MAJOR ARTICLE

TITLE

Impact of intermediate susceptibility to penicillin on antimicrobial treatment and outcomes of endocarditis caused by viridans and *gallolyticus* group streptococci

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RUNNING TITLE: Intermediate susceptibility to penicillin in streptococcal endocarditis

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SUMMARY: In a retrospective analysis of endocarditis due to viridans and *gallolyticus* groups streptococci, cephalosporin monotherapy was not associated with higher in-hospital mortality when the isolate showed intermediate susceptibility to penicillin.

ABSTRACT

Background: Evidence supporting combination treatment with a beta-lactam plus an aminoglycoside (C-BA) for endocarditis caused by viridans and *gallolyticus* group streptococci (VGS-GGS) with intermediate susceptibility to penicillin (PENI-I) is lacking. We assess the clinical characteristics and outcomes of PEN-I VGS-GGS endocarditis and compare the effectiveness and safety of C-BA vs. third-generation cephalosporin monotherapy.

Methods: Retrospective analysis of prospectively collected data of a cohort of definite endocarditis caused by penicillin-susceptible and PENI-I VGS-GGS (penicillin minimum inhibitory concentration ranging from 0.25 to 2mg/L) between 2008 and 2018 in 40 Spanish hospitals. We compared cases treated with monotherapy or with C-BA and performed multivariable analyses of risk factors for in-hospital and one-year mortality.

Results: A total of 914 consecutive cases of definite endocarditis caused by VGS-GGS with complete or intermediate susceptibility to penicillin were included. 688 (75.3%) were susceptible to penicillin and 226 (24.7%) were PENI-I. Monotherapy was used in 415 (45.4%) cases (cephalosporin in 331 cases) and 499 (54.6%) cases received C-BA. In-hospital mortality was 11.9 %, and 190 (20.9 %) patients developed acute kidney injury. Heart failure (OR 6.06; 95% CI 1.37-26.87; P = .018), central nervous system emboli (OR 9.83; 95% CI 2.17-44.49; P = .003) and intracardiac abscess (OR 13.47; 95% CI 2.24-81.08; P = 0.004) were independently associated with in-hospital mortality among PEN-I VGS-GGS cases, while monotherapy was not (OR 1.01; 95% CI 0.26-3.96; P = .982).

Conclusions: Our findings support the use of cephalosporin monotherapy in PEN-I VGS-GGS endocarditis in order to avoid nephrotoxicity without adversely affecting patient outcomes.

INTRODUCTION

Infective endocarditis (IE) is a severe disease with in-hospital mortality rates ranging from 20% to 25% [1]. Viridans and *gallolyticus* group streptococci (VGS-GGS) are the causative agents of endocarditis in one fifth of cases [2,3]. They represent the second cause of endocarditis in Europe and the United States, and the first in countries outside these regions [1,4,5].

The majority of VGS-GGS are highly susceptible to penicillin [penicillin minimum inhibitory concentration (MIC) ≤0.125 mg/L] [6], and beta-lactams are the drugs of choice. In endocarditis caused by VGS-GGS with intermediate susceptibility to penicillin (penicillin MIC ranging from 0.25 to 2 mg/L; PEN-I), current guidelines recommend the use of beta-lactams in combination with aminoglycosides (C-BA) due to their synergistic effect [7]. The evidence supporting the use of C-BA is scarce and based on experimental data [8,9] or small cohorts of patients [10], and the use of aminoglycosides can be associated to kidney toxicity. Alternatively, monotherapy with third-generation cephalosporin is accepted when the isolate shows susceptibility [7], although evidence supporting this recommendation is even scarcer [11]. More comprehensive data gathered from larger patient cohorts are clearly needed.

The objectives of the present study are: to assess the clinical characteristics and outcome of PEN-I VGS-GGS endocarditis, and to compare the efficacy and safety of targeted antibiotic therapy with C-BA vs. cephalosporin monotherapy..

