

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

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ABSTRACT

Background: The mortality rate for enterococcal infective endocarditis (EIE) is high. Ampicillin-ceftriaxone (AC) has emerged as an alternative antibiotic regimen with lower toxicity compared to ampicillin-gentamicin (AG), but evidence regarding its success in reducing EIE-associated mortality in the United States is limited. We retrospectively compared mortality in propensity score-matched EIE patients treated with AG versus AC.

Methods: We conducted a retrospective, propensity score-matched, cohort analysis of EIE patients treated with AG or AC from 2010 to 2017 at three hospitals in Pittsburgh, Pennsylvania. 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 forty-eight hours. We assessed 90-day mortality as the primary outcome, and inhospital 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 in the AC group than the AG group (21% vs 8%, p = 0.02). After propensity score-matching, 56 patients in each group remained for the outcomes analysis. We observed similar rates of 90-day mortality (6% vs 4%, p = 0.55), bacteremia relapse (0 patients in both cohorts), treatment failure (0% vs 1%, p = 0.50), and 90-day hospital readmission (24% vs 23%, p = 0.85) in the AC and AG-treated patient cohorts. Adverse events were more common in patients treated with AG, and more patients in the AG cohort switched antibiotic regimens than in the AC group.

Conclusions: EIE patients treated with AC have similar mortality rates as those treated with AG, while AG is associated with increased toxicity and adverse events. Larger, multicenter studies are still needed to compare the two antibiotic regimens.

BACKGROUND

- ✓ The mortality rate of *E. faecalis* infective endocarditis (EIE) is high
- ✓ Ampicillin-ceftriaxone (AC) is increasingly used instead of ampicillingentamicin (AG) for definitive antibiotic therapy of EIE
- ✓ There are no large clinical studies in the US comparing the two regimens for treatment of EIE
- ✓ We retrospectively compared mortality in propensity score-matched EIE patients treated with either combination
- \checkmark We examined the incidence of antibiotic therapy switch and of adverse events in the two patient cohorts

RESULTS

Clinical features and demographics of the EIE patient cohorts

Variable	AC	AG		Variable	AC	AG					
	n = 100 (%)	n = 90 (%)	F		n = 100 (%)	n = 90 (%)					
Age at admission, years	67.5 (22, 94)	63.5 (21, 85)	-	Valve affected							
Male sex	65 (65)	61 (68)		Aortic	39 (39)	44 (49)					
White race	86 (92)	79 (91)	_	Mitral	28 (28)	39 (43)					
Hispanic ethnicity	1 (1)	0	_	Tricuspid	10 (10)	11 (12)					
Nursing facility residence	20 (20)	9 (10)	_	Pulmonic	5 (5)	2 (2)					
Documented current intravenous drug use	14 (14)	17 (19)	_	Indication for surgery present	45 (45)	52 (58)					
Organ transplant	3 (3)	4 (4)	_	Valve dysfunction resulting in heart failure	9 (20)	10 (19)					
Charlson Comorbidity Index	2 (0, 10)	2 (0, 11)		Annular or aortic abscess	5 (11)	14 (27)					
Obesity	31 (31)	34 (38)		Destructive penetrating lesion	6 (13)	7 (14)					
Hospital-acquired infection	7 (8)	12 (14)		Persistent infection on appropriate							
Documented HLAR	32 (49)	6 (12)		treatment	4 (9)	1 (2)					
qSOFA	1 (0, 3)	1 (0, 3)		Mobile vegetation > 10 mm	13 (29)	22 (42)					
Pitt bacteremia score	1 (0, 6)	1 (0, 14)		Persistent/enlarging vegetation on							
Definite IE per modified Dukes criteria	75 (77)	69 (80)		appropriate treatment	1 (2)	0					
Vegetation present	72 (72)	66 (74)		Severe valvular regurgitation	27 (60)	23 (44)					
Vegetation size, mm (IQR)	12 (0.9, 40)	13 (3, 38)		Recurrent emboli	0	1 (2)					
Type of IE				Other	7 (16)	9 (17)					
Native valve IE	59 (59)	52 (58)		Surgical intervention	33 (33)	44 (49)					
Prosthetic valve IE	16 (16)	27 (30)		IE complications	32 (32)	38 (42)					
Pacemaker IE	30 (30)	10 (11)		Heart failure	9 (9)	9 (10)					
Complete pacemaker removal	17 (57)	3 (30)		Paravalvular complications	2 (2)	8 (9)					
Vasopressor use during hospital admission	26 (26)	15 (17)	_	Stroke	11 (11)	19 (21)					
Completion of antibiotic treatment course	69 (78)	70 (89)		Septic pulmonary emboli	6 (6)	1 (1)					
Figure 1. Antibiotic treatment of EIE shifted from AG to AC during the study period			_	Other emboli	8 (8)	11 (12)					
			L	None	68 (68)	52 (58)					
န္ ¹⁰⁰]	Ampicillin-ceftria	kone	Г								
	\sim			Statistically significant diffe	rences betwee	n the two					
00 at		~		treatment cohorts are highlighted in orange.							



METHODS

- Study population: Patients admitted at any of three Pittsburgh hospitals from 2010-2017 with EIE and treated with ampicillin-ceftriaxone (100 patients) or ampicillin-gentamicin (90 patients) for ≥48h
- Variables used for propensity score-matching: age, qSOFA score, CCI, inpatient vasopressor use, nursing facility residence, prosthetic valve endocarditis, surgical intervention
- \checkmark After propensity-score matching, there were 56 patients in each treatment cohort
- ✓ Primary outcome: all-cause 90-day mortality
- ✓ Secondary outcomes: in-hospital mortality, bacteremia relapse, treatment failure, hospital length of stay, estimated duration of bacteremia

After propensity-score matching, presence of annular or aortic abscess, complete pacemaker removal, and documented aminoglycoside resistance were significantly different between the two groups.

Clinical outcomes did not differ significantly between AC and AG treatment in the propensity-score matched EIE patient cohorts



Rates of adverse events and antibiotic therapy switch were higher in EIE patients receiving gentamicin

Adverse event	AC (n = 100)	AG (n = 90)	P value		AC (n = 56)	AG (n = 56)	Р
	1	1		Number of patients with therapy switch	5 (10%)	24 (43%)	<
oxicity	0	8		Duration of AC or AG therapy prior to			
openia	1	4		switch, days	13 (3, 19)	11 (7, 24)	
biotic associated diarrhea	4	7		Reason for switch			
stridium difficile colitis	8	5		Adverse event	4	12	
te kidney injury	6	13		Treatment failure	0	1	
er	5	1		Other	1	11	
I number of adverse events	25	39	0.0091	Unknown	0	3	

CONCLUSIONS AND FUTURE DIRECTIONS

- treated with ampicillin-gentamicin
- regimens for *E. faecalis* infective endocarditis

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RESULTS

After propensity-score matching, clinical outcomes did not differ between EIE patients treated with ampicillin-ceftriaxone or ampicillin-gentamicin

Antibiotic therapy switch and adverse events were more common in EIE patients

EIE patient mortality remains high despite changes in treatment practices

A randomized clinical trial is necessary to compare different antibiotic treatment

Further studies on pharmacodynamics and susceptibility patterns of EIE *E*. faecalis strains are critical to improving patient outcomes