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Linezolid for infective endocarditis
A structured approach based on a national database experience

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Abstract
Current data on the frequency and efficacy of linezolid (LNZ) in infective endocarditis (IE) are based on small retrospective series. We used a national database to evaluate the effectiveness of LNZ in IE.

This is a retrospective study of IE patients in the Spanish GAMES database who received LNZ. We defined 3 levels of therapeutic impact: LNZ < 7 days, LNZ high-impact (≥ 7 days, > 50% of the total treatment, and > 50% of the LNZ doses prescribed in the first weeks of treatment), and LNZ ≥ 7 days not fulfilling the high-impact criteria (LNZ-NHI). Effectiveness of LNZ was assessed using propensity score matching and multivariate analysis of high-impact cases in comparison to patients not treated with LNZ from the GAMES database matched for age-adjusted comorbidity Charlson index, heart failure, renal failure, prosthetic and intracardiac IE device, left-sided IE, and *Staphylococcus aureus*. Primary outcomes were in-hospital mortality and one-year mortality. Secondary outcomes included IE complications and relapses.

From 3467 patients included in the GAMES database, 295 (8.5%) received LNZ. After excluding 3 patients, 292 were grouped as follows for the analyses: 99 (33.9%) patients in LNZ < 7 days, 11 (3.7%) in LNZ high-impact, and 178 (61%) in LNZ-NHI. In-hospital mortality was 51.5%, 54.4%, and 19.1% respectively. In the propensity analysis, LNZ high-impact group presented with respect to matched controls not treated with LNZ higher in-hospital mortality (54.5% vs 18.2%, $P = .04$). The multivariate analysis showed an independent relationship of LNZ use with in-hospital mortality (odds ratio 9.06, 95% confidence interval 1.15–71.08, $P = .03$).

Treatment with LNZ is relatively frequent, but most cases do not fulfill our high-impact criteria. Our data suggest that the use of LNZ as definitive treatment in IE may be associated with higher in-hospital mortality.

Abbreviations: AHA = American Heart Association, CoNS = coagulase-negative staphylococci, ESC = European Society of Cardiology, IE = infective endocarditis, IQR = interquartile ranges, LNZ = linezolid, LNZ-NHI = linezolid not not fulfilling the high-impact criteria, MRSA = methicillin-resistant *Staphylococcus aureus*, POET = Partial Oral Treatment of Endocarditis trial, PS = propensity score, VRE = vancomycin-resistant enterococci.

Keywords: *Enterococcus*, infective endocarditis, linezolid, mortality, *Staphylococcus*

1. Introduction

Infective endocarditis (IE) remains a serious disease with significant morbidity and mortality.[1,2] The most common microorganisms involved in this pathology are gram-positive bacteria,[3,4] and in recent years, there has been an increase in the incidence of resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.[5]

Linezolid (LNZ), the first oxazolidinone antimicrobial, has excellent activity against gram-positive bacteria.[6] It has high bioavailability and excellent tissue penetration and is currently used as a first-line treatment for nosocomial pneumonia and skin and soft tissue infections.[7,8] However, its bacteriostatic action limits the indications for IE. Current guidelines of the European Society of Cardiology (ESC) recommend LNZ only as

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an alternative therapeutic regimen for MRSA and *Enterococcus* spp. resistant to beta-lactams, aminoglycosides, and vancomycin,[9] while the American Heart Association (AHA) does not suggest the use of LNZ for the treatment of MRSA-related infections.[10]

Clinical efficacy studies of LNZ on IE are scarce and limited to isolated cases or small series where LNZ was administered as part of a multidrug regimen. Results from the recent Partial Oral Treatment of Endocarditis (POET) trial, regarded LNZ as one of the optimal drugs for oral consolidation therapy in IE.[11] Thus, it is necessary to assess the real use of LNZ and clarify its role in the treatment of IE.

We assessed the real use of LNZ in the Spanish National Endocarditis Database (GAMES) that includes more than 3000 prospectively collected episodes. We structured LNZ use in 3 levels of therapeutic impact. The aim of this study was to determine the use of LNZ in IE and assess the outcome in patients receiving LNZ for IE treatment.

2. Methods

2.1. Design of the study

A retrospective analysis of patients from 34 Spanish hospitals registered in the GAMES database between 2008 and 2016. The characteristics and procedures of the GAMES database are published elsewhere.[5] For the study, we prospectively included patients with IE episodes who were treated with LNZ regardless of when the treatment was initiated and/or its duration.

