

Ampicillin-Ceftriaxone vs Ampicillin-Gentamicin for Definitive Therapy of *Enterococcus faecalis* Infective Endocarditis: A Propensity Score–Matched, Retrospective Cohort Analysis

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Background. Ampicillin-ceftriaxone (AC) has emerged as an alternative antibiotic regimen for enterococcal infective endocarditis (EIE) with reduced toxicity compared with ampicillin-gentamicin (AG), but evidence regarding its success in reducing EIE-associated death in the United States is limited.

Methods. We conducted a retrospective, propensity score–matched cohort analysis of EIE patients treated with AC or AG between 2010 and 2017 at 3 hospitals in Pittsburgh, Pennsylvania. We assessed all-cause 90-day mortality as the primary outcome and in-hospital mortality, length of hospital stay, hospital readmissions, adverse events, and relapse of bacteremia as the secondary outcomes.

Results. A total of 190 patients with EIE (100 treated with AC and 90 with AG) were included. Ninety-day mortality was significantly higher with AC than AG (21% vs 8%; $P = .02$). After propensity score matching, 56 patients in each group remained for the outcomes analysis. Documented aminoglycoside resistance, presence of annular or aortic abscess, and complete pacemaker removal were the significantly different variables between the 2 matched cohorts. We observed no statistically significant difference in 90-day mortality between the 2 treatment groups (11% vs 7%; $P = .55$). Adverse events were more common in patients treated with AG (25 vs 39; $P = .0091$), and more patients in the propensity score–matched AG cohort switched antibiotic regimens than in the AC group (10% vs 49%; $P < .0001$).

Conclusions. Patients treated with AC demonstrate no significant differences in mortality, treatment failure, or bacteremia relapse compared with AG in a propensity score–matched EIE cohort.

Keywords. ampicillin; ceftriaxone; *Enterococcus faecalis*; gentamicin; infective endocarditis.

INTRODUCTION

Combination therapy with 2 antibiotics is the standard of care for *Enterococcus faecalis* infective endocarditis (EIE), a serious disease that is associated with high mortality [1, 2]. Based on in vitro experiments, in vivo animal studies, case reports, and clinical analyses [3–16], ampicillin-ceftriaxone (AC) has emerged as an alternative to aminoglycoside-based treatment for EIE. Several clinical studies have examined outcomes in EIE patients managed with AC [5, 6, 11, 14–16]. The largest

of these, a 2013 multicenter observational study performed by Fernández-Hidalgo and colleagues in Europe, reported no differences in mortality, treatment failure, or relapse between EIE patients treated with AC or ampicillin-gentamicin (AG). Indeed, updated American Heart Association (AHA)/Infectious Diseases Society of America (IDSA) guidelines recommend 6 weeks of AC for management of aminoglycoside-resistant EIE, and as a reasonable alternative to AG for aminoglycoside-susceptible EIE [1]. However, clinical evidence for the efficacy of the AC regimen remains limited, and whether AC can be used rather than AG for all EIE patients has not been established. Importantly, there is a lack of data in the United States addressing the use of ceftriaxone compared with gentamicin for combination antibiotic treatment of EIE [16]. Despite limited data, the AC regimen is increasingly used in clinical practice [11].

We performed a retrospective cohort analysis of EIE patients at 3 hospitals in Western Pennsylvania from 2010 to 2017. We evaluated patient mortality, relapse, treatment failure, and adverse events with AC or AG treatment of EIE. Further, we

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examined trends in enterococcal aminoglycoside resistance, antibiotic therapy of EIE, and EIE mortality during the study period. To our knowledge, this study is the first large patient investigation in the United States to capture the change in clinical practice from AG to AC in EIE, while also comparing outcomes in EIE patients treated with AC or AG during the same time frame.

