A retrospective study of Enterococcus faecalis infective endocarditis: comparison of clinical characteristics and outcomes associated with treatment

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Abstract

Introduction:

A synergistic antibiotic combination of a penicillin and gentamicin (AG) is recommended first line management of *Enterococcus faecalis* infective endocarditis (EFIE). We compare the treatment outcomes between the conventional AG regimen to those treated with a combination of penicillin and ceftriaxone (AC). Given reported beta lactam toxicity risks, we also examine the difference in treatment outcomes between regimens of low dose, 1g 12 hourly (AC_L) and high dose ceftriaxone, 2g 12 hourly (AC_N) in combination with penicillin.

Methods:

A retrospective cohort study of patients treated for EFIE at single tertiary centre (2012–2019). Outcome measures examined are 90 & 180-day mortality, treatment associated adverse events, and relapse of bacteremia (within 1 year).

Results:

39 patients were enrolled [59% given (AC) (*n* = 24), 24% received AC_L (*n* = 10) and 34% received AC_N (*n* = 14)]. 39% received AG (*n* = 15). We found no significant difference in the mortality outcomes at 90 and 180 days between: a) those treated with a gentamicin combination and ceftriaxone combination overall (P = .114, P = .061) and b) between high and low dose ceftriaxone (P = 1.0, P = .673). No significant difference was noted between the above groups in incidence of relapsed bacteremia (P = .662, P = .414). A greater number of adverse events was observed in the gentamicin group compared to the overall ceftriaxone group (P = .009), with no difference between the high and low dose ceftriaxone groups (P = .05).

Conclusion:

Combination treatment with penicillin/ceftriaxone appears to be as effective (using low and high dose ceftriaxone) as penicillin/gentamicin in EFIE, with a lower rate of adverse events.

Introduction

Enterococcus faecalis bacteremia is the third most common pathogen causing infective endocarditis, with most data suggesting a prevalence of 11 – 26% [1-3]. Enterococcal endocarditis is increasing in incidence, in part due to the aging population [1-3]. Elderly patients are more likely to have altered pharmacokinetics and pharmacodynamics, which can complicate treatment. The general principle guiding treatment of enterococcal endocarditis involves combination antibiotic therapy with a bacterial cell wall active agent (high dose penicillin or ampicillin) and a synergistically active aminoglycoside (gentamicin) [1-4]. However more recent observational data suggests that gentamicin in the above

regimen can be replaced with ceftriaxone with successful clinical outcomes, irrespective of the presence of high-level aminoglycoside resistance (HLAR) [5-7]. There is no randomised controlled trial data to inform these recommendations.

The synergy of ceftriaxone and ampicillin or high dose penicillin in enterococcal infections been attributed to different penicillin binding proteins (PBPs) being the target of each drug, therefore resulting in PBP saturation, leading to bactericidal activity [8]. The dose of ceftriaxone recommended in *guidelines is 2g 12 hourly. This dose was based on initial pharmacokinetic studies in animal models, and the trough concentration of ceftriaxone in these models was *20mcg/L, extrapolated from *in vitro* studies [9]. High doses of beta-lactams may also be associated with increased toxicity, particularly in elderly patients.

In addition to comparing ceftriaxone-based treatment to other regimens in enterococcal endocarditis, our retrospective observational study aims to evaluate 8 years of clinical data to assess if lower-than-recommended synergistic ceftriaxone dosing (1g 12 hourly) resulted in similar clinical outcomes to higher dose ceftriaxone or aminoglycoside combinations.

Methods

We conducted a retrospective cohort study at a tertiary centre in Sydney, Australia. Patients aged 18 years and over were identified via our secure Infectious Diseases departmental blood culture and consultation database and searching terms - faecalis – enterococcal – bacteraemia – endocarditis, for the period between January 2012 and December 2019. REDCap (Research Electronic Data Capture) was used to subsequently capture and store research data.

