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# "A contemporary description of staphylococcus aureus prosthetic valve endocarditis. Differences according to the time elapsed from surgery"

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**Abstract**

*Staphylococcus aureus* prosthetic valve endocarditis (SAPVE) has a poor prognosis. There are no large series that accurately describe this entity.

This is a retrospective observational study on a prospective cohort from 3 Spanish reference hospitals for cardiac surgery, including 78 definitive episodes of left SAPVE between 1996 and 2016.

Fifty percent had a Charlson Index score >5; 53% were health care-related. Twenty percent did not present fever. Complications at diagnosis included: severe heart failure (HF, 29%), septic shock (SS, 17.9%), central nervous system abnormalities (19%), septic metastasis (4%). Hemorrhagic stroke was not higher in anticoagulated patients. Twenty-seven percent were methicilin-resistant SA (MRSA). Fifteen of 31 had positive valve culture; it was related to surgery within first 24 hours. At diagnosis, 69% had vegetation (>10 mm in 75%), 21.8% perianular extension, and 20% prosthetic dehiscence. Forty-eight percent had persistent bacteremia, related to nonsurgical treatment. Perianular extension progressed in 18%. Surgery was performed in 35 episodes (12 with stroke). Eleven uncomplicated episodes were managed with medical therapy, 8 survived. In-hospital mortality was 55%, higher in episodes with hemorrhagic stroke (77.8% vs 52.2%, odds ratio 3.2 [0.62–16.55]). Early SAPVE was nosocomial (92%), presented as severe HF (54%), patients were diagnosed and operated on early, 38% died. In intermediate SAPVE (9 weeks–1 year) diagnosis was delayed (24%), patients presented with constitutional syndrome (18%), renal failure (41%), and underwent surgery >72 hours after indication; 53% died. Late SAPVE (>1 year) was related with health care, diagnosis delay, and 60% of deceases.

Left *SAPVE* frequently affected patients with comorbidity and health care contact. Complications at diagnosis and absence of fever were frequent. Presence of MRSA was high. Positive valve culture was related to early surgery. Paravalvular extension was frequent; vegetations were large, but its absence at diagnosis was common. Some uncomplicated SAPVE episodes were safety treated with medical therapy. Surgery was feasible in patients with stroke. Mortality was high. There were differences in some clinical characteristics and in evolution according to the time elapsed from valve replacement. Prognosis was better in early SAPVE.

**Abbreviations:** AV = auriculoventricular, CHI = Charlson index, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, ESAPVE = early *Staphylococcus aureus* prosthetic valve endocarditis, HF = heart failure, HIV = human immunodeficiency virus, ICE = International collaboration on endocarditis, IDSA = infectious diseases Society of America, IE = infectious endocarditis, IQR = interquartile range, ISAPVE = intermediate *Staphylococcus aureus* prosthetic valve endocaditis, LSAPVE = late *Staphylococcus aureus* prosthetic valve endocarditis, MIC = minimum inhibitory concentration, MRSA = methicilin-resistant *Staphylococcus aureus* , MSSA = metilin-sensitive *Staphylococcus aureus*, NYHA = New York Heart Association, OR = odds ratio, SAPVE = *Staphylococcus aureus* prosthetic valve endocarditis, SS = septic shock, TEE = transesophageal echocardiogram, TTE = transthoracic echocardiogram.

**Keywords:** diagnostic period, infective endocarditis, prosthetic valve, Staphylococcus aureus

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## 1. Introduction

*Staphylococcus aureus* prosthetic valve endocarditis (*SA*PVE) is intimately linked to health care, and so an increase in its incidence in the next years is expected.[1,2] In addition, its importance relies on the poor prognosis to which it is associated, reaching a mortality rate of 50% in the most recent series.[1,3,4] There are few broad and specific series of SAPVE[3–5]; most of the evidence comes from series addressed jointly to native and prosthetic valve endocarditis, or to PVE irrespectively of its etiology. Traditional classification of PVE in 2 periods (early and late) is based essentially on the different microbiological profile of each period.[1,4,6–10] Other investigations attempted to redefine these periods according to clinical aspects, suggesting that a more precise knowledge of signs and symptoms in each period would help to shorten diagnosis time and improve prognosis. They defined intermediate PVE as an infection acquired in the postoperative period, whose diagnosis is delayed because of less striking manifestations than the earlier forms, requiring surgery more often and implicating greater mortality. Whether this classification fits *SA*PVE or not is unknown. There are also many questions about its most appropriate management after admission concerning medical,[3,11–23] surgical treatment,[3,4,5,24–28] anticoagulation in hemorrhagic stroke,[29,30] and prognostic factors,[31] among others. The need for contemporary and comprehensive descriptions of these diseases is therefore necessary.

Our aim was to describe epidemiological, clinical, echocardiographic, and therapeutic features of *SA*PVE and differences according to the time elapsed since valve replacement.

## 2. Patients and methods

### 2.1. Design

This is an observational, retrospective, cohort study performed in 3 Spanish reference hospitals for cardiac surgery. All episodes of definitive left *SA*PVE according to Duke's classification[32] treated between 1996 and 2016 were included. Variables defined before the beginning of the data collection were prospectively recorded. Seventy-eight episodes of left *SA*PVE in 78 patients were identified (Fig. 1).

### 2.2. Definitions

Diagnostic period: This is the time from prosthesis implantation to *SA* PVE diagnosis. *SA*PVE was classified in early *Staphylococcus aureus* prosthetic valve endocarditis (*ES*APVE), diagnosed in the first 8 weeks; I*SA*PVE, between 9 weeks and 1 year; L*SA*PVE, after 1 year. Nosocomial and health care associated-infection are defined in previous descriptions.[33] Delayed diagnosis: *SA*PVE confirmed >15 days after the first clinical manifestation. Form of presentation: syndrome composed of the first signs and/or symptoms presented by the patient in the first medical consultation. Forms of presentation have been described in previous reports.[34] Valvular vegetation: as described previously.[35] The maximum diameter of the largest vegetation was considered the size. Perianular extension: includes abscess, pseudoaneurysm, and fistula.[35] Persistent bacteremia: presence of positive blood cultures 48 to 72 hours after starting a correct antibiotic treatment and/or presence of a positive blood culture after having at least 1 negative. Urgent surgery: intervention performed within 72 hours after its indication, for one of the following reasons: heart failure (HF); uncontrolled infection (fever and/or persistently positive blood cultures after 1 week of correct antibiotic treatment once any metastatic foci has been controlled; emergence of new septic shock (SS) or persistence after initiation of antibiotic treatment; presence of locally uncontrolled infection [abscess, pseudoaneurysm, fistula, or growth of vegetation]); prevention of embolism.[35] Elective surgery: scheduled surgical intervention in the presence of active endocarditis, without indication of urgent surgery.

### 2.3. Procedures

Microbiologic procedures were extraction of at least 3 blood cultures at the time of clinical suspicion of infectious endocarditis (IE).

Other samples such as valvular tissue, septic metastases, and prosthetic material were sent for culture and histologic examination.

For follow-up, patients were evaluated in the outpatient clinic at 1, 3, and 6 months after discharge, and subsequently once a year. Most patients were followed for at least 1 year (97.43%).

### 2.4. Statistical analysis and ethical review

In the descriptive analysis, proportions for each variable were calculated. A $\chi^2$ analysis was performed to compare the categorical variables using the Bonferroni correction for multiple comparisons. Student $t$ test or the median test was used to compare continuous quantitative variables. Odds ratio (OR) was calculated with 95% confidence intervals (95% CI) for the evolution variables. We considered a $P$ value $<.05$ to indicate a significant difference. Statistical analysis was performed with the windows SPSS 20.0 program.

The investigation did not require approval from the hospital ethics board. Patient consent was given to use data for research. Informed consent was approved from the Hospital Clinico de Valladolid ethical board.

## 3. Results

### 3.1. Epidemiological, clinical, and microbiological features

Distribution of cases per month during the first 2 years is shown in Figure 2.

Table 1 summarizes epidemiological characteristics. The most frequent location was the mitral valve. Endocarditis settled mainly on metallic prostheses (74.4%).

The proportion of nosocomial cases was significantly higher in ESAPVE and the presence of an underlying disease was less frequent in this period (nonsignificant). The risk factor was not identified in a significantly higher percentage of episodes of ISAPVE than of ESAPVE.