METHODS

Design, patient population and data collection

We performed a retrospective analysis of prospectively collected data of adult patients (≥ 18 years old) with definite endocarditis caused by VGS-GGS between 2008 and 2018 at 40 Spanish hospitals [39 of them members the *Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España* (GAMES) prospective cohort] [2]. Data were prospectively collected using a standardized case report form. Supplementary data needed for this study, such as susceptibility test to penicillin, were retrospectively collected. This study is reported following the STROBE recommendations (Supplementary table 1).

Definitions

Definite infective endocarditis was diagnosed according to the modified Duke criteria or ESC criteria after August 2015 [7,12]. Acquisition was categorized as community-acquired or non-community-acquired (including nosocomial and health care-associated infections) according to Friedman criteria [13,14]. Cure was defined as absence of relapse or death after one year of follow-up. Relapse was defined as positive blood cultures with the same microorganism, while reinfection was defined as a new episode of endocarditis caused by a different microorganism. Chronic kidney disease was defined as a glomerular filtration rate < 60 mL/min per 1.73 m^2 of at least three months' duration. Acute kidney injury (AKI) was defined as a new in-hospital increase in serum creatinine levels of at least 1.5 times; patients who suffered AKI at the time of hospitalization but showed a progressive improvement in kidney function were not considered to have in-hospital AKI; nor were patients undergoing ambulatory haemodialysis regarded as having AKI. Surgery was indicated according to ESC or AHA criteria [7,15]. Embolic events were defined as ischemic phenomena detected either clinically or radiologically; imaging studies were performed at the discretion of the medical team. Persistent bacteraemia was defined as positive blood cultures after 48 hours of initiation of active antimicrobial therapy.

Monotherapy was defined as targeted therapy with penicillin, ampicillin or ceftriaxone. Patients with PEN-I VGS-GGS endocarditis treated with penicillin or ampicillin monotherapy were excluded from the analysis due to incompatibility with the recommendations of international guidelines. C-BA was defined as concomitant use of beta-lactam (either penicillin, ampicillin or cephalosporin) and an aminoglycoside as targeted therapy. Empirical treatment with a beta-lactam and an aminoglycoside was not considered as C-BA if the aminoglycoside

administration lasted less than 48 hours. Primary outcomes were in-hospital and one-year mortality, defined as crude mortality during the index hospitalization and after 12 months of follow-up, respectively.

Microbiology

Identification of microorganisms to the species level and antibiotic susceptibility were evaluated according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) protocols. Matrix-Assisted Laser Desorption Ionization – Time Of Flight had been used for identification at most of the participating hospitals since 2011. Viridans group streptococci (VGS) included *Streptococcus mitis* group, *S. mutans* group and *S. salivarius* group, while *gallolyticus* group streptococci (GGS) included four subspecies: *gallolyticus*, *pasteurianus*, *infantarius* and *lutetiensis*. Beta-haemolytic streptococci and *Streptococcus anginosus* group species were not included in the present study due to their higher virulence [16,17]. Strains were considered susceptible to penicillin (PEN-S) when penicillin minimum inhibitory concentration (MIC) was ≤ 0.125 mg/L. Intermediate susceptibility to penicillin was defined as MIC ranging from 0.25 to 2 mg/L [7]. Isolates resistant to penicillin (MIC ≥4 mg/L) were excluded.

Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are reported as medians and interquartile ranges. In the univariate analysis, qualitative variables were compared using χ^2 or Fisher's exact tests, and quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test. We first compared cases of definite endocarditis caused by VGS-GGS with intermediate susceptibility to penicillin with cases caused by susceptible VGS-GGS. Secondly, we compared the outcomes of patients treated with monotherapy with those treated with C-BA. In the general cohort, cases of endocarditis treated with third-generation cephalosporin monotherapy were compared to cases treated with C-BA using a propensity score-matched approach. The propensity score for receiving C-BA was estimated using a backward stepwise logistic regression model that included variables with p-values <0.1 in the univariate analysis plus other variables considered relevant. Propensity score matching was not performed in the group of PEN-I VGS-GGS endocarditis due to the low number of cases. Univariate analysis of factors potentially associated with mortality among PEN-I VGS-GGS was performed using the χ^2 test; all statistically significant (p-value <0.1

