalis	imipenem/ cilastatin and linezolid.	imipenem/ cilastatin and linezolid	Death	[31]

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

9	2022	USA	45 (F)	Kidney	6 Yr	mitral valve/ native	E. faecalis	Daptomycin 450 mg IV daily for 42 days Ampicillin sodic/ sulbactam sodic 3 gm IV BID for 42 days	Daptomycin 450 mg IV daily for 42 days Ampicillin sodic/ sulbactam sodic 3 mg IV BID for 42 days	Good recovery from her endocarditis, alive and well.	Our case

In 2012, Sakoulas et al. [32] reported a case of left-sided endocarditis with an ampicillin and vancomycin-resistant E. faecium that failed daptomycin and linezolid combination therapy [32]. The bacteremia, however, resolved with the combination of daptomycin and ampicillin. The patient had no septicemia within 24 hours of initiating this therapy, even after days of persistent bacteremia.

Hoffman et al. [7] have published several individual cases of endocarditis treated with a daptomycin and ampicillin combination. All patients had some degree of renal disease with a spectrum from chronic kidney disease, end-stage renal disease on hemodialysis, or temporary hemodialysis, when the infection occurred. A sixth case was a kidney transplant patient who had maintained renal function within normal range for 11 years [7,9]. In all these cases, the treatment was successful when used as a primary regimen or salvage therapy. In all patients, renal function was preserved in those with pre-existing renal disease; in the transplanted patient, the infection was eradicated. No recurrence was noted at a one-year follow-up. We have summarized the clinical features, renal status, and outcome in Table 3, including our case report.

The findings of Pericas et al. [3] and Herrera-Hidalgo et al. [33] contemporary reviews are in agreement with our data presented in Table 3. They show that Enterococcal endocarditis is the second most prevalent cause of infective endocarditis among the chronic hemodialysis population, trailing behind only Staphylococcus aureus with percentages of 15.4% and 47.8%, respectively. Importantly, the researchers highlight the higher occurrence of relapses compared to previous studies and an increase in both in-hospital and six-month mortality rates among hemodialysis-treated patients, reaching levels of 30.4% and 39.8%, respectively. Similar patterns were observed in our limited patient cohort in Table 3, where all seven were associated with hemodialysis had established chronic kidney disease, one was renal transplanted patient, or were iatrogenically immunosuppressed.

Many unique properties of enterococcus species have been validated and documented in the contemporary literature. A compilation of these findings is presented in Table 4.

The main drawbacks of daptomycin therapy are a well-documented association with rhabdomyolysis [34] and eosinophilic pneumonitis [35], both of which are potentially

Table 3: Sierra Hoffman et al. [7] Case series of enterococcal endocarditis treated with ampicillin and daptomycin combination in either chronic kidney disease patients, end stage renal disease patients on hemodialysis or kidney transplanted patients.

Case	Year	Country	Age (Sex)	Infected Valve	Kidney Function status	Prior Therapy	Final Therapy	Outcome	References
1	2012	USA	89(F)	Mitral	CKD	Levofloxacin 500mg x 10 days	Daptomycin 6mg/kg q/48h and Ampicillin 1g q/6h x 6weeks	Success with 11-months follow-up	[8]
2	2015	USA	79(M)	Mitral and Aortic	ESRD	Ampicillin 2g every 24h x 3 week	Daptomycin 6mg/kg q/48h and Ampicillin 2g q/d x 6weeks	Success with 6-months follow-up	[8]
3	2015	USA	83(F)	Aortic	CKD	Levofloxacin 500mg x 15 days	Daptomycin 6mg/kg q/48h and Ampicillin 2g q/12h x 6weeks	Success with 1-year follow-up	[8]
4	2015	USA	59(F)	Mitral	Acute kidney injury requiring temporary HD for 3 months	None	Daptomycin 6mg/kg q/d and Ampicillin 2g q/6h x 6weeks	Success, died at 6months from pneumonia	[8]
5	2015	USA	62(F)	Mitral annulus	ESRD	Vancomycin and gentamicin, dose, and duration unknown	Daptomycin 6mg/kg q/48h and Ampicillin 2g q/12h x 8weeks	Success with 3-months follow-up	[8]
6	2018	USA	68(F)	Aortic	Renal Transplant	Ampicillin 2g IV q/4h; Daptomycin 6mg/kg q/d for 6 weeks	Same as initial	Success with 1-year follow-up	[9]
7	2022	USA	45(F)	Mitral	Renal Transplant	None	Daptomycin 6 mg/kg q/d and Ampicillin/sulbactam 3g q/12h x 6weeks	Success with 1-year follow-up	Our patient

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.

