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 week 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.

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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

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 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:** Enterococci, infective endocarditis, linezolid, *Staphylococcus aureus*.
an alternative therapeutic regimen for MRSA and *Enterococcus* spp. resistant to beta-lactams, aminoglycosides, and vancomycin,[19] 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%.
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%).

(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.

3.2. Linezolid versus other therapies

Patients who received LNZ (295) showed significantly higher occurrence of heart failure, renal failure, and nosocomial acquisition 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).

Table 1

| 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 (1.9) | 46 (1.5) | .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 (0.44–0.72) |
| 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).
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 | 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 | No |
| 3    | 59          | M   | DM, neoplasm, IS, RF, HF | Aortic and Mi P | CoNS | Previous RF | 18 | DAP 11 | No | No | Yes | HF |
| 4    | 93          | M   | RF | PM | S. aureus | Previous RF | 29 | CLOX 28 | No | Yes | Yes | RF |
| 5    | 55          | M   | DM, lung disease, neoplasm | Mitral N | CoNS | UN | 15 | No | No | No | Yes | Resp. failure |
| 6    | 67          | M   | Lung disease, neoplasm | Tric N | CoNS | Allergic reaction to VAN | 24 | VAN 5 | No | No | No | No |
| 7    | 69          | M   | Lung disease, neoplasm | Mitral N | S. aureus | UN | 17 | DAP 9 | Septic shock, PB | No | Yes | Yes |
| 8    | 78          | F   | DM, RF, previous stroke | Tric N | S. aureus | Previous RF | 19 | GEN 5 | Septic shock | Yes | Yes | Yes |
| 9    | 59          | F   | Lung disease, HF | Aortic N | CoNS | UN | 32 | No | No | Yes | Yes | No |
| 10   | 59          | M   | HF, AF | Mitral P | S. bovis | Empiric | 35 | GEN 13 | Recurrence | No | No | No |
| 11   | 30          | M   | AF, RF | PM | S. aureus | Previous RF | 35 | GEN 13 | Recurrence | No | No | No |

AF = atrial fibrillation, CIP = ciprofloxacin, CLOX = clavulanic acid, 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, MI = 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 a higher in-hospital mortality (54.5% vs 18.2%, P = .04).

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. Its use for IE with animal models proved effective when the diseases was caused by S. aureus and vancomycin-resistant enterococci. 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 bacteria, cure rates were 70% and 88%, respectively. 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.

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. 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.

Until our study, the series of Lauridsen et al 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 and Muñoz et al 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.

In our study, comorbidities and IE complications are more frequently seen in patients who received LNZ in comparison to...
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 use 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 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| –                  |
| Peripheral 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| –                  |

### 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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