in the univariate analysis) and clinically relevant variables were included in the Cox multivariable regression model. Statistical significance was set at $P < 0.05$ and values were two-tailed. IBM SPSS Statistics Version 26 was used (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 1033 cases of endocarditis caused by viridans and *gallolyticus* streptococci were identified. Information regarding susceptibility to penicillin was available in 930 cases (90 %). After exclusion of 16 cases resistant to penicillin, 914 cases were included. There were 226/930 (24.7 %) cases of IE caused by VGS-GGS PEN-I (Figure 1) and 688/930 (75.3%) caused by VGS-GGS susceptible to penicillin. A comparison of general characteristics between penicillin-susceptible and PEN-I cases is presented in Table 1. Median age was 68 years and 15 % of patients had chronic kidney disease. Viridans group streptococci accounted for 77 % (N = 174/226) of all PEN-I isolates. PEN-I VGS-GGS endocarditis showed less presence of intracardiac abscess (8.4 vs. 15 %; P = .012). In patients with penicillin-susceptible VSG-GGS endocarditis, surgery was indicated (61.2 vs. 50.9 %; P = .006) and performed (44.8 vs. 35.8 %; P = .019) more frequently. Patients with PEN-I VGS-GGS endocarditis more frequently received C-BA (60.1 vs. 52.7 %; P = .052).

Factors associated with combination therapy in the general cohort

In the univariate analysis (Supplementary table 2), patients treated with C-BA were significantly younger (64 vs. 72 years; P < .01), had a lower age-adjusted Charlson index (median 4 vs. 5 points; P < .01) and had lower rates of chronic kidney disease (10 vs. 21.8 %; P < .01). C-BA patients had more central nervous system emboli (19.6 vs. 14 %; P = .025), mitral valve endocarditis (50.5 vs. 44.8 %; P = .086) and intracardiac complications (34.1 vs 28.3 %; P = .063). Indication (62.1 vs. 54.4 %; P = .020) and performance (47.1 vs. 37 %; P = .002) of surgery were more frequent in C-BA, with a lower one-year overall mortality rate (16 vs. 21.8 %; P = .026). In the multivariable analysis (Supplementary table 3), advanced age was independently associated with monotherapy.

Factors associated with mortality in the general cohort

Propensity score adjustment was performed using the following variables: age >65 years old, gender, age-adjusted Charlson index, prosthetic endocarditis, chronic kidney disease, overall

emboli and central nervous system emboli (Supplementary table 4). Patients receiving C-BA had lower in-hospital (6.6 vs. 13.9%; P = .006) and one-year mortality (12.4 vs 19.7%; P = .023). No differences in intracardiac complications, indication for surgery or relapse were found between patients receiving monotherapy or C-BA. Cephalosporin was the main antimicrobial in the monotherapy group, while cephalosporin plus aminoglycoside was the most frequently used combination in the C-BA group (Supplementary table 5). The univariate analysis of factors associated with mortality is displayed in Supplementary table 6.

Factors independently associated with mortality in PEN-I VGS-GGS cases

In the subgroup of 226 patients with PEN-I VGS-GGS, heart failure, central nervous system emboli and intracardiac abscess were associated with in-hospital and one-year mortality (Table 2). Cephalosporin monotherapy was associated to one-year mortality (aOR 2.96; 95% CI 1.12-7.83; P = .028) but not associated to in-hospital mortality (aOR 1.01; 95% CI 0.26-3.96; P = .982). No differences in mortality were found when comparing cases of PEN-I VGS-GGS with MIC = 0.25 with those isolates with MIC 0.5-2 (Supplementary table 7).