Clinical and microbiological features are shown in Table 2. Seventeen (21.8%) presented systemic embolism at diagnosis; 5 of them were outside the central nervous system (CNS, 6.4%). Complications at the CNS appeared at diagnosis in 15 episodes (19.2%): 8 cerebral hemorrhages (57.1%), one of them with an abscess; 6 ischemic strokes (40.2%); and 1 meningitis (6.6%). The presence of vegetation did not increase the risk of stroke (OR 0.943, 95% CI 0.281–3.158, $P>.99$). The percentage of anticoagulated patients among those with a hemorrhagic stroke was not significantly higher than in non anticoagulated patients (OR 1.122, 95% CI 0.119–10.590, $P>.99$). Anticoagulant

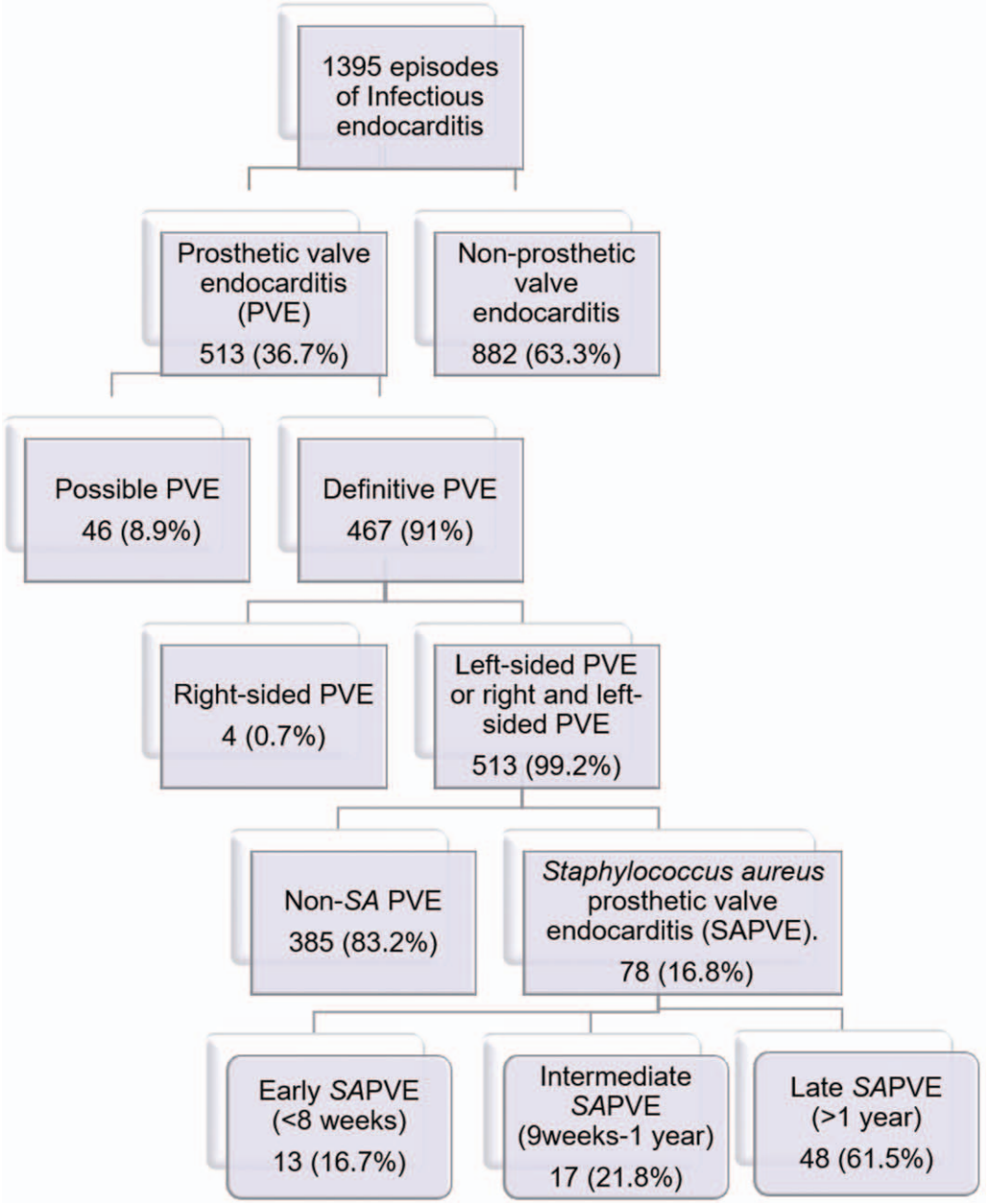


**Figure 1.** Selection of cases. Seventy-eight definitive episodes of left *Staphylococcus aureus* prosthetic valve endocarditis were recorded.

therapy was switched to low–molecular-weight heparin following diagnosis in all patients, and it was interrupted in the presence of hemorraghic stroke. Diagnosis delay was related to presentation without fever (OR 3.96, 95% CI, 1.197–13.143, $P=.01$) and with previous antibiotic treatment (OR 4.479, 95% CI 1.399–14.339, $P=.008$), but it was nonsignificantly related to presentation as fever plus constitutional syndrome (50% vs 20.5%, OR 3.867, 95% CI 0.503–29.75) and with SS at diagnosis (7.1% vs 25.4%, OR 0.226, 95% CI 0.027–1.867, $P=.21$).

Presentation as fever plus constitutional syndrome was significantly more frequent in ISAPVE. The presence of fever before diagnosis was less common in ESAPVE and HF was more usual. The occurrence of new renal failure was more frequent in ISAPVE. Diagnosis delay was inferior in ESAPVE; a delay >2 months was superior in ISAPVE.

Seven patients had negative blood cultures at diagnosis, *Staphylococcus aureus* (SA) grew from the valvular culture (3), the valvular culture and the sternal exudate (1), blood cultures 48 hours after diagnosis (1), urine culture and pleural effusion (1), and urine culture (1). Negative blood cultures were not related to previous antibiotic treatment (2/26 [7.71%] vs 4/49 [8.2%], $P=1$). The affected valve was cultured in 39.74% of cases, that is, 31 patients (29 operated and 2 deceased); the result was positive in 15 (49%).

Positive valvular culture was associated to: intervention within the first 24 hours (OR 5.6, 95% CI 0.54–57.94, $P=.16$), antibiotic treatment in the preceding 15 days (OR 0.167, 95%

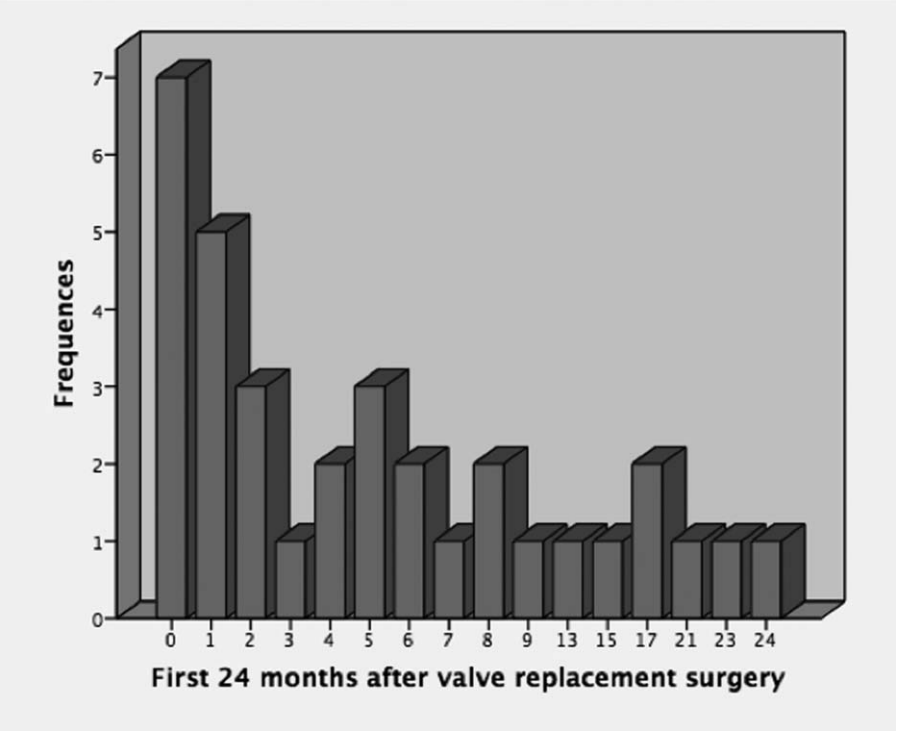


**Figure 2.** Distribution of episodes of *Staphylococcus aureus* prosthetic valve endocarditis (SAPVE) per month during the first 2 years following valve replacement. SAPVE was more frequent within the first 6 months after surgery.

CI 0.028–0.997, $P = .03$). The mean time in days from diagnosis to surgery was lower in the episodes with positive valvular culture ($4.36 \pm 11.39$ vs $11.27 \pm 8.53$; mean difference $-6.9$ [$-14.54$ to 0.72]; $P = .07$).