METHODS

Study Population

Adult patients with EIE were identified through queries of electronic medical records containing the search terms “faecalis,” “endocarditis,” and “gentamicin” or “ceftriaxone,” or “enterococcal,” “endocarditis,” and “gentamicin” or ceftriaxone,” in the progress notes at 3 hospitals in Pittsburgh, Pennsylvania, for the period between January 2010 and December 2017. Each potential case was then manually reviewed for the inclusion and exclusion criteria described below. If a patient suffered multiple episodes of EIE during the study period, only the first episode that met criteria was included in the analysis.

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at University of Pittsburgh [17, 18]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Inclusion and Exclusion Criteria

Patients were included in the analysis if they were treated for EIE with either AC or AG as the pathogen-directed antibiotic regimen for at least 48 hours. Patients treated with ampicillin-streptomycin ($n = 2$) were included in the AG cohort. The most common reasons for exclusion of patients were polymicrobial endocarditis, antibiotics other than AC or AG used as pathogen-directed treatment, and endocarditis secondary to *Enterococcus* whose species was either unavailable in the records or was a non-*faecalis* *Enterococcus* species.

Propensity Score Matching

To perform propensity score matching, a logistic regression model was fit to the data using the following variables: age group, Charlson Comorbidity Index (CCI), quick Sequential Organ Failure Assessment (qSOFA) score (≥ 2 or < 2), use of vasopressors during hospital admission (excluding the perioperative period if applicable), nursing home residence, prosthetic valve endocarditis, and surgical intervention (excluding pacemaker removal). The propensity score calculated for each observation was saved to a data set and used to match similar records from

the 2 groups (AC and AG). The macro OneToManyMTCH was used to perform a 1-to-1 match [19].

Outcomes Definitions

The primary outcome was all-cause 90-day mortality. Ninety-day mortality and readmission were defined as death or readmission, respectively, occurring within 90 days of initiation of pathogen-directed antibiotic therapy. In-hospital mortality was defined as mortality occurring during hospitalization for EIE. Patients were considered to have relapse if there were positive blood cultures documented within 3 months after completion of pathogen-directed antibiotic treatment, which were caused by the same bacterial species as the endocarditis episode. Treatment failure requiring antibiotic switch was defined by physician documentation of changing the antibiotic regimen due to treatment failure of the initial pathogen-directed antimicrobial combination. Estimated duration of bacteremia was calculated as the time in hours from first positive blood culture collection to either the last positive blood culture report or the first negative blood culture collection, depending on the availability of culture data.

Adverse Events

Recorded adverse events were as follows, with the time frame for each event in relationship to initiation of pathogen-directed antibiotic therapy in parentheses: rash (48 hours), leukopenia (48 hours), antibiotic-associated diarrhea (1 week), acute kidney injury (1 week), *Clostridioides difficile* colitis (2 months). In addition, we documented any adverse events other than those listed above which resulted in antibiotic therapy switch.

Statistical Analysis

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). Univariate logistic regression models were calculated to determine demographic and clinical factors that were different between AC and AG. Exact logistic regression was performed on those factors for which 1 group did not have any cases. Continuous variables were evaluated using the Wilcoxon signed rank test. Trends over time were evaluated using the Cochran-Armitage Trend test. P values $< .05$ were considered significant.

RESULTS

Demographics and Clinical Features

A total of 190 EIE patient cases were included in the study: 100 patients treated with AC and 90 patients managed with AG (Table 1). During the study period, we observed a shift from AG to AC for directed therapy of EIE ($P < .001$) (Supplementary Figure 1). The median age at admission was 67.5 years in the AC group and 63.5 years in the AG cohort ($P = .02$). Overall, the majority of patients were white males who were diagnosed with definite infective endocarditis per the modified Duke

Table 1. Demographics and Clinical Features of EIE Patients Treated With Ampicillin-Ceftriaxone or Ampicillin-Gentamicin