2.2. Treatment with linezolid

To assess the effect of LNZ treatment on IE, we defined 3 levels of therapeutic impact: administration of LNZ for less than 7 days (LNZ < 7 days): group of patients who received LNZ not more than 6 days at any time during IE therapy and in any pharmacological combination; LNZ high-impact: group of patients who received LNZ for 7 or more days, LNZ accounted for at least 50% of total IE treatment, at least 50% as monotherapy, and at least 50% of total dose was received in the first half of IE course of treatment; LNZ not fulfilling criteria of high impact (LNZ-NHI): group of patients who received LNZ for 7 or more days but who did not meet all of high-impact criteria.

2.3. Other definitions

Infective endocarditis (IE): based on the modified Duke criteria.[12]

Community-acquired IE: diagnosed within 48 hours of hospital admission and does not meet the criteria for nosocomial IE or healthcare-associated IE.

Nosocomial IE: develops after 72 hours of admission or associated with an invasive procedure performed during recent hospitalization.[13,14]

Date of diagnosis: the first day of positive blood cultures or day at which the first echocardiogram findings compatible with IE are available in cases for which there are no positive blood cultures.

Persistent bacteremia: positive blood cultures with the same microorganism after seven days, despite appropriate antimicrobial treatment.

Septic shock: based on the criteria by the International Sepsis Definitions Conference.[15]

Central nervous system involvement: presence of acute neurological deficit of ischemic or hemorrhagic origin evidenced during the course of IE.

Hematological toxicity: presence of drug-related anemia, neutropenia, or thrombocytopenia, or a combination of the previous manifestations.

2.4. Objectives

The primary objectives of this study were to test in-hospital and 1-year mortality among patients who received LNZ versus subjects who did not receive LNZ; secondary objectives were to evaluate frequency of use and complications associated to IE therapy, and to document in-hospital stay and recurrences.

2.5. Analysis

Descriptive analysis including baseline, clinical, and event-related variables. Comparisons between patients who underwent treatment with LNZ against those who did not, and between the 3 impact groups were carried out. To assess the effectiveness of LNZ on IE outcome, propensity score matching (PS) for age-adjusted Charlson comorbidity index, heart failure, renal failure, prosthetic and intracardiac device-related IE, left-sided IE, and *S. aureus*, and a multivariate analysis of in-hospital mortality were performed and compared against matched control cases not receiving LNZ.

2.6. Statistical analysis

Quantitative variables are expressed as means and standard deviations (SD) or medians and interquartile ranges (IQRs), as appropriate; qualitative variables are presented as frequencies and percentages. Univariate analyses for intergroup comparisons in normally distributed continuous variables were carried out using Student t-test, and in non-normal distributions, the Mann–Whitney test was applied. Categorical variables were compared using the χ^2 test or Fisher's exact test when the χ^2 test could not be used. Adjusted odds ratios (ORs) were computed using logistic regression analysis. For PSM analysis, logistic regression was ran with a 1:3 case–control ratio. Stepwise logistic regression analysis included variables present at the time of admission with a P-value < .05 in the univariate analysis or were clinically relevant. All statistical analyses were performed using the PASW Statistics 18 for Windows (SPSS Inc., Chicago, IL).

2.7. Ethical issues

The project was approved by national and local institutional review boards and ethics committees (EC 18/07).

3. Results

3.1. Population

From a cohort of 3467 patients with IE included in the GAMES database between 2008 and 2016, 295 (8.5%) had received LNZ (Table 1). Median age was 69 years (IQR 58–76) and 63.4% were male. Most cases had left-sided IE (67.1%) and native-valve IE (49.2%). The most frequent microorganisms identified were coagulase-negative staphylococci (CoNS) and *S. aureus*. Prevalence of MRSA in our series was 35.7%.

Table 1

Description of the 295 cases treated with LNZ and comparison with controls in the GAMES IE cohort.