Baires F, et al., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920394

Table 4: 21st century, new associations and features between Enterococcus and Endocarditis.

1. Number 1 cause of IE in kidney transplanted patients.[1]
2. Number 1 cause of IE in TAVI patients.[33]
3. Number 2 cause of IE in hemodialysis patients.[15]
4. Number 2 cause of most common cause of hospital acquired IE.[3]
5. Enterococcal IE is significantly more frequent among patients aged 65 years or more.[3]
6. Association between EFIE and colorectal neoplasm. [25]
7.Third most common cause of Infective Endocarditis in high-income countries.[3]
8. More frequently HCA disease occurring predominantly among elderly patients with a large burden of comorbidities and seldom a clear identifiable source.[3]
9. The aortic valve is more frequently involved in enterococcal IE cases.[3]
10. E. faecalis produced significantly more prosthetic valve IE cases than other enterococcal species while the latter produced significantly more native valve IE, which has not been noted before.[3]

IE= Infective Endocarditis, TAVI= Transcatheter Aortic Valve Implantation, EFIE= Enterococcus faecalis infective endocarditis, HCA= Health care–associated.

lethal if not recognized early. An area for improvement in the first decade of widespread daptomycin use has been the need for global access due to cost and branded formulation, which potentially favors developed countries. However, in 2023, daptomycin became available in generic form, universally accessible, and more affordable.

This case report clearly has some limitations. First of all, it is retrospective in nature. Secondly, the dosing of daptomycin for initial treatment in contemporary medicine generally is 10-12mg/kg depending on the case. We used 6mg/kg based on Sakoulas et al. [32] studies which discussed a synergy with concurrent use of daptomycin and ampicillin. Another drawback is that plain ampicillin was not available at the hospital. For our patient, we used ampicillin/sulbactam which is not ideal nor used in other cases. Once ampicillin became available, the appropriate change was done. Dosing was adjusted to the patient's renal function by the hospital's clinical pharmacist.

We need to evaluate four fundamental variables when we review the chronological universal table of *E. faecalis* infective endocarditis in kidney transplant patients. These include curing the underlying infectious disease process; preserving the cardiac valve; preserving the kidney itself; and overall survival. When these four variables are analyzed in the 9 cases of *E. faecalis* in renal transplant patients that have been reported, only 7 of 9 (77%) met that goal. This then raises the question of which of the available antibiotic combinations has achieved these goals more than once. To the best of our knowledge, the combination of daptomycin and ampicillin is the only combination that has been used more than once with a successful outcome in the cohort of all infective endocarditis with enterococcus faecalis in renal transplant patients. There are combinations that have had successful outcomes but none of them have been successfully used more than once. Such success should prompt further investigation into this combination as a second option for aminoglycoside sparing regimens.

Conclusion

EE is becoming more frequent, due to the increase in the numbers of elderly patients, those with comorbidities, and healthcare-associated infections. Long term antibiotic regimens are necessary to clear these infections and one must be vigilant of potential side effects with extended use. Due to the ototoxic and nephrotoxic nature of aminoglycosides, infectious disease practitioners are choosing to move away from their use. While ampicillin and ceftriaxone remain a first line regimen for treating EE, we must have a safe, effective, and affordable option in the event of failure. After successfully treating our now second renal transplant recipient without incurring further complications, we have concluded that the combination of ampicillin and daptomycin should be further investigated in a larger scale as it opens the doors for a second aminoglycoside sparing agent combination.