Variable	AC (n = 100), No. (%)	AG (n = 90), No. (%)	OR (95% CI)	P Value
Age at admission, ^a y	67.5 (22–94)	63.5 (21–85)		.02
Male sex	65 (65)	61 (68)	1.13 (0.62–2.07)	.69
White race	86 (92)	79 (91)	1.09 (0.39–3.04)	.87
Hispanic ethnicity	1 (1)	0	0.93 (0.05–infinity)	.52 ^b
Nursing facility residence	20 (20)	9 (10)	2.19 (0.94–5.07)	.07
Documented current intravenous drug use	14 (14)	17 (19)	0.71 (0.33–1.54)	.39
Organ transplant	3 (3)	4 (4)	0.69 (0.15–3.16)	.63
Charlson Comorbidity Index ^a	2 (0–10)	2 (0–11)		.10
Obesity	31 (31)	34 (38)	0.75 (0.41–1.37)	.36
Hospital-acquired infection	7 (8)	12 (14)	0.56 (0.21–1.50)	.25
Documented HLAR ^c	32 (49)	6 (12)	6.74 (2.58–17.63)	.0001
qSOFA score ^a	1 (0–3)	1 (0–3)		.18
Pitt bacteremia score ^a [27]	1 (0–6)	1 (0–14)		.96
Definite IE per modified Duke criteria [28]	75 (77)	69 (80)	0.84 (0.41–1.72)	.64
Vegetation present	72 (72)	66 (74)	0.9 (0.47–1.71)	.75
Vegetation size, ^a mm	12 (0.9–40)	13 (3–38)		.94
Type of IE ^d				
Native valve IE	59 (59)	52 (58)	1.05 (0.59–1.87)	.86
Prosthetic valve IE	16 (16)	27 (30)	0.45 (0.22–0.91)	.03
Pacemaker IE	30 (30)	10 (11)	3.32 (1.52–7.23)	.003
Complete pacemaker removal	17 (57)	3 (30)	2.78 (0.63–12.32)	.18
Valve affected				
Aortic	39 (39)	44 (49)	0.67 (0.38–1.19)	.18
Mitral	28 (28)	39 (43)	0.51 (0.28–0.94)	.03
Tricuspid	10 (10)	11 (12)	0.8 (0.32–1.99)	.63
Pulmonic	5 (5)	2 (2)	2.04 (0.40–10.34)	.39
Indication for surgery present	45 (45)	52 (58)	0.6 (0.34–1.07)	.08
Valve dysfunction resulting in heart failure	9 (20)	10 (19)	1.05 (0.39–2.88)	.92
Annular or aortic abscess	5 (11)	14 (27)	0.36 (0.12–1.08)	.07
Destructive penetrating lesion	6 (13)	7 (14)	1.0 (0.31–3.22)	1.00
Persistent infection on appropriate treatment	4 (9)	1 (2)	3.72 (0.47–29.38)	.21
Mobile vegetation >10 mm	13 (29)	22 (42)	0.56 (0.24–1.31)	.18
Persistent/enlarging vegetation on appropriate treatment	1 (2)	0	1.16 (0.06–infinity)	.46 ^b
Severe valvular regurgitation	27 (60)	23 (44)	1.87 (0.83–4.19)	.13
Recurrent emboli	0	1 (2)	1.16 (0–21.96)	.54 ^b
Other	7 (16)	9 (17)	0.89 (0.30–2.62)	.84
Surgical intervention ^e	33 (33)	44 (49)	0.52 (0.29–0.93)	.03
IE complications	34 (34)	42 (47)	0.59 (0.33–1.06)	.08
Heart failure	9 (9)	9 (10)	0.89 (0.34–2.35)	.82
Paravalvular complications	2 (2)	8 (9)	0.25 (0.05–1.11)	.07
Stroke	11 (11)	19 (21)	0.47 (0.21–1.05)	.07
Septic pulmonary emboli	6 (6)	1 (1)	4.1 (0.60–27.95)	.15
Other emboli	8 (8)	11 (12)	0.64 (0.24–1.66)	.35
None	66 (66)	48 (53)	1.69 (0.94–3.03)	.08
Vasopressor use during hospital admission	26 (26)	15 (17)	1.73 (0.85–3.53)	.13
Completion of antibiotic treatment course ^f	69 (78)	70 (89)	0.48 (0.20–1.13)	.09

Abbreviations: AC, ampicillin-ceftriaxone; AG, ampicillin-gentamicin; EIE, enterococcal infective endocarditis; IE, infective endocarditis; OR, odds ratio; qSOFA, quick Sequential Organ Failure Assessment.