Cases that met inclusion criteria were patients aged over 18 years diagnosed with EFIE and treated with a 4- to 6-week course of ampicillin plus gentamicin (AG), ampicillin plus low-dose ceftriaxone (1g 12 hourly) (AC_L) and ampicillin plus ceftriaxone 2g 12 hourly (AC_N) and without subsequent oral antimicrobial administration. For AG, patients required at least 2 weeks of planned gentamicin. Patients were excluded if they were treated for *E. faecalis* bacteremia alone (instead of EFIE), treated with other antibiotic regimens for more than 10 days, were lost to follow up or had polymicrobial bacteraemia. If therapy was subsequently altered, patients were included in the initial treatment group, if subsequent antimicrobial therapy did not exceed 10 days.

The primary outcomes evaluated were 90- and 180-day all-cause mortality, all-cause in-hospital mortality, and relapse of bacteraemia within 12 months. The secondary outcomes evaluated were adverse events associated with therapy, noting if switching to an alternate regimen was necessitated. The adverse events included nephrotoxicity, neurotoxicity, other beta-lactam toxicity, rash, vestibular dysfunction, ototoxicity or other.

Gentamicin dosing was generally based on synergistic dosing of 1mg/kg 8 hourly, with trough gentamicin concentrations usually collected twice weekly, aiming at < 1mg/L. A detectable trough concentration was defined as therapeutic.

Episodes of EFIE were defined based using Duke's Criteria, or if patients were determined to have endocarditis by the treating Infectious Diseases team. Relapse of bacteremia was defined as recurrence of blood cultures culturing *E. faecalis* within 12 months after completion of EFIE treatment.

Nephrotoxicity was defined (as per KDIGO 2012 Acute Kidney Injury Criteria) as an increase in serum Creatinine (SCr) by 50% over 48 hours (11). SCr was also measured at day 90 and day 180 from time of treatment initiation. Neurotoxicity was defined as symptoms of myoclonus or seizures, impaired consciousness, confusion, hallucinations, or agitation. Beta lactam toxicity included other adverse effects attributable to beta-lactam antimicrobials at the time of treatment, including hepatic dysfunction, leukopenia, and pancytopenia. Vestibular dysfunction and/or ototoxicity was defined as symptoms of tinnitus, loss of balance, dizziness, vertigo, hearing loss and documented ototoxicity or vestibular dysfunction on serial audiometry, OAE (evoked otoacoustic emission) testing or vestibular evoked myogenic potential (VEMP) testing. Antimicrobial resistance is further defined to be evidence of HLAR (high level aminoglycoside resistance), noted to be E. faecalis isolated with gentamicin MIC (minimum inhibitory concentration) >/= 500 microg/L.

Fisher's exact test was used to compare AG and AC groups for 90- and 180-day mortality, in-hospital mortality, and 12-month relapse, then AC_L and AC_N were compared. Fisher's exact test was used to compare differences in adverse events between the three groups, then AC_L and AC_N. Differences were considered statistically significant if they had a p value of < 0.05. Statistical analyses were performed with SPSS-PC+, version 15.0 (SPSS, Chicago, Illinois).

Results

53 patient records were evaluated; 14 patients were excluded due to evidence of polymicrobial bacteremia (*n*=7), being lost to follow-up (*n*=6) or receiving another regimen (*n*=1). 39 patients were enrolled [62% given (A+C) (*n*= 24), 26% received low dose (*n*=10) and 36% received A+C_N (*n*=14)]. 38% received A+G (*n*=15).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

The demographics and baseline characteristics of the patients included in the final analysis are detailed in Table 1.

Table 1: Demographics of included patients

	Ampicillin + Ceftriaxone 1g (n=10)	Ampicillin + Ceftriaxone 2g (n=14)	Ampicillin + Gentamicin (n=15)	Significance (p value <0.05)
Age, median (IQR)	80 (15)	84.5 (6)	79 (13)	0.431
Number of comorbidities, median (IQR)	2.5 (1)	3 (1)	2 (1)	0.703
Patients with complications, number (proportion)	9 (0.9)	11 (0.79)	14 (0.93)	0.502
Surgery performed, number (proportion)	0 (0)	0 (0)	5 (0.33)	0.014
Vegetation - site				
Left	6 (0.6)	7 (0.5)	9 (0.6)	0.951
Right	0 (0)	0 (0)	1 (0.07)	
Unknown	4 (0.4)	6 (0.43)	4 (0.26)	
Device-related	0 (0)	1 (0.07)	1 (0.07)	
Prosthetic Valve/IECD, number (proportion)	7 (0.7)	9 (0.64)	10 (0.66)	0.958
Gentamicin TDM performed, number (proportion)	0 (0)	0 (0)	15	
Duration of therapy, median (IQR)	43 (2)	42 (2)	41 (3)	0.03
Renal function at commencement, median (IQR)	133.5 (55)	108.5 (70)	98 (75)	0.234