Author Contributions: Conceptualization, Miguel Sierra-Hoffman and Mark L. Stevens; methodology, Erin Arias and María José Díaz Ramos; validation, Fernando Baires and Guillermo Lopez; investigation, Miguel Sierra-Hoffman and Mark L. Stevens; resources, Juan S. Llompart, Jana Radwanski and Cesar Burgos; data curation, Cesar Burgos; writing—original draft preparation, Fernando Baires; writing—review and editing, Anupamjeet Kaur Sekhon, Jarmanjeet Singh; visualization, Tywaun Tillman; supervision, Chetan Jinadatha; project administration, Miguel Sierra-Hoffman and Mark L. Stevens. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were not applicable for this case report as data was collected retrospectively and the patient received standard of care.

Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgments: Dr. Juan Llompart Zeno for his contributions to medicine over 43 years, without whose help and guidance this manuscript would not be possible.

References

1. Ioannou P, Alexakis K, Kofteridis DP. Endocarditis in kidney transplant recipients: a systematic review. Journal of Chemotherapy 33 (2021): 269-275.
2. Lentine KL, Smith JM, Miller JM, et al. OPTN/SRTR 2021 Annual Data Report: Kidney. American Journal of Transplantation 23 (2023): S21-S120.
3. Pericàs JM, Llopis J, Muñoz P, et al. A Contemporary Picture of Enterococcal Endocarditis. J Am Coll Cardiol 75 (2020): 482-494.
4. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. Circulation 132 (2015): 1435-1486.
5. Correction to: 2023 ESC Guidelines for the management of endocarditis: Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM), European Heart Journal, 2023, ehad776. Available from: https://doi.org/10.1093/eurheartj/ehad776
6. 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. Clinical Infectious Diseases 56 (2013): 1261–1268.
7. Sierra-Hoffman M, Iznaola O, Goodwin M, et al. Combination Therapy with Ampicillin and Daptomycin for Treatment of Enterococcus faecalis Endocarditis. Antimicrobial Agents and Chemotherapy 56 (2012): 6064.
8. Sierra-Hoffman M, Iznaola O, Lamp KC, et al. Daptomycin and Ampicillin Combination for Treatment of Enterococcus faecalis Endocarditis. Infectious Diseases in Clinical Practice 23 (2015).
9. Castro-Lainez MT, Sierra-Hoffman M, Valladares V, et al. A rationale for combination ampicillin and daptomycin in renal transplant patients with Enterococcal infective endocarditis. IDCases 14 (2018): e00460.
10. Sierra-Hoffman M, Deliz RJ, Sekhon AK, et al. A multi-national study for the treatment of Enterococcal endocarditis with Ampicillin-Daptomycin combination therapy. 30th European Congress of Clinical Microbiology and Infectious Diseases Abstract book, abstract 4165 (2020) pp: 1993.
11. Hoen B, Duval X. Infective Endocarditis. New England Journal of Medicine 369 (2013): 784-785.
12. Murdoch DR, Corey GR, Hoen B, et al. Investigators, I. C. on E. C. S. (ICE-P. (2009). Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis–Prospective Cohort Study. Archives of Internal Medicine 169 (2009): 463-473.
13. Chirouze C, Athan E, Alla F, et al. Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study. Clinical Microbiology and Infection 19 (2013): 1140-1147.
14. Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA 316 (2016): 1083-1092.
15. Pericàs JM, Llopis J, Jiménez-Exposito MJ, et al. Infective Endocarditis in Patients on Chronic Hemodialysis. Journal of the American College of Cardiology 77 (2021): 1629-1640.
16. Pericás JM, Zboromyrska Y, Cervera C, et al. Enterococcal endocarditis revisited. Future Microbiology 10 (2015): 1215-1240.
17. Arias CA, Mendes RE, Stilwell MG, et al. Unmet Needs and Prospects for Oritavancin in the Management of Vancomycin-Resistant Enterococcal Infections. Clinical Infectious Diseases 54 (2012): S233-S238.
18. Nappi F, Avtaar Singh SS, Jitendra V, et al. Bridging Molecular and Clinical Sciences to Achieve the Best Treatment of Enterococcus faecalis Endocarditis. Preprints (2023).
19. Pericas JM, Cervera C, del Rio A, et al. Changes in the treatment of Enterococcus faecalis infective endocarditis in Spain in the last 15 years: from ampicillin plus gentamicin to ampicillin plus ceftriaxone. Clinical Microbiology and Infection 20 (2014): O1075-O1083.
20. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). European Heart Journal 36 (2015): 3075-3128.