DISCUSSION

In our study PEN-I VGS-GGS isolates accounted for 25 % of the total and were predominantly caused by viridans group streptococci [mainly by *mitis*, *oralis*, and *sanguis* species (data not reported)]. Endocarditis caused by PEN-I VGS-GGS had a lower rate of intra cardiac abscess, was treated with cardiac surgery less frequently and showed similar in-hospital mortality and relapse rate with respect to cases caused by susceptible strains. A third-generation cephalosporin was the antibiotic drug of choice, either alone (31.9 %) or with an aminoglycoside (29.6 %). Of note, cephalosporin monotherapy was not associated with in-hospital mortality in the multivariable analysis in the subgroup of PEN-I VGS-GGS endocarditis.

In a series of cases of VGS endocarditis, Kohl et al. found a low (<10%) percentage of resistance to penicillin, with most of the cases showing MIC between 0.5 and 1.0 µg/mL [8]. However, the rate of non-susceptible VGS-GGS isolates is significantly high [10,18], and so attention should be paid to these cases. The impact of susceptibility to penicillin on outcomes in endocarditis is not well defined: while some retrospective studies have linked amoxicillin MIC with mortality [10], others have not found this relationship [19,20]. In our cohort we found a lower rate of intra cardiac abscess and performance of surgery in PEN-I VGS-GGS endocarditis, but in-hospital mortality and relapse were comparable with PEN-S VGS-GGS

endocarditis. Previous cohorts of endocarditis caused by penicillin non-susceptible VGS-GGS have not found lower rates of intracardiac valve abscess [8] or performance of surgery [21]. It might be hypothesized that acquisition of antibiotic resistance could be associated with a virulence cost for streptococcal species. However, the exact association between antibiotic susceptibility and abscess formation (and thus the indication and performance of surgery) can only be identified by a specific analysis.

Susceptibility to penicillin is one of the main variables determining the choice of treatment strategies for IE caused by VGS-GGS [7,15]. While high-dose beta-lactams are the mainstay [22], aminoglycosides are recommended when PEN-I is detected [7,15] based on *in vitro* and *in vivo* studies that have demonstrated synergism between aminoglycosides and beta-lactams [23–25]. C-BA and beta-lactam monotherapy in cases of VGS-GGS IE with intermediate susceptibility to penicillin have not been compared in clinical trials [26]. In our study, patients with PEN-I VGS-GGS endocarditis received a third-generation cephalosporin alone in 32 % and different combinations with aminoglycosides in nearly two thirds of cases.

Aminoglycosides are frequently associated with the development of nephrotoxicity. Post-operative acute kidney injury has been associated with the use of aminoglycosides, among other nephrotoxic agents [27]. Interestingly, acute kidney injury was significantly associated with in-hospital and one-year mortality in our study, a complication that was numerically more frequently observed (without statistical significance) in patients treated with C-BA.

In our analysis cephalosporin monotherapy was not associated with higher in-hospital mortality or relapse in PEN-I VGS-GGS endocarditis. This suggests that cephalosporin may represent a valid antibiotic strategy for these patients. In the general cohort, however, monotherapy was apparently associated with higher mortality. We believe that the bias of indication for the use of monotherapy or C-BA cannot be totally corrected by propensity score matching. Patients receiving monotherapy were older, a circumstance that may have led clinicians to avoid the use of aminoglycosides. In addition, patients receiving C-BA had higher chances of receiving surgery when this was formally indicated, compared to patients receiving monotherapy.

Our study has certain limitations that should be acknowledged. The first is its retrospective nature, with the drawbacks inherent in this design. We sought to correct the indication bias by using a propensity score approach in order to homogenize groups of comparison and adjust for potential confounding factors. American and European

recommendations on MIC breakpoints for defining intermediate susceptibility in VGS-GGS endocarditis are different, and our results may not be generalizable to centres not using microdilution techniques recommended by EUCAST.. Finally, relapse may be a more relevant outcome when analysing the treatment of streptococcal endocarditis, but due to the low number of events this end-point could not be suitable. We consider that our analysis of a large, contemporary cohort and the statistical considerations applied strengthens our results, which support those of other authors who have called for the expansion of aminoglycoside-free regimens [20].