There was no statistically significant difference in number of comorbidities (p = 0.703) or complications (p=0.502) of IE between the 3 groups.There was a statistically significant difference in the surgeries performed between the three groups (p=0.014), with no cases of surgery performed in the AC_N or AC_L groups, but 5 cases in the AG group. There was no statistically significant difference in the location or number of vegetations (p= 0.951), presence of prosthetic valve or intracardiac device (IECD) (p=0.958) or renal function (SCr in micromol/L) at commencement of therapy (p=0.234). The median duration of therapy was statistically different between the three groups (p=0.03), with the median duration of therapy in days for the AG, AC_N and AC_L groups 41, 42, and 43 days respectively.

There were 3 cases of HLAR (high level aminoglycoside resistance) in the AC_N and AC_L groups.

PRIMARY OUTCOME MEASURES:

The mortality of all study patients included with EFIE was 20.5% at 90 days, with mortality of 30%, 28.6% and 6.7 % for the $AC_{L,}$ AC_N and AG groups respectively (please see Table 2). The mortality of all study patients included with EFIE was 23.1% at 180 days, with mortality of 40%, 28.6% and 6.7 % for the $AC_{L,}$ AC_N and AG respectively (please see Table 3). We found no significant difference in the mortality outcomes at 90 and 180 days between: a) those treated with a gentamicin combination and ceftriaxone combination overall (P=.114, P=.061) and b) between high and low dose ceftriaxone (P=1.0, P=.673).

Table 2: Mortality at 90-days

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Total	39	10	14	15
Dead	8	3	4	1
	20.5%	30.0%	28.6%	6.7%
Alive	31	7	10	14
	79.5%	70.0%	71.4%	93.3%

Table 3: Mortality 180-days

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Total	39	10	14	15
Dead	9	4	4	1
	23.1%	40.0%	28.6%	6.7%
Alive	30	6	10	14
	76.9%	60.0%	71.4%	93.3%

Table 4: In hospital death

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Total	39	10	14	15
Yes	8	3	4	1
	20.5%	30.0%	28.6%	6.7%
No	31	7	10	14
	79.5%	70.0%	71.4%	93.3%

In hospital death was noted in 20.5% of all EFIE patients included in analyses, with in hospital death of 6.7 %, 28.6%, 30%, and for the AG, AC_N, and AC_L respectively (see Table 4). No significant difference was noted between the AG and AC groups overall (P=0.117, 0.082), or AC_N and AC_L (P=1.0, P=.643).

Relapse of bacteremia was not demonstrated in either the AG or AC_L groups but was demonstrated in 14.3% of the AC_N group (see Table 5). No significant difference was noted between the above groups in incidence of relapsed bacteremia (P=.662, P=.414).

Table 5: Relapse of bacteraemia within 12 months

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Total	39	10	14	15
Yes	2	-	2	-
	5.1%		14.3%	
No	29	7	9	13
	74.4%	70.0%	64.3%	86.7%
NA	8	3	3	2
	20.5%	30.0%	21.4%	13.3%

SECONDARY OUTCOME MEASURES:

A greater number of adverse events was observed in the gentamicin group compared to the overall ceftriaxone group (P=.009), with no difference between the high and low dose ceftriaxone groups (P=.051). The adverse events are listed in Table 6 and 7 (below).

