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MAJOR ARTICLE

Outpatient Parenteral Antibiotic Treatment vs Hospitalization for Infective Endocarditis: Validation of the OPAT-GAMES Criteria

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Background. Outpatient parenteral antibiotic treatment (OPAT) programs are increasingly used to manage infective endocarditis (IE), but current criteria for indicating OPAT are markedly conservative. We aimed to investigate whether more liberal criteria for indicating OPAT in IE can be safely used.

Methods. This was a prospective multicenter nationwide cohort study (2008–2018). Rates of readmission, recurrences, and 1-year mortality were compared between hospital-based antibiotic treatment (HBAT) and OPAT. Risk factors for readmission and mortality in OPAT patients were investigated by logistic regression. Patients did not fulfill OPAT-GAMES (Grupos de Apoyo al Manejo de la Endocarditis en ESpaña) criteria if they had any of the following: cirrhosis, severe central nervous system emboli, undrained abscesses, severe conditions requiring cardiac surgery in nonoperable patients, severe postsurgical complications, highly difficult-to-treat microorganisms, or intravenous drug use.

Results. A total of 2279 HBAT patients and 1268 OPAT patients were included. Among OPAT patients, 307 (24.2%) did not fulfill OPAT-GAMES criteria. Overall, OPAT patients presented higher rates of readmission than HBAT patients (18.2% vs 14.4%; $P = .004$), but no significant differences were found in the propensity analysis. Patients not fulfilling OPAT-GAMES criteria presented significantly higher rates of readmission than HBAT and OPAT-GAMES (23.8%, 14.4%, 16.4%; $P < .001$), whereas no significant differences were found in mortality (5.9%, 8%, 7.4%; $P = .103$) or recurrences (3.9%, 3.1%, 2.5%; $P = .546$). Not fulfilling OPAT-GAMES criteria was associated with higher risk of readmission (odds ratio [OR], 1.43; 95% CI, 1.03–1.97; $P = .03$), whereas cardiac surgery was associated with lower risk (OR, 0.72; 95% CI, 0.53–0.98; $P = .03$).

Conclusions. OPAT-GAMES criteria allow identification of IE patients at higher risk of long-term complications to whom OPAT cannot be safely administered.

Keywords. infective endocarditis; mortality; outpatient parenteral antibiotic treatment; readmission; recurrences.

Over the last 3 decades, increasing evidence has shown that outpatient parenteral antibiotic treatment (OPAT) is an efficacious, safe, cost-effective, and comfortable alternative to hospital-based antibiotic treatment (HBAT) for a variety of infections [1–4]. The coronavirus disease 2019 (COVID-19) pandemic has demonstrated the necessity of implementing alternatives to conventional hospitalization as a measure to alleviate the overwhelmed capacity of hospitals worldwide, particularly during surges [5]. In 2001, Andrews and von Reyn proposed the first recommendations for indicating OPAT in patients with IE, still in place as of today, which are largely restrictive [6]. The latest versions of both the European Society of Cardiology [7] and American Heart Association [8] IE guidelines recommend using the criteria described by Andrews and von Reyn. Long hospitalization periods, as in the case of a complete HBAT course for IE [9], are associated with increased risk of nosocomial infections, antimicrobial resistance, morbidity, death, and financial costs [10].

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Several studies have provided preliminary evidence that OPAT can be safely used for treating IE with less restrictive criteria than those proposed by Andrews and von Reyn [11–17]. In a study comparing the outcomes of 429 patients receiving OPAT and 1003 patients receiving HBAT from 2008 to 2012, we found that efficacy and safety did not differ between HBAT and OPAT despite only 22% of OPAT patients fulfilling Andrews and von Reyn's criteria [18]. We therefore proposed a new set of less restrictive criteria than those of Andrews and von Reyn [18] (OPAT-GAMES criteria) to guide the administration of OPAT in patients with IE.

The aim of this study was to validate our findings in a larger cohort and to assess whether GAMES-OPAT criteria allow identification of patients at higher risk of complications to whom OPAT should not be administered.