Our study analyses the largest cohort of definite cases of endocarditis caused by PEN-I VGS-GGS strains and provides insights into the management and outcomes of these patients. Our results show that in patients with PEN-I VGS-GGS endocarditis, third-generation cephalosporin monotherapy is associated with outcomes similar to those obtained with C-BA, such as mortality or relapse rate. These findings should be borne in mind when treating patients with PEN-I VGS-GGS endocarditis in order to avoid drugs with renal toxicity, and should be considered in the future international guideline recommendations.

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Conflict of interest

None to declare

ETHICS APPROVAL

This observational study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Comité Ético de Investigación Clínica of each participating hospital. To protect personal privacy, identifying information in the electronic database was anonymized for each patient. The need for informed consent was waived by the ethics committee because no intervention was involved and no patient-identifying information was included.

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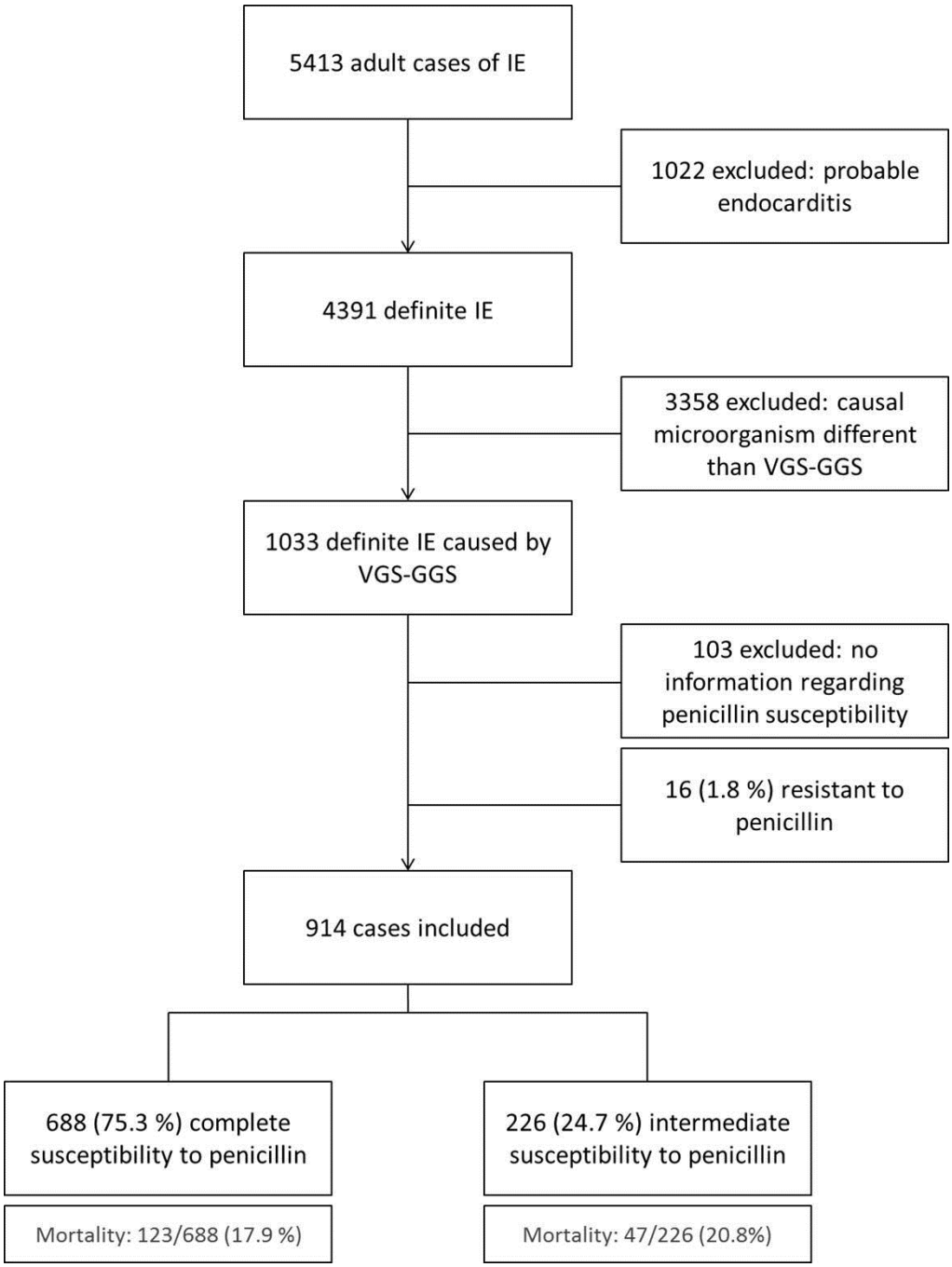
525 **FIGURES**