Table 6: Occurrence of adverse event

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Total	39	10	14	15
Yes	17	5	1	11
	43.6%	50.0%	7.1%	73.3%
No	22	5	13	4
	56.4%	50.0%	92.9%	26.7%

Table 7: Type of adverse event

		THERAPY		
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Had an adverse event	17	5	1	11
Rash	1	1	-	-
5.9%	20.0%			
Beta lactam toxicity	1	1	-	-
5.9%	20.0%			
Nephrotoxicity	9	1	-	8
52.9%	20.0%			72.7%
Neurotoxicity	2	1	1	-
11.8%	20.0%	100.0%		
Vestibular dysfunction or ototoxicity	3	-	-	3
17.6%				27.3%
Other	1	1	-	-
5.9%	20.0%			

Table 8: If Adverse event, did it necessitate change in antibiotic

		|THERAPY|	
	Total	Ampicillin + Ceftriaxone 1g	Ampicillin + Ceftriaxone 2g	Ampicillin + Gentamicin
Had an adverse event	17	5	1	11
Yes	9	4	-	5
	52.9%	80.0%		45.5%
No	8	1	1	6
	47.1%	20.0%	100.0%	54.5%

In 4 cases of the AC_L group, adverse events necessitated a change in antimicrobials, in 3 out of 4 cases (on day 14, 17 and 21 of treatment respectively) to a combination of vancomycin and ceftriaxone, and in 1 out of 4 cases, to daptomycin and gentamicin (after 16 days of treatment) (see Table 8). In 5 cases of the AG group, adverse events necessitated a change to antimicrobials, in 4 out of 5 cases to AC_L (on day 12, 10, 14 and 22 of treatment)and in 1 out of 5 cases to AC_L. There was a statistically significant difference in adverse events necessitating change in antimicrobial regimen between the groups (p = 0.26). There were no cases of adverse events necessitating change in the antimicrobial regimen in the AC_N group.

Discussion

To our knowledge, this is the second study examining the clinical outcomes of using lower-than-recommended synergistic ceftriaxone dosing (1 g 12 hourly) in dual beta lactam therapy to treat EFIE [11]. It is the first study to administer and evaluate lower dose ceftriaxone regimens in EFIE treatment in inpatient settings and evaluate treatment outcomes.

Our findings are in keeping with previous studies, in demonstrating similar efficacy in terms of mortality, in hospital death and rates of relapse between patients treated with ceftriaxone and aminoglycoside-based regimens, and a higher incidence of adverse events in those treated with an aminoglycoside-based regimen [4-7, 11-19]. Though a difference was noted in terms of in hospital death and all-cause mortality between the AG and AC group overall, it was not of statistical significance.

A recent study evaluating outpatient EFIE treatment with continuous benzylpenicillin infusion in combination with once daily aminoglycoside or ceftriaxone, found no difference in treatment success between the groups, and included patients who had been treated with low and high dose ceftriaxone (2 g

once daily or 1 g 12 hourly) [11]. Additionally, our study demonstrated that a statistically significant number of adverse events in the aminoglycoside treated patients required a change in antimicrobial therapy.

There was no significant difference between the 3 groups in the demographic measures of age, comorbidities, baseline renal function, complications of IE or presence of prosthetic device. However, a significantly greater number of cardiac and extracardiac surgeries were required during the treatment course of EFIE for patients treated with AG; this may

The adverse event most associated with aminoglycoside therapy within our study, was nephrotoxicity, reflecting the findings of previous studies. Only 1 case of nephrotoxicity was noted in our study, in the AC_L group (7%), with none in the AC_N (0 %) group; 8 cases were noted in the AG group (53%). In keeping with the recommendations in previous studies, we would advocate for consideration of ceftriaxone based dual beta lactam therapy to be initiated in cases of patients with or at risk of renal impairment with EFIE [6,7,11-14].

The alternative option suggested, to reduce toxicity and treatment related adverse events, is a shorter course of therapy in both AG and AC regimens. Two studies have examined shorter course (4 weeks as opposed to 6 weeks) AC regimens in treating E. faecalis endocarditis, one of which found the shorter course regimen was associated with a higher rate of relapse [14,15]. Multiple Danish studies demonstrated efficacy in clinical cure, mortality and incidence of relapse with a 6-week ampicillin and 2-week aminoglycoside regimen for EFIE, the first of which resulted in a change to the Danish Society of Cardiology recommendations for aminoglycoside therapy duration in EFIE [16,17].

Many centres utilise outpatient parenteral therapy programs to facilitate ongoing administration of either AG or AC regimens in EFIE. Herrera Hidalgo et al recently demonstrated the administration of a single daily dose of 4 g ceftriaxone with ampicillin-based outpatient regimens had a higher rate of relapse in comparison to a 12 hourly 2 g dose of ceftriaxone [18]. Two other small retrospective case series have demonstrated the efficacy of EFIE treatment with outpatient penicillin infusions in combination with ceftriaxone at 2 g 12 hourly dosing at achieving clinical cure [19,20].