METHODS

Design and Definitions

This was a multicenter prospective observational study including 35 Spanish centers from January 2008 to December 2018. Guidance for cohort studies according to the STROBE statement [19] was followed. The indication for OPAT or HBAT was independently decided by attending physicians at each center [18]. The characteristics of the GAMES (Grupos de Apoyo al Manejo de la Endocarditis en ESpaña) cohort, definitions, and collection of data have been described elsewhere [20]. Noticeably, recurrences included all episodes of IE occurring in the 12 months after the initial IE episode and encompassed both relapses (new episode of IE caused by the same microorganism as the initial episode during the first 6 months) and reinfections (new episode caused by a different microorganism or by the same microorganism but at least 6 months after the first IE episode, except in the case that it was shown that it was the same strain as in the initial episode by molecular biology techniques). Persistent bacteremia was defined as persistence of positive blood cultures for 7 days after appropriate antibiotic treatment initiation.

Patients

Included were adult individuals with IE diagnosed according to Duke modified criteria [21] who survived the initial admission. Individuals who died at the hospital during the initial admission due to IE were excluded from the analysis because they could not opt into OPAT, and therefore the comparison of outcomes as defined in the current study was not possible. Patients lost to follow-up at 1 year were also excluded.

Groups

The HBAT group included patients who completed antibiotic treatment at the hospital; The OPAT group included patients who completed antibiotic treatment through hospital-at-home programs. OPAT patients were separately analyzed according to fulfillment of the OPAT-GAMES criteria (Table 1). These criteria were developed by a multidisciplinary expert opinion consensus group from GAMES and first tested in a previous work from our group [18].

Table 1. OPAT-GAMES Criteria to Guide Indication of Outpatient Parenteral Antibiotic Treatment for Patients With Infective Endocarditis (Adapted From Pericàs et al. [18])

Inclusion criteria: All patients are potential candidates once the acute critical phase[a] has been overcome, except for those presenting with the following criteria:
Exclusion criteria:
1. Patients with Child B or C liver cirrhosis
2. Severe central nervous system emboli Multiple (>3), large (>2 cm), hemorrhagic, or with fixed neurologic deficits
3. Not drained large spleen or renal abscess
4. Vertebral abscesses requiring neurosurgery
5. Periannular complications or other severe conditions requiring surgery when this is contraindicated[b] Perivalvular abscess, fistula, perforation, pseudoaneurysm, severe pericardial effusion with signs of cardiac tamponade, etc.
6. Severe postsurgical complications Ischemic stroke, brain hemorrhage, worsening of prior stroke/bleeding, hemodynamic collapse, surgical wound bleeding requiring new surgery, infection of the surgical wound (mediastinitis/osteomyelitis), ventilator-associated pneumonia, acute kidney failure requiring dialysis, cardiac blockade requiring pacemaker, critically ill–associated polyneuropathy
7. Highly difficult-to-treat microorganisms Those requiring intravenous antibiotic combinations that cannot be administered by means of OPAT or that require strict monitoring of drug levels either in blood or in other fluids owing to their potential toxicity or narrow therapeutic index (eg, methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci also resistant to alternative drugs such as daptomycin and linezolid, multidrug or extensively drug-resistant gram-negative rods, highly penicillin-resistant viridans group streptococci, fungi other than *Candida* spp.)
8. Active intravenous drug users

Abbreviations: GAMES, Grupos de Apoyo al Manejo de la Endocarditis en ESpaña; OPAT, outpatient parenteral antibiotic treatment.

[a]Except for patients with noncomplicated native viridans group streptococcal endocarditis, for whom transfer to OPAT can be considered after 5–7 days of antibiotic treatment, at least 10–14 days of antibiotic treatment should be completed at the hospital.

[b]Transfer to the patient's home or other outpatient setting for palliative purposes is also possible after careful discussion and agreement with the patient and/or relatives.

Outcomes

The primary outcome was hospital readmission rate. The Secondary outcomes were 1-year mortality and recurrences.

Patient Consent

Clinical research institutional review boards in each of the GAMES participating centers approved the prospective collection of data in the central repository. All patients provided written informed consent.

Statistical Analysis

A propensity score analysis [22] was used to adjust for potential confounding variables. HBAT patients were matched 2:1 to OPAT patients using individual propensity scores. Variables

used for matching were sex, age, and type of IE (native, prosthetic, and cardiac implantable electronic device–related IE), as these are variables that have consistently been shown to impact IE prognosis. Patients not fulfilling OPAT-GAMES criteria were excluded from the propensity score analysis. The causative microorganism was not used as a matching criterion because the OPAT-GAMES criteria already include a variable related to the type of causative microorganism. The matching tolerance was a propensity score difference of 0.05.