Variables (%)	LNZ 295	Controls 3172	P	95% CI Lower-Upper
Age, median (IQR)	69 (58 − 76)	69 (57 − 77)	.98	–
Sex (males)	187 (63.4)	1921 (60.5)	.37	–
Comorbidities				
Ischemic heart disease	79 (26.7)	815 (25.6)	.74	–
Heart failure	**131 (44.4)**	**1020 (32.1)**	**<.01**	**1.68 (1.32–2.14)**
Diabetes mellitus	94 (31.9)	870 (27.5)	.25	–
Renal failure	**62 (21.0)**	**473 (15.0)**	**.02**	**1.57 (1.22–2.03)**
Previous IE	23 (7.8)	230 (7.3)	.78	–
Charlson index (median, IQR)	5 (3 − 7)	5 (3 − 7)	.51	–
Type of IE				
Aortic	**116 (39.3)**	**1580 (49.8)**	**<.01**	**0.65 (0.51–0.83)**
Mitral	**104 (35.3)**	**1390 (43.8)**	**< .01**	**0.69 (0.54–0.89)**
Tricuspid	21 (7.1)	163 (5.1)	.15	–
Native	**145 (49.2)**	**1965 (61.9)**	**<.01**	**0.59 (0.47–0.75)**
Prosthetic	4 (31.9)	46 (29.8)	.45	–
Non-valvular	**69 (23.4)**	**358 (11.3)**	**<.01**	**2.39 (1.78–3.20)**
Acquisition				
Community	**136 (47.6)**	**1873 (61.5)**	**<.01**	**0.56 (0.44–.072)**
Nosocomial	**126 (44.1)**	**900 (29.6)**	**<.01**	**1.87 (1.46–2.39)**
Healthcare-related	24 (8.4)	271 (8.9)	.77	–
Etiology				
S. aureus	**84 (28.5)**	**692 (21.8)**	**.01**	**1.42 (1.09–1.86)**
Coagulase negative staphylococci	88 (29.8)	522 (16.5)	<.01	2.15 (1.65–2.81)
Enterococcus spp.	36 (12.2)	436 (13.7)	.46	–
Streptococcus spp.	34 (11.5)	847 (26.7)	<.01	0.35 (0.24–0.56)
Complications				
Persistent bacteremia	**47 (15.9)**	**349 (11.0)**	**.01**	**1.56 (1.12–2.18)**
Central nervous system involvement	49 (16.6)	624 (19.6)	.23	–
Renal failure	**139 (47.1)**	**1108 (35.2)**	**<.01**	**1.63 (1.28–2.08)**
Septic shock	**56 (18.9)**	**364 (11.4)**	**<.01**	**1.79 (1.31–2.45)**
Cardiac surgery	146 (49.5)	1414 (44.6)	.11	–
Clinical course				
Median in-hospital stay (days, IQR)	**39 (27 − 61)**	**36 (21 − 52)**	**<.01**	**1.01 (1.00–1.02)**
Median duration of treatment for IE (days, IQR)	**42 (26 − 50)**	**36 (25 − 44)**	**<.01**	**1.05 (1.02–1.08)**
In-hospital mortality	91 (30.8)	856 (27.0)	.16	–
One-year follow-up mortality	12 (4.0)	186 (5.8)	.25	–
Recurrences	6 (3.1)	52 (2.4)	.73	–

Bold indicates not significant (NS).

Targeted LNZ treatment was used in 262 cases (88.8%) and empirical therapy in 33 (11.2%). In 81% of cases, LNZ was administered in combination with other antibiotics at some stage of treatment.

As for the outcome, 91 patients (30.8%) died during first hospital admission, 12 (4.0%) died within 1 year, and 6 cases relapsed (3.1%). Median in-hospital stay was 39 days (IQR 27–61), median duration of total IE treatment was 42 days (IQR 26–50), and median treatment with LNZ was 14 days (IQR 5–21). Adverse events attributable to LNZ were reported in 32 patients (10.8%), mostly hematological (25 patients, 78.1%).

3.2. Linezolid versus other therapies

Patients who received LNZ (295) showed significantly higher occurrence of heart failure, renal failure, and nosocomial acquisitioning in comparison to the rest of cases in the GAMES cohort (3172). On the contrary, LNZ-treated individuals had less previous valvular disease and developed less left-sided IE, and native-valve IE. Regarding complications, in the LNZ cohort, more frequent persistent bacteremia, impairment of renal function, and SS were found, as well as longer in-hospital stay (Table 1).

3.3. Therapeutic impact of linezolid

We excluded 3 cases with insufficient data regarding duration of LNZ treatment (Table 2). The 292 cases included in this analysis were distributed as follows:

(1) LNZ < 7 days: 99 patients (33.9%). Median age 70 was years (IQR 63–77); 55.6% male. The age-adjusted Charlson index was 5 (IQR 3–8). As for the type of IE, 81.8% of the cases were left-sided and 51.5% were native-valve. The most frequent identified microorganism was *S. aureus* (33 cases; 33.3%). Median duration of complete IE treatment was 26 days (IQR 13–42) and median duration of LNZ treatment was 4 days (IQR 2–6). In-hospital mortality for this group was 51.5% and mortality during the follow-up year was 2.0%.