526 **Figure 1.** Flowchart of included and excluded cases of infective endocarditis, and susceptibility
527 profile of the patients included.



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532 **TABLES**

533 **Table 1**. Comparison of demographics, clinical characteristics, treatment and outcomes of
534 endocarditis caused by VGS-GGS susceptible to penicillin vs. VGS-GGS with intermediate
535 susceptibility to penicillin.

	Total (N = 914)	**PEN-S (N = 688)**	**PEN-I (N = 226)**	**P**
Median age, y (IQR)	68 (54 - 77)	68 (54 – 77)	68 (56 – 77)	.527
Male gender, No. (%)	637 (69.7)	487 (70.7)	150 (66.3)	.210
Chronic kidney disease (%)	140 (15.3)	104 (15.1)	36 (15.9)	.768
Age-adjusted Charlson index, No. (IQR)	4 (2 – 6)	4 (2 – 6)	4 (2 – 6)	.501
Affected valve. No. (%)				
Native	700 (76.6)	519 (75.4)	181 (80.1)	.152
Prosthetic	205 (22.4)	157 (22.8)	48 (21.2)	.621
Aortic	525 (57.4)	399 (58.0)	126 (55.8)	.554
Mitral	439 (48.0)	324 (47.1)	115 (50.9)	.322
Tricuspid	32 (3.5)	28 (4.1)	4 (1.8)	.103
Pulmonary	16 (1.8)	11 (1.6)	5 (2.2)	.561
Intracardiac device	17 (1.9)	16 (2.3)	1 (0.4)	.088
Microorganism, No. (%)				
viridans group streptococci	617 (67.5)	443 (64.4)	174 (77.0)	**<0.01**
gallolyticus group streptococci	297 (32.5)	245 (35.6)	52 (23.0)	**<0.01**
Ceftriaxone MIC ≤ 0.5 mg/L ***	221 (24.1)	168 (24.4)	53 (23.4)	.768
Ceftriaxone MIC > 0.5 mg/L ***	14 (1.5)	10 (1.4)	4 (1.7)	.737
Acquisition, No. (%)				
Community-acquired	841 (92.0)	630 (91.6)	211 (93.4)	.388
Healthcare-associated	41 (4.5)	32 (4.7)	9 (4.0)	.673
Nosocomial	32 (3.5)	26 (3.8)	6 (2.7)	.534
Intracardiac complications, No. (%)	288 (31.5)	225 (32.7)	63 (27.9)	.175