21. Dahl A, Rasmussen RV, Bundgaard H, et al. Enterococcus faecalis Infective Endocarditis. Circulation 127 (2013): 1810-1817.

22. Beganovic M, Luther MK, Rice LB, et al. A Review of Combination Antimicrobial Therapy for Enterococcus faecalis Bloodstream Infections and Infective Endocarditis. Clinical Infectious Diseases 67 (2018): 303-309.

23. Koehler P, Jung N, Cornely OA, et al. Combination Antimicrobial Therapy for Enterococcus faecalis Infective Endocarditis. Clinical Infectious Diseases 69 (2019): 900.

24. Schleifer KH, Kilpper-Balz R. Transfer of Streptococcus faecalis and Streptococcus faecium to the Genus Enterococcus norn. rev. as Enterococcus faecalis comb. nov. and Enterococcus faecium comb (1984).

25. Pericàs JM, Corredoira C, Moreno A, et al. Relationship Between Enterococcus faecalis Infective Endocarditis and Colorectal Neoplasm: Preliminary Results From a Cohort of 154 Patients. Revista Española de Cardiología 70 (2017): 451-458.

26. Pericàs JM, García-de-la-Mària C, Brunet M, et al. Early in vitro development of daptomycin non-susceptibility in high-level aminoglycoside-resistant Enterococcus faecalis predicts the efficacy of the combination of high-dose daptomycin plus ampicillin in an in vivo model of experimental endocarditis. Journal of Antimicrobial Chemotherapy 72 (2017): 1714–1722.

27. Paterson DL, Dominguez EA, Chang FY, et al. Snydman, Nina Singh, Infective Endocarditis in Solid Organ Transplant Recipients, Clinical Infectious Diseases 26 (1998): 689-694.

28. Pour-reza-Gholi F, Farrokhi F, Einollahi B, et al. Successful treatment of infective endocarditis in four kidney transplant recipients. Iran J Kidney Dis 1 (2007): 43-5.

29. Andrews J, Borooah S. Endocarditis and monocular blindness. BMJ Case Rep 26 (2016): 2016.

30. Pereira L, Meng C, Guedes L, et al . Infective endocarditis in renal transplant recipients: one center´s experience. Port J Nephrol Hypert [Internet] 32 (2018): 319-323.

31. Bao P, Zhang Z, Zhao W, et al. Isolation and whole-genome sequencing of a new type of linezolid- resistant Enterococcus faecalis from two cases of infective endocarditis following renal transplantation. J Glob Antimicrob Resist 20 (2020): 346-347.

32. Sakoulas G, Bayer AS, Pogliano J, et al. Ampicillin Enhances Daptomycin- and Cationic Host Defense Peptide-Mediated Killing of Ampicillin- and Vancomycin-Resistant Enterococcus faecium. Antimicrob Agents Chemother 56 (2012): 838-44.

33. Herrera-Hidalgo L, Fernández-Rubio B, Luque-Márquez R, et al. Treatment of Enterococcus faecalis Infective Endocarditis: A Continuing Challenge. Antibiotics (Basel) 12 (2023): 704.

34. Gunn J, Zajac KK, Esser K, et al. Case of Daptomycin-Induced Rhabdomyolysis: A Life and Limb Threatening Complication. Cureus 15 (2023): e38285.

35. Ref Portalatin GM, Chin JA, Foster B, et al. Daptomycin-Induced Acute Eosinophilic Pneumonia. Cureus 13 (2021): e13509.

Citation: Fernando Baires, Erin Arias, María José Díaz Ramos, Cesar Burgos, Guillermo Lopez, Juan S Llompart, Jana Radwanski, Tywaun Tillman, Fernando Valerio-Pascua, Anupamjeet Kaur Sekhon, Jarmanjeet Singh, Chetan Jinadatha, Miguel Sierra-Hoffman, Mark L Stevens. Ampicillin and Daptomycin Combination Therapy for Enterococcus Faecalis Endocarditis After Renal Transplantation: A Case Report and Review. Cardiology and Cardiovascular Medicine. 8 (2024): 303-311.