(2) LNZ high impact: Fifteen patients met the high-impact criteria, but there were no data on IE etiology for 4 cases and were excluded; thus, the analysis was carried out on 11 cases (Table 3). Median age was 59 years (IQR 55–78); 63.6% were male. The most frequent comorbidities were renal failure (45.5%) and heart failure (36.4%). The age-adjusted Charlson index was 5 (IQR 2–7) and 72.8% were left-sided

Table 2

Descriptive and comparative analysis of the 3 levels of therapeutic impact.

Variable	LNZ < 7 days (n=99)	LNZ-NHI (n=178)	LNZ High-impact (n=11)	P	95% CI Lower-Upper
Age, median (IQR)	70 (63–77)	68 (55–76)	59 (55–78)	NS	–
Sex (males)	55 (55.6)	120 (67.4)	7 (63.6)	NS	–
Comorbidities					
Ischemic heart disease	29 (29.3)	46 (25.8)	2 (18.2)	NS	–
Heart failure	46 (46.5)	76 (42.7)	4 (36.4)	NS	–
Renal failure	38 (38.4)	55 (30.9)	5 (45.5)	NS	–
Charlson index (median, IQR)	**5 (3 - 8)**	**4 (2 - 6)**	**5 (2 – 7)**	**.042***[*]	**1.09 (1.01–1.31)**
Type IE					
Aortic	42 (42.4)	67 (37.6)	3 (27.3)	NS	–
Mitral	39 (39.4)	60 (33.7)	5 (45.5)	NS	–
Tricuspid	**3 (3.0)**	**15 (8.4)**	**3 (27.3)**	**.012**[†]	**12.00 (2.07–69.42)**
Native	51 (51.5)	84 (47.2)	6 (54.5)	NS	–
Prosthetic	33 (33.3)	55 (30.9)	4 (36.4)	NS	–
Intracardiac-device	14 (14.1)	41 (23.0)	2 (18.2)	NS	–
Acquisition					
Community	48 (48.5)	81 (45.5)	3 (27.3)	NS	–
Nosocomial	39 (39.4)	80 (44.9)	7 (63.6)	NS	–
Health care related	9 (9.1)	12 (6.7)	1 (9.1)	NS	–
Etiology					
S. aureus	33 (33.3)	46 (25.8)	5 (45.5)	NS	–
Coagulase negative staphylococci	23 (23.2)	60 (33.7)	5 (45.5)	NS	–
Enterococcus spp.	9 (9.1)	25 (14.0)	0	NS	–
Streptococcus spp.	13 (13.1)	19 (10.7)	1 (9.1)	NS	–
Complications					
Persistent bacteremia	15 (15.2)	30 (16.9)	2 (18.2)	NS	–
Central nervous system involvement	19 (19.2)	30 (16.9)	0	NS	–
Renal failure	55 (55.6)	77 (43.3)	4 (36.4)	NS	–
Septic shock	**27 (27.3)**	**26 (14.6)**	**2 (18.2)**	**.016***	**0.46 (0.25–0.84)**
Cardiac surgery	42 (42.4)	94 (52.8)	4 (36.4)	NS	–
Clinical course					
In-hospital mortality	**51 (51.5)**	**34 (19.1)**	**6 (54.5)**	**< .01**[*,‡]	**0.22 (0.12–0.38)**
One-year follow-up mortality	2 (2.0)	10 (5.6)	0	NS	–
Median duration of treatment for IE (days, IQR)	**26 (13 - 42)**	**45 (32 - 56)**	**34 (19 – 46)**	**<.01**[*,‡]	**1.06 (1.04–1.08)**
Median duration of LNZ (days, IQR)	**4 (2 - 6)**	**16 (13 - 25)**	**27 (17 – 38)**	**<.01**[*,†,‡]	**1.96 (1.62–2.37)**
Interval from the diagnosis of IE to first LNZ (days, IQR)	**2 (0 - 19)**	**25 (5 - 41)**	**5 (0 – 17)**	**.01**[*,‡]	**1.01 (1.00–1.02)**

NS = non significant.

[*] Significant difference between LNZ < 7 days and LNZ-NHI.