Valve perforation	148 (16.2)	109 (15.8)	39 (17.3)	.617
Abscess	122 (13.3)	103 (15.0)	19 (8.4)	**.012**
Pseudoaneurysm	45 (4.9)	32 (4.7)	13 (5.8)	.507
Fistulae	16 (1.8)	14 (2.0)	2 (0.9)	.382
Complications, No. (%)				
Persistent bacteraemia	39 (4.3)	33 (4.8)	6 (2.7)	.189
Embolic phenomena	204 (22.3)	158 (23.0)	46 (20.4)	.413
Central nervous system emboli	158 (17.3)	121 (17.6)	37 (16.4)	.675
Acute kidney injury	190 (20.9)	145 (21.0)	45 (19.9)	.708
Surgery, No. (%)				
Surgery indicated	536 (58.6)	421 (61.2)	115 (50.9)	**.006**
Surgery performed	389 (42.6)	308 (44.8)	81 (35.8)	**.019**
Prognosis, No. (%)				
In-hospital mortality	109 (11.9)	82 (11.9)	27 (11.9)	1
One-year mortality	170 (18.6)	123 (17.9)	47 (20.8)	.328
One-year relapse *	12 (1.5)	9 (1.4)	2 (1.0)	.613
Treatment, No. (%)				
Monotherapy	415 (45.4)	325 (47.2)	90 (39.8)	.052
Penicillin	48 (5.3)	33 (4.8)	15 (6.6)	.282
Cephalosporin	331 (36.2)	259 (37.9)	72 (31.9)	.116
Beta-lactam **	36 (4.4)	33 (4.8)	3 (1.3)	**.020**
C-BA	499 (54.6)	363 (52.7)	136 (60.1)	.052
Penicillin + aminoglycoside	149 (16.3)	101 (14.7)	48 (21.2)	**.021**
Cephalosporin + aminoglycoside	256 (28.0)	189 (27.5)	67 (29.6)	.528
Beta-lactam ** plus aminoglycoside	94 (10.3)	73 (10.6)	21 (9.3)	.571
Treatment duration in days, median (IQR)	31 (28 - 42)	32 (28 – 42)	30 (28 – 42)	.147
Hospital stay in days, median (IQR)	31 (20 - 44)	31 (20 – 44)	30 (19 – 44)	.279

* Only evaluated in patients alive after hospital discharge (606 in the susceptible to penicillin group and 199 in intermediate susceptibility to penicillin).

** Use of penicillin and/or cephalosporin, either concomitantly or sequentially. *** Data available in 235 cases (178 PEN-S and 57 PEN-I). C-BA: combination therapy with aminoglycoside; IQR: interquartile range; PEN-S: susceptible to penicillin; PEN-I: intermediate susceptibility to penicillin.

Table 2. Univariate and multivariable analysis of factors associated with in-hospital and one-year mortality in the subgroup of patients with PEN-I VGS-GGS (226 cases) not adjusted by propensity score matching.

	In-hospital mortality					One-year mortality				
	Survived (N = 199)	**Deceased (N = 27)**	***P***	**aOR (95% CI)**	***P***	**Survived (N = 179)**	**Deceased (N = 47)**	***P***	**aOR (95% CI)**	***P***
Median age, y (IQR)	68 (55 – 77)	70 (62 – 79)	.284			67 (54 – 76)	74 (64 – 82)	**.002**	1.04 (1.00 – 1.10)	.044
Male gender. No. (%)	134 (67.3)	16 (59.2)	.404			121 (67.6)	29 (61.7)	.446		
Chronic kidney disease (%)	31 (15.6)	5 (18.5)	.695			24 (13.4)	12 (25.5)	.070		
Age-adjusted Charlson index. No. (IQR)	4 (2 – 6)	5 (3 – 6)	.091			4 (2 – 5)	6 (4 – 7)	**<0.01**	1.09 (0.84 – 1.40)	.505
Affected valve. No. (%)										
Native	160 (80.4)	21 (77.8)	.749			144 (80.4)	37 (78.7)	.792		
Prosthetic	39 (19.6)	9 (33.3)	.102			35 (19.6)	13 (27.7)	.227		
Aortic	108 (54.3)	18 (66.7)	.224			98 (54.7)	28 (59.6)	.553		
Mitral	103 (51.8)	12 (44.4)	.476			92 (51.4)	23 (48.9)	.764		
Tricuspid	4 (2.0)	0	-			4 (2.2)	0	-		
Pulmonary	5 (2.5)	0	-			5 (2.8)	0	-		
Intracardiac device	1 (0.5)	0	-			1 (0.6)	0	-		
Microorganism. No. (%)										
viridans group streptococci	151 (75.9)	23 (85.2)	.281			136 (76.0)	38 (80.9)	.480		
gallolyticus group streptococci	48 (24.1)	4 (14.8)				43 (24.0)	9 (19.1)			