^aValues are median (interquartile range), and *P* value is by Wilcoxon signed rank test.

^bMedian unbiased estimate.

^cAntibiotic susceptibility data were missing for some patients.

^dThere were many patients with >1 type of endocarditis (Supplementary Table 2).

^eExcluding pacemaker removal.

^fCompletion of antibiotic treatment course for EIE based on physician documentation, regardless of antibiotic switch.

criteria. Patients in both cohorts had a median CCI of 2 and a median qSOFA score of 1 at the time of admission. Fourteen of the AC-treated patients (14%) and 17 of the AG-treated patients (19%) were documented intravenous drug users at the time of admission ($P = .39$). Hospital-acquired infection was noted in 7 (8%) of the AC patients and 12 (14%) of the AG patients ($P = .25$). Of the patients with available antibiotic susceptibility data, high-level aminoglycoside resistance (HLAR) was recorded in 49% of AC-treated patients and 12% of AG-managed patients ($P = .0001$). We observed no significant change in prevalence of HLAR strains during the study (Supplementary Figure 2). The distribution of the type of EIE was as follows: native valve (59% vs 58%; $P = .86$), prosthetic valve (16% vs 30%; $P = .03$), and pacemaker (30% vs 11%; $P = .003$) for the AC group vs AG group, respectively. Of the subjects afflicted with pacemaker EIE, 17/30 (AC; 57%) and 3/10 (AG; 30%) patients underwent complete pacemaker removal ($P = .18$). Approximately one-third of the AC-managed population underwent surgery, excluding pacemaker removal, compared with half of the AG-treated cohort (AC vs AG: 33% vs 49%; $P = .03$). Prescribed duration of antibiotic therapy (on average 42 days) and percentage of patients completing the treatment course (AC vs AG: 78% vs 89%; $P = .09$) were similar between the 2 groups.

The patients in the 2 cohorts were matched for age, qSOFA score, CCI, vasopressor use during hospital admission, nursing facility residence, presence of prosthetic valve endocarditis, and surgical intervention. After propensity score matching, documented aminoglycoside resistance (AC vs AG: 51% vs 10%; $P = .001$), presence of annular or aortic abscess (AC vs AG: 6% vs 29%; $P = .04$), and pacemaker removal (AC vs AG: 8/13 patients vs 0/5 patients; $P = .03$) were the significantly different variables between the 2 groups (Supplementary Table 1). Receipt of vancomycin or daptomycin as part of an empiric antibiotic regimen before pathogen-directed treatment did not significantly differ between the 2 matched cohorts (vancomycin: AC 79% vs AG 66%; daptomycin: AC 5% vs AG 4%).

Outcomes

Table 2 summarizes the outcomes in the propensity score-matched EIE patient cohorts managed with either AC or AG combination therapy. For the primary outcome, 6 patients (10.7%) had died at 90 days from the start of pathogen-directed antibiotic therapy in the AC group, whereas 90-day mortality in the AG cohort was seen in 4 patients (7.1%). This difference was not statistically significant ($P = .55$). We observed no significant trend in patient 90-day mortality throughout the study period (Supplementary Figure 3). Secondary outcomes in the propensity score-matched patient cohorts were similar between the 2 groups, including in-hospital mortality (AC vs AG: 0% vs 2%; $P = .50$), hospital readmission at 90 days (AC vs AG: 43% vs 41%; $P = .85$), and median length of hospital stay (15 days in both groups; $P = .80$). The rates of treatment failure requiring a change in antibiotic therapy, and of bacteremia relapse, were low (1 patient in the matched AG group experienced treatment failure that prompted antibiotic switch).