[†] Significant difference between LNZ < 7 days and LNZ high-impact.

[‡] significant difference between LNZ-NHI and LNZ high-impact.

IE. There was higher frequency of tricuspid involvement (27.3%) in comparison to the other 2 groups. Acquisition was mainly nosocomial (63.6%), and the most frequent isolated microorganisms were *S. aureus* and CoNS (45.5% each). The main reasons for LNZ administration were renal failure (6 cases [5 chronic renal failures and 1 acute renal failure]), empiric treatment (1 case), and intolerance to vancomycin (1 case); in 3 cases, the reasons for choosing LNZ were unclear. Median duration of complete IE treatment for this group was 34 days (IQR 19–46). The duration of treatment with LNZ was 27 days (IQR 17–38) and median number of days before receiving the first dose of LNZ after the diagnosis was 5 days (IQR 0–17). The most frequent complications were renal failure (36.4%), SS (18.2%), and persistent bacteremia (18.2%). Four patients (36.4%) underwent cardiac surgery. In-hospital mortality was 54.5% (6 cases). The causes of death were septic shock (3 cases), heart failure (1 case), renal failure (1 case), and respiratory failure (1 case). There were no deaths and 1 recurrence during follow-up.

(3) LNZ-NHI: One hundred seventy-eight patients (61%). Median age was 68 years (IQR 55–76); age-adjusted Charlson index was 4 (IQR 2–6). Most were left-sided IE (71.3%) and the most frequent etiology was CoNS (33.7%). Median time to first LNZ administration from IE diagnosis was 25 days (IQR 5–41). Median duration of complete treatment was 45 days (IQR 32–56) and for LNZ 16 days (IQR 13–25). In-hospital mortality was 19.1% (34 patients), and after 1 year of follow-up, 10 patients died (5.6%). This group presented significantly lower mortality and longer duration of complete IE treatment than the other two groups. In addition, the interval between IE diagnosis and the administration of the first dose of LNZ was significantly longer in comparison to LNZ < 7 days and LNZ high-impact.

3.4. High-impact group versus patients not treated with linezolid

To evaluate the real impact of LNZ treatment on IE, we performed a PSM analysis with a 1:3 ratio that included the

Table 3

Detailed description of the 11 cases included in the high-impact group.

Case	Age (years)	Sex	Comorbidities	Type of IE	Etiology	Indication for LNZ	Duration of LNZ, days	Another antibiotic, days	Complications	CSx	In-hospital mortality	Cause of death
1	17	F	Neoplasm, hepatic failure	Tric N	*S. aureus*	UN	65	VAN 7 Other 5	No	No	No	
2	80	F	Lung disease, previous stroke, RF	Aortic P	CoNS	Previous RF	29	CTX 3 VAN 2	No	No	No	
3	59	M	DM, neoplasm, IS, RF, HF	Aortic and Mi P and N	CoNS	Previous RF	18	DAP 11 Other 6	No	No	Yes	HF
4	93	M	RF	PM	*S. aureus*	Previous RF	29	CLOX 28	No	Yes	Yes	RF
5	55	M		Mitral N	CoNS	New RF	45	Other 8 DAP 16	RI, PB, septic shock	Yes	Yes	Septic shock
6	67	M	DM, lung disease, neoplasm	Tric N	CoNS	Allergic reaction to VAN	24	VAN 5	No	No	No	
7	69	M	Lung disease, neoplasm	Mitral N	*S. aureus*	UN	15	No	No	No	Yes	Resp. failure
8	78	F	DM, HF, RF, previous stroke	Tric N	*S. aureus*	Previous RF	17	DAP 9	Septic shock, PB	No	Yes	Septic shock
9	59	F	Lung disease, HF	Aortic N	CoNS	UN	19	GEN 5	Septic shock	Yes	Yes	Septic shock
10	59	M	HF, AF	Mitral P	*S. bovis*	Empiric	32	No	No	Yes	No	
11	30	M	AF, RF	PM	*S. aureus*	Previous RF	35	GEN 13	Recurrence	No	No	

AF = atrial fibrillation, CIP = ciprofloxacin, CLOX = cloxacillin, CoNS = coagulase-negative staphylococci, CSx = cardiac surgery, CTX = ceftriaxone, DAP = daptomycin, DM = diabetes mellitus, F = female, GEN = gentamicin, HF = heart failure, IS = immunosuppression, M = male, MF = multiorgan failure, N = native, P = prosthetic, PB = persistent bacteremia, PM = pacemaker, Resp failure = respiratory failure, RF = renal failure, Tric = tricuspid, UN = unknown, VAN = vancomycin.