Positive blood cultures at diagnosis were significantly more frequent in LSAPVE than in ESAPVE. The presence of methicilin-resistant SA (MRSA) was more frequent in ESAPVE than in LSAPVE.

### 3.2. Echocardiographic and radiological features

Sixty-six episodes (84.6%) had echocardiographic findings at diagnosis. Fifty-four (69%) had vegetation. Twenty-four patients without vegetations showed: new moderate-severe insufficiency (2), valvular dehiscence (5), perianular extension (5). Median of vegetation size was 13 mm without significant differences by periods (Table 2).

Twelve patients did not have echocardiographic manifestations of infective endocarditis at diagnosis. Ten of them showed a vegetation or perivalvular extension in the evolution, all of them fit criteria of possible endocarditis with a major criterion and 2 minor criteria (fever and intracardiac device) at diagnosis. The remaining 2 patients without echocardiograhic findings fit criteria of definitive endocarditis: one of them had 1 major criterion and 3 minor criteria (fever, intracardiac device, and embolic phenomena) and the other one had 1 major criterion, 2 minor criteria (fever and intracardiac device), and he presented septic and cardiogenic shock and necropsia was diagnostic.

In 30 episodes, a cerebral computed tomography scan was performed (43.5%); it was pathological in 17 episodes. In 6 patients, brain magnetic resonance image was performed (8.7%), showing abnormalities in 4 of them. Arteriography was performed in 3 patients without findings.

### 3.3. Medical treatment

Thirty-three patients (42.3%) were treated following guideline recommendations with cloxacilin or vancomycin plus aminoglycoside and rifampin. Rifampin was used in 55 episodes (70.5%) and gentamicin in 61 (78.2%). Thirty episodes of MSSA (57.7%) were treated with alternative combinations: betalactams with daptomycin (9) (2 also with rifampin, 4 with rifampin and gentamicin, 1 with gentamicin alone); vancomycin with rifampin and gentamicin (6); betalactam with vancomycin (5) (3 with gentamicin, 1 with gentamicin and rifampin).

In 8 episodes of MRSA (42.1%), an alternative combination was used: daptomycin and rifampin (2, one also with amikacin), teicoplanin and rifampin (3), other combinations (3). Data on medical treatment are summarized in Table 3. Dose of daptomycin was 10 mg/kg/day in 13 episodes, 6 mg/kg/day in 1 episode and 8 mg/kg/day in 1 episode.

### 3.4. Clinical and echocardiographic evolution before surgery

Comparison on clinical and echocardiographic evolution before surgery, surgical treatment, and mortality among diagnostic periods is summarized in Table 4. Twenty-one in 44 episodes had persistent bacteremia (47.7%). It was more frequent among nonoperated patients (63.6% vs 31.8%, $P = .03$). Persistent bacteremia appeared in 10 in 16 patients treated with regimens based in vancomycin and in 10 in 26 patients treated with

**Table 1**

**Epidemiological characteristics in the whole sample and per diagnostic periods of 78 episodes of SAPVE.**

| | | ESAPVE | ISAPVE | LSAPVE | |
|---|---|---|---|---|---|
| | | N = 13 | N = 17 | N = 48 | |
| | TOTAL | A | B | C | *P* |
| Median age (IQR) | 66 (58.7–77) | 65 (59–76) | 64 (49.5–74.5) | 67.5 (59.7–77) | .38 |
| Median Charlson index score (IQR) | 5 (2–6) | 4.5 (3–5.2) | 5 (2–7) | 5 (2–6) | .82 |
| Male n (%) | 41 (56) | 6 (46.2) | 11 (64.7) | 24 (59) | .51 |
| Nosocomial | 32 (41) | 12 (92.3) BC | 8 (47.1) | 12 (25) | |
| Health care-related | 9 (11.5) | 1 (7.7) | 1 (5.9) | 7 (14.6) | **<.001** |
| Previous endocarditis | 13 (16.7) | 1 (7.7) | 5 (29.4) | 7 (14.6) | .23 |
| Underlying disease | 41 (52.6) | 3 (23.1) | 10 (58.8) | 28 (58.3) | .06* |
| Diabetes mellitus | 20 (25.6) | 1 (7.7) | 6 (35.3) | 13 (27.1) | .21 |
| Kidney disease | 17 (21.8) | 0 | 4 (23.5) | 13 (27.1) | .1 |
| Chronic anemia | 14 (17.9) | 0 | 3 (17.6) | 11 (22.9) | .16 |
| COPD | 5 (6.4) | 2 (15.4) | 1 (5.9) | 2 (4.2) | .34 |
| Cancer | 4 (5.1) | 0 | 1 (5.9) | 4 (5.1) | .65 |
| Immunosuppression | 4 (5.1) | 0 | 1 (5.9) | 3 (6.3) | .65 |
| Skin disease | 3 (3.8) | 0 | 1 (5.9) | 2 (4.2) | .69 |
| Alcoholism | 2 (2.6) | 0 | 0 | 2 (4.2) | .52 |
| Anticoagulant therapy | 60/71 (84.5) | 8/9 (88.9) | 11/15 (73.3) | 41/47 (87.2) | .4 |
| Previous antibiotic therapy | 26 (34.2) | 2 (15.4) | 9 (52.9) | 15 (32.6) | .09* |
| Risk factor | | | | | |
| Catheter | 15 (19.2) | 4 (30.8) | 2 (11.8) | 9 (18.8) | .42 |
| Local infection | 9 (11.5) | 2 (15.4) | 1 (5.9) | 6 (12.5) | .68 |
| Unidentified | 34 (43.6) | 0 | 10 (58.8) | 24 (50) | **.002** |
| Metal prosthesis | 58 (74.4) | 8 (61.5) | 11 (64.7) | 39 (81.2) | |
| Biological prosthesis | 18 (23.1) | 4 (30.8) | 6 (35.3) | 8 (16.7) | .29 |
| Metal + biological | 2 (2.6) | 1 (7.7) | 0 | 1 (2.1) | |
| Aortic | | | | | |
| Metal | 23 (29.5) | 3 (23.1) | 4 (23.5) | 16 (33.3) | .64 |
| Biological | 16 (20.5) | 3 (23.1) | 4 (23.5) | 9 (18.8) | .88 |
| Mitral | | | | | |
| Metal | 41 (52.6) | 6 (46.2) | 8 (47.1) | 27 (56.2) | .71 |
| Biological | 5 (6.4) | 2 (15.4) | 2 (11.8) | 1 (2.1) | .13 |
| Endocarditis in ≥2 locations | 16 (20.5) | 3 (23.1) | 4 (23.5) | 9 (18.8) | .88 |

Comparison of ESAPVE (A) with ISAPVE (B), ISAPVE (B) with LSAPVE (C) and ESAPVE (A) with LSAPVE (C) applying Bonferroni correction for multiple comparisons. For each significant pair the category key with the lowest column ratio appears below the category with the highest column proportion. The overall *P* of the comparison is presented.

Significant values (*P* values <.05) should appear in bold.

COPD = chronic obstructive pulmonary disease, ESAPVE = early *Staphylococcus aureus* prosthetic valve endocarditis, IQR = interquartile range, ISAPVE = Intermediate *Staphylococcus aureus* prosthetic valve endocarditis, LSAPVE = Late *Staphylococcus aureus* prosthetic valve endocarditis.

* $P > .05 < .12$.

combinations containing beta-lactams or daptomycin (62.5% vs 38.46%, $P = .314$).

Clinical complications during evolution included: renal failure (28, 35.9%), new febril episode (23, 29.5%), SS (19, 24.4%), new atrioventricular block (8, 10.3%) and a new embolic event (13, 16.6%). Location of embolism was exclusively CNS in 8 cases (10.25%), 5 of them (22.7%) had recurrent episodes; 5 presented embolisms in several territories. Only 1 mycotic aneurysm was found, not associated with symptomatology; 18 of 22 of embolic events (81.8%) occurred in the first 2 weeks of treatment.

There were no significant differences in the frequency of persistent bacteremia among periods. Complications in the evolution were numerically less frequent in LSAPVE; conduction disturbance was uncommon in this period.

A new vegetation appeared in 11 of the 24 episodes that did not present it at diagnosis (14.1%); 10 (12.8%) developed a new moderate-severe valvular insufficiency. Perianular extension progressed in 14 (17.9%).

Vegetation growth was less frequent in ISAPVE. The appearance of new vegetation, new perianular extension, or new moderate-severe valvular insufficiency was more frequent in ESAPVE than in the ISAPVE, and less frequent in ISAPVE than in LSAPVE.