Penicillin susceptibility										
MIC = 0.25	42 (21.1)	9 (33.3)	.154			36 (20.1)	15 (31.9)	.085		
0.5 ≥ MIC ≤ 2	122 (61.3)	12 (44.4)				111 (62.0)	23 (48.9)			
Acquisition. No. (%)										
Community-acquired	187 (94.0)	24 (88.9)	.320			171 (95.5)	40 (85.1)	**.011**	0.56 (0.06 – 5.10)	.611
Healthcare-associated	4 (2.0)	2 (7.4)	.153			4 (2.2)	2 (4.3)	.607		
Nosocomial	8 (4.0)	1 (3.7)	.937			4 (2.2)	5 (10.6)	**.021**		
Intra cardiac complications. No. (%)										
Valve perforation	37 (18.6)	2 (7.4)	.183			34 (19.0)	5 (10.6)	.177		
Abscess	11 (5.5)	8 (29.6)	**<0.01**	13.47 (2.24 – 81.08)	.004	11 (6.1)	8 (17.0)	**.017**	4.11 (0.87 – 19.33)	.073
Pseudoaneurysm	11 (5.5)	2 (7.4)	.658			11 (6.1)	2 (4.3)	.620		
Fistulae	0	2 (7.4)	-			0	2 (4.3)	-		
Complications. No. (%)										
Heart failure	45 (22.6)	14 (51.8)	**.001**	6.06 (1.37 – 26.87)	.018	38 (21.2)	21 (44.6)	**.002**	3.34 (1.19 – 9.36)	.021
Persistent bacteraemia	5 (2.5)	1 (3.7)	.538			5 (2.8)	1 (2.1)	.801		
Embolic phenomena	39 (19.6)	7 (25.9)	.443			35 (19.6)	11 (23.4)	.559		
Central nervous system emboli	27 (13.6)	10 (37.0)	**.002**	9.83 (2.17 – 44.49)	.003	23 (12.8)	14 (29.8)	**.005**	4.17 (1.15 – 15.11)	.030
Acute kidney injury	34 (17.1)	11 (40.7)	**.004**	1.77 (0.43 – 7.14)	.422	30 (16.8)	15 (31.9)	**.021**	1.25 (0.39 – 3.97)	.699

Surgery. No. (%)										
Surgery indicated	94 (47.2)	21 (77.8)	**.003**	1.38 (0.27 – 7.05)	.696	86 (48.0)	29 (61.7)	0.96		
Surgery performed	70 (35.2)	11 (40.7)	.572			67 (37.4)	14 (29.8)	.331		
Treatment. No. (%)										
Monotherapy*	74 (37.2)	16 (59.3)	**.028**	1.01 (0.26-3.96)	.982	63 (35.2)	27 (57.4)	**.006**	2.96 (1.12 – 7.83)	.028
C-BA	125 (62.8)	11 (40.7)				116 (64.8)	20 (42.6)			
Treatment duration in days. median (IQR)	30 (28 – 42)	19 (9 – 28)	**<0.01**	0.95 (0.92 – 0.99)	.036	30 (28 – 42)	28 (13 – 33)	**<0.01**	0.95 (0.92 – 0.98)	.008

546 * 80 % of patients with PEN-I VGS-GGS endocarditis received ceftriaxone.

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