high-impact group paired with controls not receiving LNZ from the GAMES database (Table 4). We excluded the other 2 groups from this analysis because it was difficult to assess the specific role of LNZ on the outcome. Variables used for matching were age, heart failure, renal failure, age-adjusted Charlson index, prosthetic IE, left-sided IE, intracardiac IE device, and *S. aureus*. Regarding the type of IE, only acquisition was different between the 2 groups, with a higher frequency of nosocomial origin in the high-impact group respect to controls (63.6% vs 24.2%, $P = .04$). In the primary outcome, patients treated with LNZ presented higher in-hospital mortality (54.5% vs 18.2%, $P = .04$).

A multivariate analysis for in-hospital mortality (Table 5) was carried out including the variables prosthetic IE, left-sided IE, heart failure, *S. aureus*, age-adjusted Charlson index > 6, and treatment with LNZ. Factors independently associated with in-hospital mortality were age-adjusted Charlson index > 6 (OR 25.77, 95% CI 1.81–366.15, $P = .01$) and use of LNZ (OR 9.06, 95% CI 1.15–71.08, $P = .03$).

4. Discussion

In this study, we determined that LNZ is given quite frequently for the management of IE. Eight point five per cent of 3467 IE patients in our series received LNZ, although only in 11 cases, the duration and contribution of the therapy can be considered a definitive IE treatment. In these cases, LNZ was significantly associated with higher in-hospital mortality.

In 2000, the United States Food and Drug Administration approved LNZ for the treatment of skin and soft-tissue infections and nosocomial pneumonia.[16] Its use for IE with animal models proved effective when the diseases was caused by *S. aureus* and vancomycin-resistant enterococci.[17,18] Discordant results have been reported on the effect of LNZ administration for the

treatment of bloodstream infections. In 2 compassionate use studies, in which LNZ was administered to patients infected with gram-positive bacteremia, cure rates were 70% and 88%, respectively.[19,20] Despite these promising findings, a non-inferiority clinical trial did not demonstrate the superiority of LNZ over vancomycin and was associated with an increased risk of mortality, thus precluding the approval of LNZ for the treatment of bacteremia.[21]

There is no consensus in existing IE guidelines regarding the use of LNZ. The ESC guidelines recommend as an alternative treatment for IE caused by MRSA and enterococci resistant to beta-lactams, aminoglycosides, and vancomycin, while the AHA guidelines do not preclude its/their use in MRSA-related IE.[9,10] Information regarding LNZ use is based on single-case reports or small retrospective series in which the time of initiation of LNZ, treatment duration, and combination with other drugs are not well structured.[22–30]

Until our study, the series of Lauridsen et al[28] had reported the largest number of IE cases treated with LNZ (38 cases). The authors retrospectively compared individuals who had received LNZ with a control group, and no significant differences in in-hospital mortality or at one year of follow-up were detected. Tascini et al[29] and Muñoz et al[30] reported similar results, that is, treatment of IE with LNZ was not associated with higher mortality rates. In these studies, the authors did not specify the time of initiation or duration of the LNZ therapy nor its effect on IE. More recently, the POET trial compared a consolidation phase with oral vs intravenous antibiotic IE treatment, with LNZ being one of the oral options in the consolidation phase. However, its use was not based on a delayed start and in combination with another active agent.[11]

In our study, comorbidities and IE complications are more frequently seen in patients who received LNZ in comparison to

Table 4

Propensity score of high-impact group versus controls.