### 3.5. Surgical treatment and mortality

Distribution of patients according to surgical treatment and mortality is represented in Figure 3. Thirty-five patients were operated on (44.9%). Eleven patients without urgent surgery indication were managed with medical treatment exclusively. In comparison to the remaining patients (patients that were operated on and patients managed with medical treatment but with indication of urgent surgery) this 11 patients had a similar median age, percentage of Charlson Index score >5 was 71.4% versus 44.8% ($P = .06$), constitutional syndrome at presentation appeared in 27.3% versus 1.5% ($P < .001$), 45.5% versus 18.2% had diagnosis delay ($P = .05$), at diagnosis none had systemic embolism or metastatic infection. Other characteristics included: SS (1), perianular extension (1), severe valvular insufficiency (2), persistent bacteremia (3, all of them died). Risk of SS[36] was lower (median 12.1 vs 21.16, $P = .09$); 57.1% presented only 1 predictor of SS (*SA* etiology) at diagnosis versus 29.1% in the remaining. Mortality rates

**Table 2**

**Clinical, microbiological, and echocardiographic manifestations in 78 episodes of SAPVE in the whole sample and per diagnostic periods.**

| | | ESAPVE | ISAPVE | LSAPVE | |
|---|---|---|---|---|---|
| | | N = 13 | N = 17 | N = 48 | |
| N (%) | Total | A | B | C | *P* |
| Presentation forms | | | | | |
| No fever | 16 (20.5) | 3 (23.1) | 2 (11.8) | 11 (22.9) | .60 |
| Only fever | 28 (35.9) | 2 (15.4) | 6 (35.3) | 20 (41.7) | .21 |
| Fever + cardiac form | 19 (24.4) | 1 (7.7) | 3 (17.6) | 13 (27.1) | .73 |
| Fever + neurological form | 12 (15.4) | 2 (15.4) | 3 (17.6) | 7 (14.6) | .95 |
| Fever + cutaneous form | 7 (9) | 1 (7.7) | 2 (11.8) | 4 (8.3) | .89 |
| Fever + constitutional syndrome | 4 (5.1) | 1 (7.7) | 3 (17.6) AC | 0 | **.01** |
| Fever + rheumatism | 3 (3.8) | 1 (7.7) | 0 | 2 (4.2) | .54 |
| Signs and symptoms at diagnosis | | | | | |
| Previous fever | 49 (66.2) | 4 (30.8) BC | 11 (78.6) | 34 (72.3) | **.01** |
| Dispnea | 30 (39) | 6 (46.2) | 7 (41.2) | 17 (36.2) | .79 |
| New murmur | 13 (16.7) | 2 (15.4) | 2 (11.8) | 8 (17) | .87 |
| NYHAIII-IV | 23 (29.48) | 7 (53.84) | 3 (17.64) | 13 (27.08) | .09* |
| Thoracic pain | 6 (6.7) | 1 (7.7) | 3 (17.6) | 2 (4.2) | .2 |
| Cough | 12 (15.4) | 1 (7.7) | 5 (29.4) | 6 (12.5) | .17 |
| Abdominal pain | 6 (6.7) | 1 (7.7) | 1 (5.9) | 4 (8.3) | .94 |
| Sepsis shock | 14 (17.9) | 3 (23.1) | 4 (23.5) | 7 (14.6) | .61 |
| Esplenomegaly | 2 (2.6) | 0 | 0 | 2 (4.2) | .52 |
| New kidney failure | 18 (23.1) | 1 (7.7) | 7 (41.2) | 10 (20.8) | .08* |
| | 3 (3.8) | 0 | 0 | 3 (6.2) | .37 |
| Artralgia | 5 (6.4) | 0 | 0 | 5 (10.4) | .18 |
| Systemic embolism | 17 (21.8)† | 3 (23.1) | 3 (17.6) | 11 (22.9) | .89 |
| Stroke | 14 (17.9) | 3 (23.1) | 3 (17.6) | 8 (16.7) | .86 |
| Conduction disturbances | 12 (15.4) | 1 (7.7) | 3 (17.6) | 8 (16.7) | .4 |
| Metastatic infections | 3 (3.8)‡ | 0 | 0 | 3 (6.2) | .37 |
| Diagnosis delay | | | | | |
| >15 days | 17 (22.1) | 1 (7.7) | 4 (23.5) | 12 (25) | .38 |
| >1 mo | 10 (12.8) | 1 (7.7) | 4 (23.5) | 5 (10.4) | .31 |
| >2 mo | 7 (9) | 0 | 4 (23.5) C | 3 (6.2) | **.04** |
| Microbiological features | | | | | |
| Positive blood cultures at diagnosis | 67/76 (88.2) | 10/13 (76.9) C | 16/17 (94.1) | 45/47 (95.7)A | .07* |
| Positive blood cultures at 48–72 h | 21/45 (46.7) | 3/6 (50) | 4/9 (44.4) | 14/30 (46.7) | .97 |
| Positive valve culture | 15/31 (48.8) | 4/6 (66.7) | 2/6 (33.3) | 9/19 (47.4) | .5 |
| Vancomycin MIC ≥1.5 μg/mL | 7/30 (23.3) | 1/4 (25) | 1/7 (14.2) | 5/19 (26.3) | .81 |
| MSSA | 55/74 (74.3) | 6/11 (54.5) | 11/16 (68.8) | 39/47 (83) | **.03** |
| Gentamicin susceptible | 43/45 (95.6) | 4/4 (100) | 7/8 (87.5) | 32/33 (97) | .45 |
| Rifampin susceptible | 24/24 (100) | 1/1 (100) | 4/4 (100) | 19/19 (100) | — |
| Vancomycin susceptible | 47/47 (100) | 4/4 (100) | 11/11 (100) | 7/8 (87.5) | — |
| Vancomycin MIC ≥1.5 μg/mL | 5/29 (17.2) | 1/2 (50) | 0/5 (0) | 4/22 (18.8) | .27 |
| *MRSA* | 19/74 (26.7) | 6/11 (54.4) C | 5/16 (31.2) | 8/47 (17) A | **.03** |
| Gentamicin susceptible | 12/18 (66.7) | 4/5 (80) | 2/5 (40) | 6/8 (75) | .32 |
| Rifampin susceptible | 4/6 (80) | 2/3 (66.7) | 1/1 (100) | 1/1 (100) | .65 |
| Vancomycin susceptible | 17/18 (94.4) | 5/5 (100) | 5/5 (100) | 7/8 (87.5) | .51 |
| Vancomycin MIC ≥1.5 μg/mL | 3/10 (30) | 1/4 (25) | 1/4 (25) | 1/2 (50) | .78 |
| Diagnostic echocardiogram | | | | | |
| Presence of vegetation | 54 (69.2) | 8 (61.5) | 14 (82.4) | 32 (66.7) | .39 |
| Perianular extensión | 17 (21.8) | 2 (15.4) | 5 (29.4) | 10 (20.8) | .36 |
| Abscess | 14 (17.9) | 1 (7.7) | 5 (29.4) | 8 (16.7) | .28 |
| Pseudoaneurism | 7 (9) | 1 (7.7) | 3 (17.6) | 3 (6.2) | .52 |
| Fístula | 2 (2.6) | 0 | 0 | 2 (4.2) | .36 |
| Prosthesis dehiscence | 16 (20.5) | 3 (23.1) | 1 (5.9) | 12 (25) | .30 |
| Moderate-severe valvular insufficiency | 17 (21.8) | 2 (15.4) | 6 (35.3) | 10 (20.8) | .36 |
| Median vegetation size (IQR) | 13 (10–17.5) | 15 (9–17.5) | 13.5 (11–17.5) | 11.5 (9.75–20) | .97 |
| Vegetation >10 mm | 31 (75.6) | 4 (80) | 8 (80) | 19 (73.1) | .88 |

Comparison of ESAPVE (A) with ISAPVE (B), ISAPVE (B) with LSAPVE (C), and ESAPVE (A) with LSAPVE (C) applying Bonferroni correction for multiple comparisons. For each significant pair the category key with the lowest column ratio appears beside the category with the highest column proportion. The overall *P* of the comparison is presented.

Significant values (*P* values <.05) should appear in bold.

* Indicates *P* > .05 < .12.

† CNS (14 patients, 2 of them also in kidney and spleen), spleen (2), lower and upper extremity (1).

‡ Meningitis, splenic abscess, brain abscess.