Adverse Events and Pathogen-Directed Antibiotic Switch

We examined the incidence of adverse events in the total EIE patient cohorts (Table 3). 25 adverse events occurred in patients treated with AC, vs 39 adverse events in the patient cohort treated with AG ($P = .0091$). Ototoxicity occurred in 8 patients managed with AG. Six patients in the AC cohort compared with 13 patients in the AG group suffered from acute kidney injury (6% vs 14%), whereas the rate of *Clostridioides difficile* colitis was slightly higher in AC-treated patients (AC 8% vs AG 6%). Leukopenia (1% vs 4%) and antibiotic-associated diarrhea (4% vs 8%) occurred at higher rates in patients treated with AG. None of these differences reached statistical significance.

We also explored the incidence of pathogen-directed antibiotic therapy switch in the propensity score-matched EIE patients (Table 4). Before treatment completion, pathogen-directed antibiotic therapy was changed in 5 AC-managed patients compared with 24 AG-treated patients (10% vs 49%; $P < .0001$). The median duration of antibiotic treatment before

Table 2. Primary and Secondary Outcomes in Propensity-Matched EIE Cohorts Treated With Ampicillin-Ceftriaxone or Ampicillin-Gentamicin for Definitive Therapy

Outcome	AC (n = 56), No. (%)	AG (n = 56), No. (%)	OR	95% CI	P Value
90-d mortality	6 (10.7)	4 (7.1)	1.50	(0.40–5.662)	.55
In-hospital mortality	0	1 (1.8)	1.00	(0–19.0)	.50 ^b
Treatment failure requiring antibiotic switch	0	1 (2.0)	1.00	(0–19.0)	.50 ^b
Bacteremia relapse	0	0			
90-d hospital readmission	24 (42.9)	23 (41.1)	1.07	(0.51–2.28)	.85
Hospital length of stay, ^c d	15 (7–68)	15 (6–100)			.80
Estimated duration of bacteremia, ^c h	102.3 (3–1475)	51.5 (0.5–272.6)			.007

Abbreviations: AC, ampicillin-ceftriaxone; AG, ampicillin-gentamicin; EIE, enterococcal infective endocarditis; OR, odds ratio; qSOFA, quick Sequential Organ Failure Assessment.

^aVariables utilized for matching: age group, Charlson Comorbidity Index, qSOFA ≥ 2 , vasopressor use during hospitalization, nursing home residence, prosthetic valve endocarditis, surgical intervention (excluding pacemaker removal).

^bMedian unbiased estimate.

^cValues are median (interquartile range), and P value is by Wilcoxon signed rank test.

Table 3. Comparison of Adverse Events in the Entire EIE Patient Cohort Treated With Ampicillin-Ceftriaxone or Ampicillin-Gentamicin

	AC (n = 100)	AG (n = 90)	PValue
Rash	1	1	
Ototoxicity	0	8	
Leukopenia	1	4	
Antibiotic associated diarrhea	4	7	
<i>Clostridioides difficile</i> colitis	8	5	
Acute kidney injury	6	13	
Other	5	1	
Total number of adverse events ^a	25	39	.0091

Abbreviations: AC, ampicillin-ceftriaxone; AG, ampicillin-gentamicin; EIE, enterococcal infective endocarditis.

^aSeveral patients had multiple documented adverse events.

the switch was 13 days in the AC group and 11 days in the AG patients ($P = .55$).

DISCUSSION

In this study, we captured the shift in clinical practice over the past decade from AG to AC for combination antibiotic treatment of EIE. We report no significant differences between AC and AG therapy in the rates of all-cause 90-day or in-hospital mortality, treatment failure, bacteremia relapse, and hospital readmission after propensity score matching for age, CCI, qSOFA score, nursing home residence, vasopressor use during hospital admission, prosthetic valve endocarditis, and surgical intervention.