Variable	LNZ High-impact (n=11)	Controls (n=33)	P	95% CI Lower-Upper
Age, median (IQR)	59 (55–78)	62 (52–74)	.84	–
Sex (males)	7 (63.6)	22 (66.6)	.85	–
Comorbidities				
Ischemic heart disease	2 (18.2)	14 (42.4)	.26	–
Diabetes mellitus	3 (27.3)	5 (15.2)	.36	–
Peripherical vascular disease	2 (18.2)	7 (21.2)	.82	–
Neoplasia	4 (36.4)	5 (15.2)	.13	–
Hepatic disease	1 (9.1)	1 (3.0)	.40	–
Charlson index (median, IQR)	5 (2–7)	4 (1–7)	.47	–
Type IE				
Aortic	3 (27.3)	11 (33.3)	.70	–
Mitral	5 (45.5)	9 (27.3)	.26	–
Tricuspid	3 (27.3)	3 (9.1)	.12	–
Pulmonary	1 (9.1)	2 (6.1)	.73	–
Acquisition				
Community	**3 (27.3)**	**22 (66.6)**	**.01**	**0.17 (0.03–0.78)**
Nosocomial	**7 (63.6)**	**8 (24.2)**	**.04**	**5.25 (1.21–22.7)**
Healthcare related	1 (9.1)	2 (6.0)	.72	–
Etiology				
S. aureus	5 (45.5)	12 (36.4)	.59	–
Coagulase negative staphylococci	5 (45.5)	5 (15.2)	.09	–
Enterococcus spp.	0	3 (9.1)	.56	–
Streptococcus spp.	1 (9.1)	5 (15.2)	.61	–
Complications				
Persistent bacteremia	2 (20.0)	6 (18.2)	.89	–
Central nervous system involvement	0	8 (24.2)	.08	–
Renal failure	4 (36.4)	13 (39.4)	.85	–
Septic shock	2 (18.2)	4 (12.1)	.61	–
Cardiac surgery	4 (36.4)	14 (42.4)	.72	–
Evolution				
In-hospital mortality	**6 (54.5)**	**6 (18.2)**	**.04**	**5.40 (1.22–23.72)**
One-year follow-up mortality	0	1 (3.0)	.56	–
Overall mortality	**6 (54.5)**	**7 (21.2)**	**.05**	**4.45 (1.04–19.01)**
Median duration of treatment for IE (days, IQR)	34 (19 – 46)	37 (28 – 43)	.58	–
Median in-hospital stay (days, IQR)	34 (27 – 57)	32 (27 – 44)	.37	–

the rest of patients included in the GAMES database, which probably leads to the selection of a higher risk group for potentially poorer evolution. When we segregated LNZ cases into 3 levels of therapeutic impact, the proportional contribution of LNZ differs considerably. Only for the high-impact group, LNZ was a definitive treatment in IE. In this cohort, in-hospital mortality is higher than in controls, and as determined with the multivariate analysis, LNZ is an independent risk of mortality.

The retrospective design and small sample size are the main limitations of this study. Another limitation is the possibility of a selection bias in the LNZ group, characterized by a larger number of comorbidities, more IE complications, and higher frequency of

nosocomial acquisition (particularly in high-impact patients) with respect to controls. The criteria applied for selecting the groups of therapeutic impact may have led to include cases with an increased mortality, reflected in significantly differences in the median duration of total IE treatment between LNZ < 7 days versus LNZ-NHI and LNZ high-impact versus LNZ-NHI. These variables may contribute to a poorer outcome in LNZ high-impact patients. The propensity score analysis treat to avoid the selection bias and the multivariate analysis demonstrates that LNZ use is an independent risk factor for in-hospital mortality in IE.

Among the strengths of this study is the stratification of cases in therapeutic impact groups that offers a clarification on the LNZ in clinical practice. Finally, we propose definitions of therapeutic requirements that may be useful when evaluating antimicrobial effectiveness in a disease as complex as IE.

5. Conclusion

Treatment with LNZ is relatively frequent, but most cases do not fulfill our high-impact criteria. Our data suggest that the use of LNZ as definitive treatment of IE may be associated with higher in-hospital mortality.

Table 5

Multivariate analysis of in-hospital mortality (N=44).

Factor	OR	95% CI	P
Prosthetic IE	0.04	0.002–1.20	.06
Left-sided IE	15.19	0.96–238.77	.06
Heart failure	5.75	0.96–34.29	.06
S. aureus	0.70	0.06–8.26	.77
Age-adjusted Charlson index > 6	**25.77**	**1.81–366.15**	**.01**
Linezolid	**9.06**	**1.15–71.08**	**.03**