**Table 3**

**Medical treatment. Combination and length of antibiotic therapy used in 78episodes SAPVE in the whole sample and per diagnostic periods.**

| | Total | ESAPVE | ISAPVE | LSAPVE | *P* |
|---|---|---|---|---|---|
| MSSA treatment (N = 52), n (%) | | | | | |
| Cloxacillin + rifampin + gentamicin | 22/52 (42.3) | 1/5 (20) | 4/11 (36.4) | 17/36 (47.2) | |
| Other combinations | 30/52 (57.7) | 4/5 (80) | 7/11 (63.6) | 19/36 (52.8) | .46 |
| MRSA treatment (N = 19), n (%) | | | | | |
| Vancomycin + Rifampin + Gentamicin | 11/19 (57.9) | 5/6 (83.3) | 2/5 (40) | 4/8 (50) | |
| Other combinations | 8/19 (42.1) | 1/6 (16.7) | 3/5 (60) | 4/8 (50) | .29 |
| Median duration of antibiotic therapy (IQR) | 29.5 (12.25–45) | 28 (13.2–57.7) | 42 (8–53) | 28 (13–42) | .6 |
| Median duration of antibiotic therapy before surgery (IQR) | 8 (3.75–14.25) | 9 (0–16) | 11 (6.5–13.5) | 7 (3–15) | .82 |
| Median duration of antibiotic therapy in survivors (IQR) | 42 (34.5–56) | 37 (21–62) | 48 (42–57) | 42 (30–55) | .53 |
| Median in-hospital stay (IQR) | 50.5 (39.25–64.75) | 51 (27–83) | 48 (28–60) | 51 (43–70) | .5 |

**Table 4**

**Evolution. Clinical and echocardiographic complications in the evolution, surgical treatment, and mortality.**

| | ESAPVE (N = 13) | ISAPVE (N = 17) | LSAPVE (N = 48) | OR ESAPVE vs ISAPVE (95% CI) *P* | OR ESAPVE vs LSAPVE (95% CI) *P* | OR ISAPVE vs LVPE (95% CI) *P* |
|---|---|---|---|---|---|---|
| Persistent bacteremia | 3/5 (60) | 5/9 (55.6) | 13/30 (43.3) | 1.2 (0.13–11.05) .87 | 0.28–13.5 | 0.36–7.32 |
| Clinical complications before surgery | | | | | | |
| New embolic event | 1 (7.7) | 4 (23.5) | 8 (16.7) | 0.271 (0.026–2777) .35 | 0.417 (0.047–3.674).41 | 1.538 (0.397–5.956) .71 |
| New febrile episode | 6 (46.2) | 4 (23.5) | 13 (27.1) | 2.786 (0.583–13.30) .19‡ | 2.38 (0.653–8.157) .18‡ | 0.828 (0.228–3.006) .77 |
| New HF | 2 (15.4) | 6 (35.3) | 8 (16.7) | 0.333 (0.055–2.027) .4 | 0.909 (0.168–4.912) .91 | 2.727 (0.78–9.51) .1 |
| New renal failure | 5 (38.5) | 8 (47.1) | 15 (31.3) | 0.703 (0.162–3.052) .62 | 1.375 (0.385–4.912) .62 | 1.956 (0.631–6.601) .24 |
| New septic shock | 5 (38.5) | 4 (23.5) | 10 (20.8) | 2.031 (0.417–9.886) .37 | 2.375 (0.637–8.861) .29‡ | 0.81 (0.312–4.375) .81 |
| New conduction disturbance | 3 (23.1) | 3 (17.6) | 2 (4.2) | 1.4 (0.233–8.42) > .99 | **6.9 (1.016–46.85) .06** | 4.929 (0.747–32.51) .1‡ |
| New stroke | 0 | 3 (17.6) | 7 (14.6) | — | — | 1.25 (0.285–5.527) .71 |
| Echocardiographic complications before surgery | | | | | | |
| Vegetation progression | 2 (15.4) | 1 (5.9) | 10 (20.8) | 2.9 (0.23–36.163) .56 | 0.691 (0.131–3.63) .66 | 0.238 (0.028–2.013) .15‡ |
| New vegetation | 1 (7.7) | 1 (5.9) | 9 (18.8) | 1.33 (0.076–23.54) > .99 | 0.361 (0.041–3.147) .33 | 0.271 (0.032–2.317) .2 |
| New perianular extension | 3 (23.1) | 2 (11.8) | 9 (18,8) | 2.25 (0.31–15.97) .62 | 1.3 (0.296–5.71) .72 | 0.507 (0.112–2.99) .5 |
| New moderate-severe insufficiency | 2 (15.4) | 1 (5.9) | 7 (14.6) | 2.9 (0.234–36.164) .58 | 1.065 (0.193–5.868) .94 | 0.366 (0.042–3.217) .34 |
| Surgery indicated but not performed | 3 (23.1) | 8 (47.1) | 21 (43.8) | 0.338 (0.068–1.678) .17‡ | 0.386 (0.094–1.581) .17‡ | 1.143 (0.37–3.46) .81 |
| Surgery | 7/13 (53.8) | 6/17 (35.3) | 22/48 (45.8) | 2.139 (0.489–9.358) .31 | 1.379 (0.403–4.71) .6 | 0.645 (0.205–2.026) > .99 |
| 24 h | 2/7 (28.6) | 0 | 3/22 (13.6) | — | 2.53 (0.329–19.531) .56 | 1.15 (0.98–1.367) > .99 |
| 24–72 h | 2/7 (28.6) | 0 | 4/22 (18.2) | 1.2 (0.059–24.472) > .99 | 1.8 (0.252–12.848) .61 | — |
| 72 h–7 days | 0 | 3/6 (50) | 5/22 (22.7) | — | — | 3.4 (0.51–22.406) .19 |
| Urgent surgery | 4/7 (57.1) | 0 | 5/22 (22.7) | 6 (0.422–85.24) .26 | 4.53 (0.75–27.38) .15‡ | 1.294 (1.032–1.623) .55 |
| Surgery indications: | | | | | | |
| HF | 4/7 (57.1) | 1/6 (16.7) | 4/22 (18.2) | 6.667 (00.487–91.331) .26 | 6 (0.945–38.078) .04 | 0.9 (0.081–9.970) .99 |
| Locally uncontrolled surgery | 2/7 (28.6) | 3/6 (50) | 11/22 (50) | 0.4 (0.04–3.95) .59 | 0.4 (0.063–2.5) .41 | 1 (.164–6.082) .67 |
| Persistent infection | 3/7 (42.9) | 3/6 (50) | 7/22 (31.8) | 0.75 (0.084–6.710) > .99 | 1.6 (0.281–9.204) .66 | 2.143 (.342–13.42) .63 |
| Embolism prevention | 1/7 (14.3) | 2/6 (33.3) | 3/22 (13.6) | 0.333 (0.022–5.027) .55 | 1.056 (0.092–12.137) .69 | 3.167 (0.392–25.576) .28 |
| New intervention | 1/7 (14.3) | 1/6 (16.7) | 2/22 (9.1) | 0.833 (0.041–16.994) > .99 | 1.667 (0.128–21.73) > .99 | 2 (0.15–26.73) .53 |
| Clinical complications after surgery | | | | | | |
| New febrile episode | 5/7 (71.4) | 4/6 (66.7) | 9/22 (40.9) | 1.25 (0.118–13.24) > .99 | 3.611 (0.57–22.897) .21‡ | 2.899 (0.433–19.281) .37 |
| New HF | 4/7 (57.1) | 1/6 (16.7) | 8/22 (36.4) | 0.08 (0.487–91.331) .26 | 2.333 (0.401–13.171) .4 | **0.35 (0.035–3.548) .63** |
| New renal failure | 2/7 (28.6) | 5/6 (83.3) | 6/22 (27.3) | 0.08 (0.005–1.192) .1‡ | 1.067 (0.161–7.056) > .99 | 13.33 (1.28–138.845) .02 |
| New septic shock | 0 | 2/6 (33.3) | 5/22 (22.7) | — | — | 1.7 (.237–12.173) .62 |
| New conduction disturbance | 1/7 (14.3) | 2/6 (33.3) | 6/22 (27.3) | 0.333 (0.022–5.027) .55 | 0.444 (0.044–4.503) .64 | 1.33 (0.192–9.273) > .99 |
| Mortality | | | | | | |
| In-hospital death | 5/13 (38.5) | 9/17 (52.9) | 29 (60.4) | 0.556 (0.128–2.412) .43 | 0.409 (0.116–1.441) .15‡ | 0.737 (0.242–2.246) .59 |
| Endocarditis-related death | 5/5 (100) | 7/9 (77.8) | 27/29 (93.2) | 1.286 (0.907–1.823) .5 | 1.074 (0.973–1.186) > .99 | 0.259 (0.031–2.179) .23 |
| Cardiac death | 2/5 (40) | 3/9 (33.3) | 18/29 (62.1) | 1.333 (0.139–12.81) > .99 | 0.407 (0.059–2.835) .62 | 0.306 (0.063–1.477) .24 |
| Causes of death | | | | | | |
| Septic shock | 2/5 (40) | 4/9 (44.4) | 13/29 (44.8) | 0.833 (.09–7.675) > .99 | 0.821 (0.119–5.67) > .99 | 0.985 (0.219–4.434) > .99 |
| HF | 1/5 (20) | 1/9 (11.1) | 11/29 (37.9) | 2 (.098–41) > .99 | 0.409 (0.04–4.147). 63 | 0.205 (0.022–1.865) .13‡ |
| Pump failure | 0 | 0 | 2/29 (6.9) | — | 1.704 (0.973–1.186) > .99 | 1.074 (0.973–1.186) > .99 |
| Stroke | 0 | 0 | 3/29 (10.3) | — | 1.115 (0.986–1.262) > .99 | 1.115 (0.986–1.262) > .99 |
| Hemorrhagic shock | 1/5 (20) | 0 | 2/29 (6.9) | 0.8 (.516–1.24) .35 | 3.375 (0.246–46.36) .38 | 1.074 (0.973–1.186) > .99 |
| Multiorganic failure | 4/5 (80) | 4/9 (44.4) | 4/29 (13.8) | 5 (0.388–64.38) .3 | **25 (2.196–284.6) .007** | **5 (0.926–26.99) .04** |
| Other cause | 0 | 2/9 (22.2)* | 1/29 (3.6)† | 1.286 (0.907–1.823) .5 | 1.307 (0.966–1.114) .99 | 7.714 (0.608–97.846) .14 |
| Unknown | 0 | 0 | 0 | — | — | — |