Our retrospective analysis has several caveats. Propensity score matching does not produce perfectly randomized groups, as evidenced by the differences in the presence of annular or aortic abscess and pacemaker removal in the matched cohorts, with significantly higher rates of both features in the AC-treated patients (Supplementary Table 1). These variables would be expected to affect clinical outcomes. There certainly may be other unmeasured factors that influenced our results. Next, as cause of death information was unavailable to us for all patients deceased at 90 days, we reported all-cause mortality, resulting in an overestimation of EIE-specific mortality. Of the 8 patients who died during hospitalization, cause of death was attributable to EIE in 5 patients (63%; 3/5 AC patients, 2/3 AG

patients) and indirectly related to EIE in 1 patient (cardiac arrhythmia after implantable cardioverter defibrillator removal).

Our findings are largely in agreement with the results of prior clinical studies conducted in Europe [6, 11] and the United States [16], lending further support to the conclusion that synergistic therapy with ceftriaxone for EIE is equally efficacious to using gentamicin, and overall safer. However, while ceftriaxone use is associated with fewer adverse events compared with gentamicin, it is not without harmful effects. Although the difference did not reach statistical significance, patients receiving ceftriaxone experienced higher rates of *Clostridioides difficile* infection (8% vs 6% in AG-treated patients), a disease with substantial morbidity and mortality [20]. There are limited published data on the frequency of *C. difficile* infection in AC-treated EIE patients, and it was beyond the scope of our study to explore long-term adverse outcomes associated with *C. difficile* infection in our cohorts. Increased incidence of *C. difficile* colitis is a key potential consequence to consider with escalating ceftriaxone use.

Overall patient mortality in EIE remains high despite changes in treatment practices (Supplementary Figure 3) ([11, 21]). In fact, we observed a 90-day mortality rate of 21% in all EIE patients who received AC (Supplementary Table 3), underscoring the need for better treatment options for this disease. We propose that using AC rather than AG may not be a “one size fits all” therapeutic strategy. For example, a short duration of AG treatment followed by AC combination therapy is a possible

Table 4. Definitive Antibiotic Therapy Switch in Propensity-Matched EIE Patients Initially Treated With Ampicillin-Ceftriaxone or Ampicillin-Gentamicin

	AC (n = 49) ^a	AG (n = 49) ^a	PValue
No. of patients with therapy switch (%)	5 (10)	24 (49)	<.0001
Duration of AC or AG therapy before switch, ^b d	13 (3–19)	11 (7–24)	.55
Reason for switch, ^c No.			
Adverse event	4	12	
Treatment failure	0	1	
Other	1	11	
Unknown	0	3	

Abbreviations: AC, ampicillin-ceftriaxone; AG, ampicillin-gentamicin; EIE, enterococcal infective endocarditis.

^aMissing data for 7 patients in each matched group.

^bValues are median (interquartile range).

^cSeveral patients had multiple documented reasons for switching definitive antibiotic therapy.

regimen for patients in whom a long course of gentamicin should be avoided [22–24]. Indeed, of the 24 patients in our matched AG cohort who switched antibiotic regimens, only 1 patient (4%) died at 90 days.

Interestingly, duration of bacteremia was significantly higher in the matched AC-treated patients (median duration of 102 hours vs 52 hours in patients treated with AG), suggesting the value of microbiologic studies on pharmacodynamics and susceptibility patterns of EIE *E. faecalis* strains. Additionally, comparing the efficacy of antibiotic regimens in subsets of EIE patient populations, particularly those with poorer prognosis, will help guide physicians when tailoring combination therapy choices to each patient as recommended in the AHA/IDSA guidelines. Other avenues that warrant further research are the use of cephalosporins other than ceftriaxone [7] and switching to oral antibiotics in clinically stable patients, as in the POET trial [25, 26]. As such, there is a critical necessity for multicenter randomized clinical trials that compare different antibiotic treatment regimens to improve survival in EIE patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The study was reviewed by the Institutional Review Board at the University of Pittsburgh and designated as “exempt.” The IRB approved a waiver of HIPAA authorization to access protected health information.

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