Our study did not find a significant difference in mortality, relapse of bacteraemia or in hospital death between the low dose and high dose ceftriaxone regimen groups. However, it also did not note a significant difference in adverse events between these two groups. Beta lactam toxicity, particularly in the elderly, has been linked to altered pharmacokinetics due to multifactorial mechanisms including reduced renal clearance, and the pathophysiological changes associated with critical illness [20,21]. Theoretically, modified, or reduced dosing could lower the risk of development of beta lactam related toxicity [20]. However, most pharmacokinetic studies propose altered dosing be guided by therapeutic drug monitoring (i.e., with ceftriaxone levels) in at risk or elderly patients [20,21].

LIMITATIONS AND FUTURE DIRECTIONS:

There were several limitations to our study, mainly the small sample size, the implications on the statistical power of our findings, and retrospective cohort design. This was not a randomised or prospective study, and no intention to treat analysis was performed. Excluding patients who were lost to follow up, or who had different antibiotic regimens for more than 14 days, could also have contributed to selection bias. The significant differences in the demographic measures of surgeries performed and duration of treatment should also be interpreted in the context of small numbers of patients evaluated in each of the 3 antimicrobial regimen cohorts.

Additionally, we did not explore differences in clinical outcomes between patients treated with varying penicillin-based regimens (i.e., benzylpenicillin or ampicillin); this study did not explore the stability of benzylpenicillin continuous infusions in combination with outpatient ceftriaxone therapy. More recent studies have suggested lower rates of synergism with benzylpenicillin/ceftriaxone combination therapy as opposed to ampicillin/ceftriaxone therapy, as well as higher rates of unplanned readmissions [18,23]. However, given differing doses and frequency of dosing in ceftriaxone doses used concurrently in these studies, such results are difficult to attribute to one component of therapy alone; this should be an avenue of further study.

TDM (therapeutic drug monitoring) was not assessed in our study for ceftriaxone. Trough gentamicin concentrations, though collected, were not always correlated with clinical evidence of gentamicin toxicity such as ototoxicity or nephrotoxicity. Though a standard 1mg/kg, three times daily gentamicin dose was used, there was some variability, at the discretion of the treating physician, in dosing for obese patients.

There is preliminary data supporting the use of dalbavancin or teicoplanin in clinically stable EFIE patients [18,24,25]. Exploration of alternative therapies is required, particularly regarding logistics, toxicity, and clinical cure in outpatient settings as well as evaluation of early transition to oral agents [18,24,25].

Further randomised controlled data, with evaluation of therapeutic drug monitoring of beta lactam antimicrobials, is needed to guide recommendations around lower dose ceftriaxone in EFIE.

Conclusion

Our findings support existing data, advocating for use of AC regimens in EFIE, particularly in patients with or at risk of aminoglycoside toxicity such as renal impairment, with no difference between mortality and rates of relapse found between AC regimens (including low and high dose ceftriaxone) and AG. Higher rates of adverse events were associated with aminoglycoside therapy. Though there was no difference in adverse events between low and high dose ceftriaxone regimens, no significant difference in mortality or relapse rates was observed; further data incorporating therapeutic drug monitoring of ceftriaxone and larger clinical trials are required.

Declarations

Ethics approval and consent to participate:

Ethics approval was obtained on June 4, 2020, from Sydney Local Health District Human Research Ethics Committee, Concord Repatriation General Hospital. Reference Number is CH62/6/2019-149. Given the this is a retrospective audit, consent for participation and publication was waived.

All methods were performed in accordance with the relevant guidelines and regulations and the Declaration of Helsinki.

Consent for publication:

Given this is a retrospective audit, consent for participation and publication was waived.

Availability of data and materials:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author's contributions:

First author has contributed to obtaining ethics approval, study design, collection and analysis of data and write-up of manuscript. The second author has contributed to ethics approval, study design, analysis of data and write-up of manuscript.

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Competing interests:
No conflicts of interest declared, no financial or non-financial competing interests noted for both authors.

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