Statistically significant 95% CIs appear in bold. CI = confidence interval, ESAPVE = early *Staphylococcus aureus* prosthetic valve endocarditis, HF = heart failure, ISAPVE = intermediate *Staphylococcus aureus* prosthetic valve endocarditis, LSAPVE = late *Staphylococcus aureus* prosthetic valve endocarditis, OR = odds ratio.

* Other: massive hemoptysis (1), bronchoaspiration (1).

† Other: massive atelectasis of 1 lung.

‡ Indicates OR <0.4 or> 1.6.

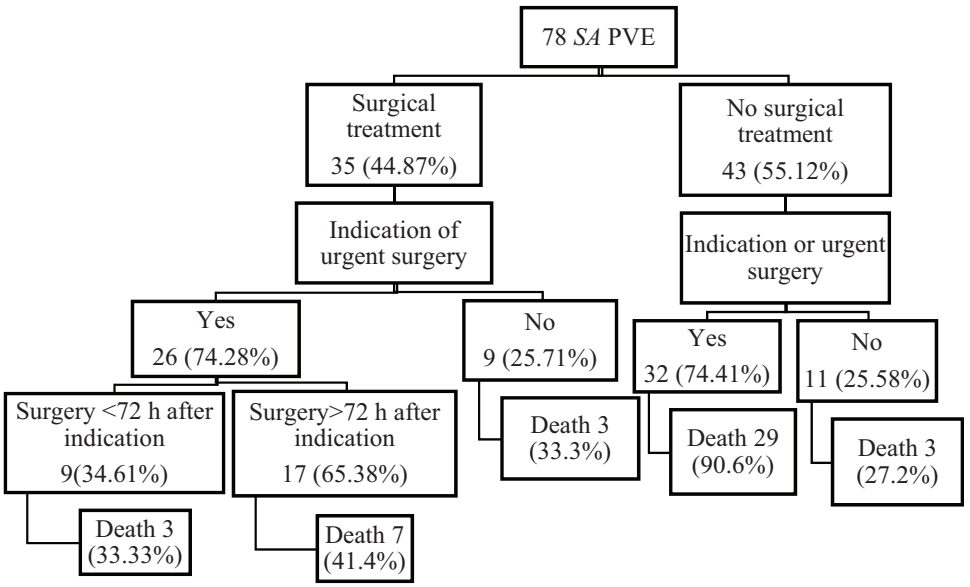


**Figure 3.** Distribution of the 78 episodes of *Staphylococcus aureus* prosthetic valve endocarditis according to the type of treatment performed (only medical or medical-surgical), presence of any indication of urgent surgery, the time from indication to surgery, and death. Mortality was similar in all groups (around 30%) with the exception of patients with urgent surgery indication who were operated on >72 hours after the indication, whose mortality was slightly superior (41%) and the subgroup of patients with urgent surgery indication who did not undergo surgery, whose mortality was the highest of the series (91%).

were 27.3% versus 59.7% ($P=.05$) and it was related to endocarditis in 66.7% versus 92.5% ($P=.13$).

Indications for cardiac surgery were mainly uncontrolled infection, with perianular extension in 16 cases (45.7%). The majority of patients were operated on with >1 indication. Of the 22 patients with CNS abnormalities in the evolution, 12 were operated on (54.54%) (Fig. 4), mostly within the first 14 days after the event (Fig. 5).

On ESAPVE episodes, surgery was performed more frequently; urgent surgery was discarded less often and performed within the first 24 hours more frequently than in the other periods. No patient with indication of urgent surgery was operated on within the first 72 hours from the indication in ISAPVE group.

The indication varied according to the diagnostic period, being HF the main indication in ESAPVE, and persistent infection in ISAPVE.

Forty-three patients died during admission (55.1%). Mortality at 1 year of follow-up was 61%. Two patients were lost to follow-up after discharge. The main cause of death was SS (21 cases, 41.2%) followed by HF (14, 27.5%). Analyzing the causes of death among the operated and nonoperated patients, we found that fewer patients in the surgical group died of SS (31.2% vs 45.7%, $P=.37$) or stroke (0 vs 8.6%, $P=.54$) and more patients died because of pump failure (12.5% vs 0, $P=.09$), hypovolemic shock (12.5% vs 2.9%, $P=.22$), and multiorgan failure (31.2% vs 20%, $P=.48$). Mortality in patients with stroke was 14 of 22 (63%) versus 29 of 56 (51,8%) in the remaining episodes ($P=.34$), but difference is higher considering only hemorrhagic stroke (77.8% vs 52.2%, OR 3.2 [0.62–16.55], $P=.17$). When surgery was performed within the first

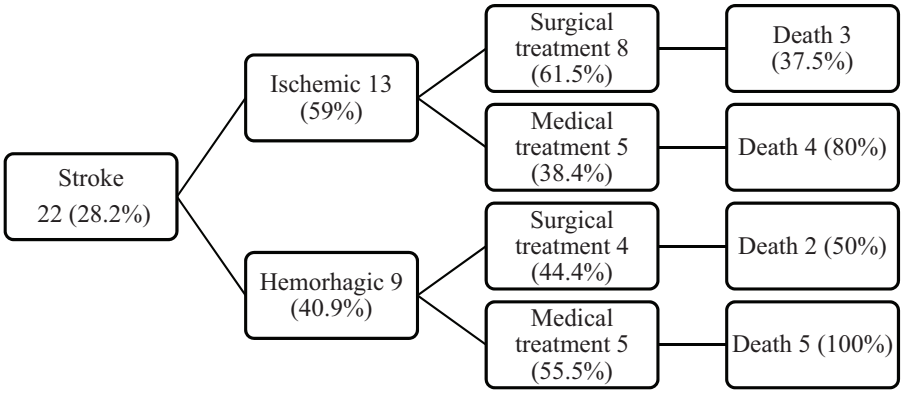


**Figure 4.** Description of the 22 patients with *Staphylococcus aureus* prosthetic valve endocarditis with ischemic or hemorrhagic stroke according to whether or not cardiac surgery was performed, and its evolution. Twelve patients with stroke were operated on (4 with hemorrhagic stroke and 8 with ischemic stroke). Mortality was inferior in patients with ischemic stroke managed with surgical treatment and patients with hemorrhagic stroke had a deleterious prognosis with or without surgery.