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References

[1] Cuervo G, Escrihuela-Vidal F, Gudiol C, et al. Current challenges in the management of infective endocarditis. Front Med (Lausanne) 2021;8:641243.
[2] Thuny F, Giorgi R, Habachi R, et al. Excess mortality and morbidity in patients surviving infective endocarditis. Am Heart J 2012;164:94–101.
[3] Munoz P, Kestler M, De Alarcon A, et al. Current epidemiology and outcome of infective endocarditis: a multicenter, prospective, cohort study. Medicine (Baltimore) 2015;94:e1816.
[4] Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. J Am Coll Cardiol 2017;69:325–44.
[5] Falcone M, Russo A, Venditti M. Optimizing antibiotic therapy of bacteremia and endocarditis due to staphylococci and enterococci: new insights and evidence from the literature. J Infect Chemother 2015;21:330–9.
[6] Gajdacs M. The continuing threat of methicillin-resistant Staphylococcus aureus. Antibiotics (Basel) 2019;8:
[7] Leong HN, Kurup A, Tan MY, et al. Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics. Infect Drug Resist 2018;11:1959–74.
[8] Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). Eur Respir J 2017;50:1700582.
[9] 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). Eur Heart J 2015;36:3075–128.
[10] Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435–86.
[11] Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019;380:415–24.
[12] Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633–8.
[13] Ortega-Loubon C, Munoz-Moreno MF, Andres-Garcia I, et al. Nosocomial vs community-acquired infective endocarditis in Spain: location, trends, clinical presentation, Etiology, and survival in the 21st century. J Clin Med 2019;8:
[14] Ambrosioni J, Hernandez-Meneses M, Tellez A, et al. The changing epidemiology of infective endocarditis in the twenty-first century. Curr Infect Dis Rep 2017;19:21.
[15] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.
[16] Rodvold KA, McConeghy KW. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. Clin Infect Dis 2014;58(Suppl 1):S20–7.
[17] Patel R, Rouse MS, Piper KE, et al. Linezolid therapy of vancomycin-resistant Enterococcus faecium experimental endocarditis. Antimicrob Agents Chemother 2001;45:621–3.
[18] Oramas-Shirey MP, Buchanan LV, Dileto-Fang CL, et al. Efficacy of linezolid in a staphylococcal endocarditis rabbit model. J Antimicrob Chemother 2001;47:349–52.
[19] Birmingham MC, Rayner CR, Meagher AK, et al. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin Infect Dis 2003;36:159–68.
[20] Jang HC, Kim SH, Kim KH, et al. Salvage treatment for persistent methicillin-resistant Staphylococcus aureus bacteremia: efficacy of linezolid with or without carbapenem. Clin Infect Dis 2009;49:395–401.
[21] Wilcox MH, Tack KJ, Bouza E, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: non-inferiority of linezolid in a phase 3 study. Clin Infect Dis 2009;48:203–12.
[22] Archuleta S, Murphy B, Keller MJ. Successful treatment of vancomycin-resistant Enterococcus faecium endocarditis with linezolid in a renal transplant recipient with human immunodeficiency virus infection. Transpl Infect Dis 2004;6:117–9.
[23] Balkhair A, Al Muharrmi Z, Darwish L, et al. Treatment of vancomycin-intermediate Staphylococcus aureus (VISA) endocarditis with linezolid. Int J Infect Dis 2010;14(Suppl 3):e227–9.
[24] Bassetti M, Di Biagio A, Del Bono V, et al. Successful treatment of methicillin-resistant Staphylococcus aureus endocarditis with linezolid. Int J Antimicrob Agents 2004;24:83–4.
[25] de Feiter PW, Jacobs JA, Jacobs MJ, et al. Successful treatment of Staphylococcus epidermidis prosthetic valve endocarditis with linezolid after failure of treatment with oxacillin, gentamicin, rifampicin, vancomycin, and fusidic acid regimens. Scand J Infect Dis 2005;37:173–6.
[26] Jasovich A, Ganaha MC, Ebi C, et al. Endocarditis due to vancomycin-resistant Enterococcus raffinosus successfully treated with linezolid: case report and review of literature. Rev Argent Microbiol 2008;40:204–7.
[27] Wareham DW, Abbas H, Karcher AM, et al. Treatment of prosthetic valve infective endocarditis due to multi-resistant Gram-positive bacteria with linezolid. J Infect 2006;52:300–4.
[28] Lauridsen TK, Bruun LE, Rasmussen RV, et al. Linezolid as rescue treatment for left-sided infective endocarditis: an observational, retrospective, multicenter study. Eur J Clin Microbiol Infect Dis 2012;31:2567–74.
[29] Tascini C, Bongiorni MG, Doria R, et al. Linezolid for endocarditis: a case series of 14 patients. J Antimicrob Chemother 2011;66:679–82.
[30] Munoz P, Rodriguez-Creixems M, Moreno M, et al. Linezolid therapy for infective endocarditis. Clin Microbiol Infect 2007;13:211–5.