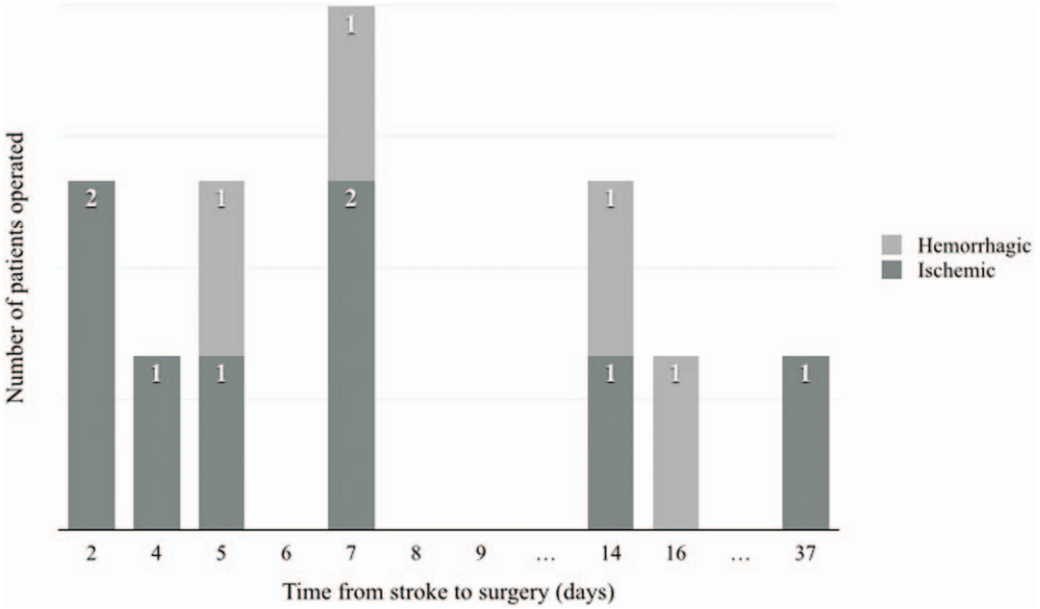


**Figure 5.** Number of patients with ischemic or hemorrhagic stroke operated and time elapsed from the embolic event to surgery (days). Ten of 12 operated patients underwent surgery within the first 14 days after stroke (80%), 67.5% in the first week, including 50% of hemorrhagic episodes.

14 days after stroke, mortality was 66.7% versus 0% of patients operated later ($P = .06$).

The percentage of patients who died in the ESAPVE was lower than in ISAPVE and LSAPVE periods (38.5%, 52.9%, and 60.4%, nonsignificant). Death owing to multiorgan failure was more frequent in the ESAPVE and ISAPVE than in the LSAPVE, whereas death from HF was more frequent in the late period.

Comparison of the main differences among periods is represented in Figure 6.

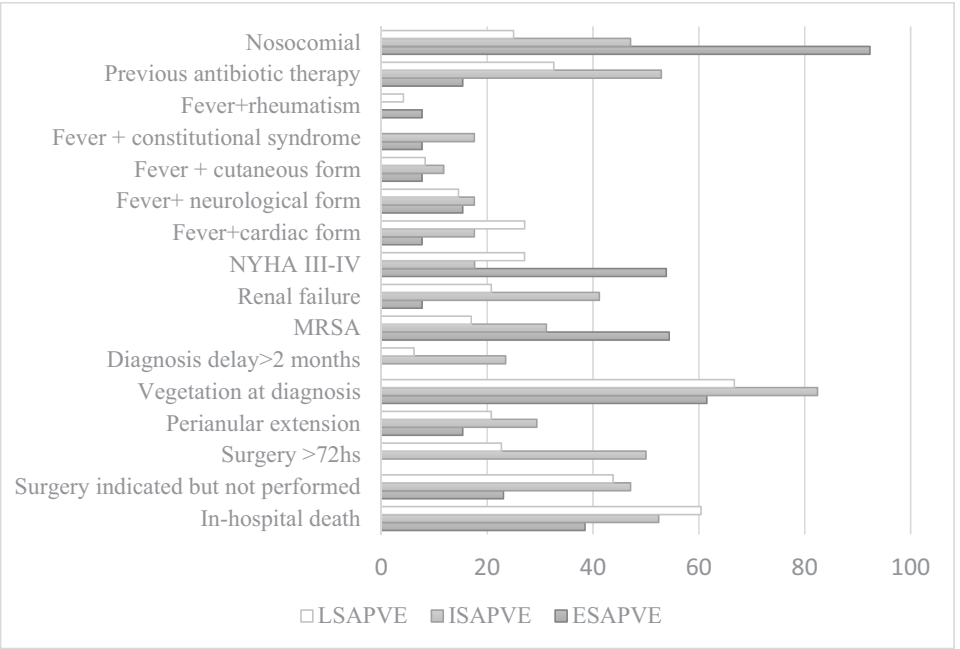


**Figure 6.** Comparison of epidemiological, clinical, microbiological, echocardiographic features, surgical therapy and outcomes among periods (ESAPVE, ISAPVE, and LSAPVE). The percentage of patients in each period with the characteristic studied is represented. ESPAVE = early *Staphylococcus aureus* prosthetic valve endocarditis, LSPAVE = late *Staphylococcus aureus* prosthetic valve endocarditis, MRSA = methicillin-resistant *Staphylococcus aureus*, SAPVE = *Staphylococcus aureus* prosthetic valve endocarditis.

## 4. Discussion

### 4.1. SAPVE general features

There was a higher percentage of PVE than in other series[6–8,37–42]; however, the frequency of SAPVE was lower (16% vs 23%).[1] Some epidemiological features are common with previous publications: the highest number of SAPVE in the first 6 months after surgery [1,43]; the mean age of patients and the preference for the male sex[3,4,44]; the high comorbidity and increasing association with health care[1,8,45,46]; the frequent association with catheter-related bacteremia and the more common involvement of metallic prostheses.[4,43,47] We found differences in some characteristics: the low percentage of intravenous drug users,[5] or patients with HIV infection[24] and the more frequent involvement of mitral prostheses instead of the aortic location, more prevalent in all series[3,44] except for Fernández-Guerrero et al.[24] The involvement of several valves is superior to other series of PVE[1] or SAPVE.[4,44]

The most frequent presentation was fever alone, followed by cardiac manifestations. It is remarkable that up to 20% of the patients did not present fever at the onset of endocarditis, contrary to what is established in the literature,[34] and this was related to diagnosis delay. Thus, it is important to consider SAPVE in the presence of other signs or symptoms of endocarditis (eg, AV block) even in the absence of fever, especially in those with previous antibiotic treatment. At diagnosis, the presence of a new murmur was rare (17% vs 55% in Fernández Guerrero et al);[24] perhaps the improvement of echocardiography and other imaging techniques may have contributed to an earlier diagnosis with less local destruction. Complications were common: moderate-severe HF, stroke, and SS in agreement with other studies.[3,44]

Complications at the CNS were similar to that described in other studies, that is, 32% versus 27% to 35% during the entire course[3,4,34,44,48] and 18% versus 15.5% at diagnosis[3]; a lower frequency of cerebral abscesses was observed with respect to older series.[3] The low frequency of mycotic aneurysms is striking, although only 40% of the patients were brain-imaged and arteriography was not performed in all hemorrhagic events. In our cohort, the same as in a description of episodes of endocarditis collected in Denmark for a decade, the presence of vegetations was not associated with a higher frequency of intracranial complications.[48] A role of the anticoagulant therapy in the high frequency of bleeding events has been suggested[24]; however, we did not confirm this point.

The majority of embolic events outside the CNS appeared at diagnosis; the frequency was similar to that previously described (6% vs 3%). Metastatic infection at diagnosis was even more exceptional than in other series (4% vs 9%).[3]

The percentage of positive blood cultures at diagnosis was inferior to previous reports[49]; this might be due to an earlier diagnosis than before 90 s, when the TEE was not available, when infection is initially located in the annulus.

Our MR*SA* frequency is closer to that of ICE (32.2%)[44]; in other published series is much lower[3,4,24] and this probably depends on the age of the series or the prevalence of MR*SA* in the area. Although there are missing data, MS*SA* was fully susceptible to rifampin and vancomycin, and almost to gentamicin, whereas MR*SA* showed a more resistant profile, which is important to establish an empirical treatment. There is very little data regarding antibiotic susceptibility in literature.[3–5,24,44]

Nearly 100% of the patients presented echocardiographic findings during the entire course and, as previous reports, around 80% had them at diagnosis[24]; the most remarkable finding was that vegetations were not always present at diagnosis and paravalvular complications were frequent. Published data regarding echocardiography in *SA* PVE are scarce; in a cohort of 61 episodes, 47.5% presented a vegetation and 29%, intracardiac abscesses.[5] These findings are explained by the pathophysiology of prosthetic endocarditis, which often begins at the interface between the ring and the prosthesis, and highlight the tendency of *SA* PVE to produce extensive perianular destruction.[3,24,50] We found vegetations $> 10$ mm in 75% of episodes, although previous reports describe small vegetations in *Staphylococcus aureus* IE.[24,50] We highlight the elevated frequency of progression of echocardiographic involvement, which justifies the recommendation to repeat the echocardiogram early during antibiotic treatment, especially if early surgery is not performed. The lack of published data on this field does not allow comparison.

In our series the use of beta-lactams or vancomycin was less frequent than in previous reports; conversely, the use of alternative regimens containing daptomycin (with betalactams and/or gentamicin and / or rifampin) was frequent, even in MS*SA* episodes. This combinations shows synergistic activity in vitro.[51–53] A high percentage of patients with MSSA IE were treated with vancomycin; maybe they died before knowing the susceptibility study or maybe they were allergic to beta-lactams. In Sohail et al they found 3.64% and 1.8% of cases in this situations.[4] The use of aminoglycosides was similar to previous reports, but the use of rifampin seems to be superior (70% vs 21%–33%).[3,4] Some of the current recommendations include aminoglycosides in the treatment of SAPVE,[35] although there is some evidence indicating the absence of benefit of its addition even in the presence of prosthetic material.[54] The use of aminoglycosides was less frequent in patients treated with daptomycin, probably because the presence of renal failure was more frequent in this group, or because new synergistic combinations were used.

Up to 22% of MR*SA* strains exhibited vancomycin MIC $\geq 1.5\,\mu g$ / ml which has been related with treatment failure, persistent Bacteremia[16–23] and increased in-hospital mortality.[12,20] A change in susceptibility cut off points and methodology of vancomycin MIC determination in the years of the study did not allow conclusions.

The median duration of antibiotic in survivors was similar to other studies.[3] The median time from diagnosis to surgery was similar than that of *ICE* series, 8 days[5] and lower than that of John et al, 19 days.[3]

Persistent bacteremia appeared especially in non-operated patients, which is related to the absence of focus control. It was numerically higher in patients treated with vancomycin, that has a slow bactericidal activity. Fernández-Guerrero et al. also described a high frequency of persistent bacteremia.[24]

Complications in evolution were frequent, especially renal failure, recurrent fever and SS. There was a high rate of embolisms, mainly to the CNS. The frequency of recurrent CNS embolisms was similar in John et al's and just as in our data, most took place within the first 2 weeks of treatment.[3] These results reinforce an early surgery to reduce embolic risk and mortality.[3,26–28,55] Nevertheless, recent studies have found that it is possible to treat a selected group of patients without cardiac complications with only a medical approach. These researches

are not without limitations: all are retrospective and come from cardiac surgery referral centers[4,5,44]; included episodes before the introduction of TEE; the prevalence of MRSA was lower than currently; indications for surgery, type of intervention (urgent or elective), and causes of death were not collected.[4,5] In our cohort, 11 patients without clinical or echocardiographic complications and low punctuation in SS risk score were managed conservatively. Three of them died (all with persistent bacteremia). Although we did not record whether management was deliberately conservative or their high risk precluded surgery, we think that perhaps patients with these features could be initially managed with medical treatment and closely monitored, and if persistent bacteremia or other clinical or echocardiographic complications develops, surgery should be performed.

The most frequent indications for surgery in SAPVE were HF, prosthetic dehiscence, and intramyocardial abscesses.[24] The majority of our patients were operated on with >1 indication; the most frequent was uncontrolled infection. It has been reported that patients with neurological events are less frequently operated[3]; however, when SA was the etiological agent, surgery was precluded or deferred less often.[56] It is still unknown when is the ideal moment for the intervention; clinical practice guidelines recommend delaying it 2 to 4 weeks according to the type of stroke (ischemic or hemorrhagic).[35,57] However, both the ICE investigators and Gaca et al did not find significant differences in mortality when patients with ischemic stroke were operated on within 7 days of embolic event.[56,58] Our data show that in SAPVE, the condition of patients did not allow to wait that period of time, and most patients got surgery in <7 days after stroke, with higher mortality in patients operated within the first 14 days. Moreover, although mortality of patients with hemorrhagic stroke who underwent surgery was high, mortality was still higher in patients with both ischemic and hemorrhagic stroke who did not undergo surgery.

Mortality was high and similar to the most recent series[44]; in-hospital mortality in previous publications ranges from 37% to 48%.[3–4,24] In our study, we did not find significant differences in the causes of exitus between patients who were operated on and those who were not, probably because of the small sample size; however, less patients in the intervention group died of SS or stroke, which suggests that an early surgery might avoid the development of these complications. The higher mortality in patients with hemorrhagic stroke reinforces the indication of surgery to prevent this complication in SAPVE.

### 4.2. Description of the characteristics of SAPVE episodes according to the time elapsed since valve replacement surgery

ESAPVE were more often nosocomial, affected patients with less comorbidity, and the risk factor was identified in all cases. ISAPVE affected more male and younger patients and the risk factor was not identified in a high percentage of episodes; the later suggests that they were acquired in the perioperative period and manifested later. LSAPVE affected more often older patients, with more comorbidity than in ESAPVE; the percentage of non-nosocomial health care-associated infections was the highest of the 3 periods, with catheter-associated bacteremia being the main risk factor. Previous antibiotic treatment was more frequent in ISAPVE and this could indicate that symptoms secondary to endocarditis were interpreted and treated as other infections.

In ESAPVE the most frequent presentations were severe HF and fever alone. ISAPVE was distinguished by a more frequent debut with constitutional syndrome, a lower proportion of severe HF, a higher percentage of renal failure, and a higher diagnosis delay than ESAPVE. Differences in the inoculum volume, in the defensive capacity of host or in the expression of virulence factors of the causal strain, could be responsible that an infection acquired during surgery manifested later. The higher percentage of renal failure could be compatible with a longer infection and the formation of immunocomplexes. Diagnosis of LSAPVE was delayed in comparison to ESAPVE, maybe because of a lower degree of suspicion.

In almost all of the LSAPVE episodes, blood cultures at diagnosis were positive; the percentage was lower in the other periods, perhaps in relation to previous antibiotic treatment and the initial location of infection (in the annulus rather than in the surface of the valve). The frequency of MRSA was higher in ESAPVE, as its acquisition was mainly nosocomial.

No statistically significant differences were found in the echocardiographic findings at diagnosis among the 3 periods.

Duration of medical treatment before surgery was shorter in ESAPVE than in LSAPVE (nonsignificant) according to a higher percentage of urgent surgery in this period.

Sepsis manifestations appear to be relatively delayed with respect to HF in ESAPVE, finding a higher frequency of new episodes of SS in evolution before surgery. ISAPVE episodes develop more frequent renal failure and HF than LSAPVE ones. Conduction disturbances were less frequent in LSAPVE, maybe because infection initially affects the valve surface and not the anular interface.

In EPVP episodes, surgery was discarded less often and was performed in the first 72 hours more frequently, being HF the main indication. ISAPVE episodes were operated less precociously. The most frequent indication of surgery in ISAPVE and LSAPVE was uncontrolled infection. ISAPVE appear to have a more unfavorable evolution after surgery, frequently with SS and renal failure. Perhaps, the greater diagnosis delay, the deferred surgery, and intervention performed frequently because of uncontrolled infection may explain the poorer outcomes of this patients.

Death was less frequent in ESAPVE; this difference, although not statistically significant, is numerically important. In series of PVE in which the cutoff point between ESAPVE and LSAPVE is 1 year, it has been described a higher mortality rate of ESAPVE episodes.[48,59] Nevertheless, these differences are not statistically significant in studies specifically addressed to SAPVE.[3,4] In other series, it has been described a better evolution of patients who were operated under the indication of HF in comparison with those operated for other reasons[24]; this could be the main factor determining prognosis of ESAPVE, although it is probable that an earlier diagnosis, the greater frequency of surgery, and the lower comorbidity of patients in this period were conditioning a more favorable evolution.

## 5. Study limitations

Given that SAPVE is a rare disease, the small sample size makes it difficult to find statistically significant differences in some subgroups of patients and among male and female patients. The participating centers are all reference hospitals for cardiac surgery, which could lead to a reference bias, with the possibility of precluding the most complicated patients from surgery. The

dilated in time collection of data could entail a survival bias, given that the improvement of surgical techniques and medical resources could explain a better prognosis in more recent episodes. Indications of surgery and punctuation in surgery risk scores of patients who did not undergo surgery were not collected. Thus, it was not possible to make an accurate comparison with patients who were operated on.

## 6. Conclusions

SAPVE was uncommon. It affected patients with comorbidity and health care contact. Absence of fever at diagnosis was not uncommon; thus, another signs or symptoms in patients with prosthetic valves should rise the suspicion. Diagnosis delay was related to presentation without fever and with previous antibiotic treatment. Heart failure, systemic embolisms, renal failure, and SS were frequent at diagnosis, as it was periannular extension. Presence of MRSA was high. Positive valve culture was related to shorter duration of antibiotic treatment. Absence of vegetation was not rare, but, if present, it was >10 mm in the majority of episodes. Complicated evolution was habitual, with a high rate of persistent bacteremia related to nonsurgical treatment, and a high rate of progression of echocardiographic affectation. Some patients with uncomplicated SAPVE were safety treated with medical therapy alone. Surgery was feasible in patients with stroke. Mortality was high, especially in patients with indication of urgent surgery or hemorrhagic stroke who were not operated. There were differences in some clinical characteristics and in evolution according to the time elapsed from valve replacement surgery. Prognosis was better in ESAPVE.

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