Differences between groups were measured using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables, or the analysis of variance test or Kruskal-Wallis test where applicable. The cumulative probability of hospital readmission and death at 1 year was calculated using the Kaplan-Meier estimate and adjusted by predictors. For the analysis of risk factors of readmission, 1-year mortality, and recurrences, a logistic regression model that included variables with $P < .30$ in the univariate analysis was used. A 2-sided $P < .05$ was considered statistically significant. The statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Sample

After excluding patients who died during initial admission, the total analyzed sample included 3547 patients, 2279 (64.3%) in the HBAT group and 1268 (35.7%) in the OPAT group. Within the latter group, 961 (75.8%) fulfilled OPAT-GAMES criteria, whereas 307 (24.2%) did not. In the HBAT group, 1485 patients (65.2%) fulfilled OPAT-GAMES criteria, whereas 794 (34.8%) did not. The main reasons for not fulfilling OPAT-GAMES criteria in the OPAT group were perivalvular complications for which the patient had not undergone surgery and severe postsurgical complications (Figure 1). The characteristics and outcomes of HBAT and OPAT patients are shown in Supplementary Table 1. Comparisons between HBAT patients and OPAT patients according to fulfillment of the OPAT-GAMES criteria are shown in Supplementary Tables 2 and 3.

Causes and Risk Factors for Hospital Readmission, Mortality, and Recurrences

There were no significant differences in IE-related causes of readmission between groups, being IE-related reasons the most frequent causes of readmission in both the HBAT and OPAT groups. Notably, readmission due to causes related to the venous catheter, antibiotic side effects, or the surgical wound in patients undergoing cardiac surgery was significantly less frequent in the HBAT group (Supplementary Table 4). Causes of death at 1 year are shown in Supplementary Table 5.

In the multivariable model, cardiac surgery during initial admission was associated with a significantly lower risk of readmission (odds ratio [OR], 0.72; 95% CI, 0.53–0.98; $P = .03$), whereas not fulfilling OPAT-GAMES criteria was significantly associated with higher risk of readmission (OR, 1.43; 95% CI, 1.03–1.97; $P = .03$) (Table 2). Age-adjusted Charlson morbidity score was associated with a higher likelihood of death at 1 year (OR, 1.17; 95% CI, 1.08–1.27; $P < .001$), whereas cardiac surgery was associated with a lower risk of death (OR, 0.39; 95% CI, 0.22–0.68; $P = .01$) (Supplementary Table 6). Renal and spleen abscesses were associated with recurrences (Supplementary Table 7).

Supplementary Figure 1 shows Kaplan-Meier curves for readmission and mortality at 1 year comparing the HBAT and OPAT groups (log-rank test $P < .001$ for both).

Safety of OPAT Compared With HBAT in a Propensity Score Analysis

When comparing patients from the HBAT and OPAT groups, both fulfilling OPAT-GAMES criteria (Table 3), we found no significant differences in readmission, mortality, or recurrence rates between groups.

DISCUSSION

This study validates our preliminary findings on the safety of OPAT for treating IE [18], confirming that less restrictive criteria than those currently recommended [6] could be used for indicating OPAT in IE patients. However, as opposed to our earlier findings, we found an overall significantly higher rate of readmissions among OPAT patients. Importantly, OPAT-GAMES criteria allow identification of OPAT patients at higher risk of readmission who are not eligible for OPAT.

We did not find significant differences in readmissions, sequelae, 1-year mortality, or recurrences between HBAT and OPAT patients fulfilling GAMES criteria. However, OPAT patients not fulfilling GAMES criteria presented a significantly higher rate of readmissions than both HBAT patients and patients fulfilling GAMES criteria. OPAT reduced the length of stay by a median (IQR) of 19 (13–29) days when OPAT-GAMES were met, whereas it reduced the median length of stay (IQR) by 17 (11–28) days when not met; that is, OPAT patients fulfilling GAMES criteria were discharged from the hospital to continue antibiotic treatment significantly earlier than OPAT patients not fulfilling GAMES criteria. In both cases, the ability to save over 2 weeks of hospital admission in patients who have already been hospitalized for a long time should be considered for the potential cost-saving effects, the avoidance of nosocomial infections, and the increase in patient comfort.

Current recommendations state that HBAT should generally be continued after the critical phase (weeks 0–2) for patients either presenting complications (congestive heart failure,

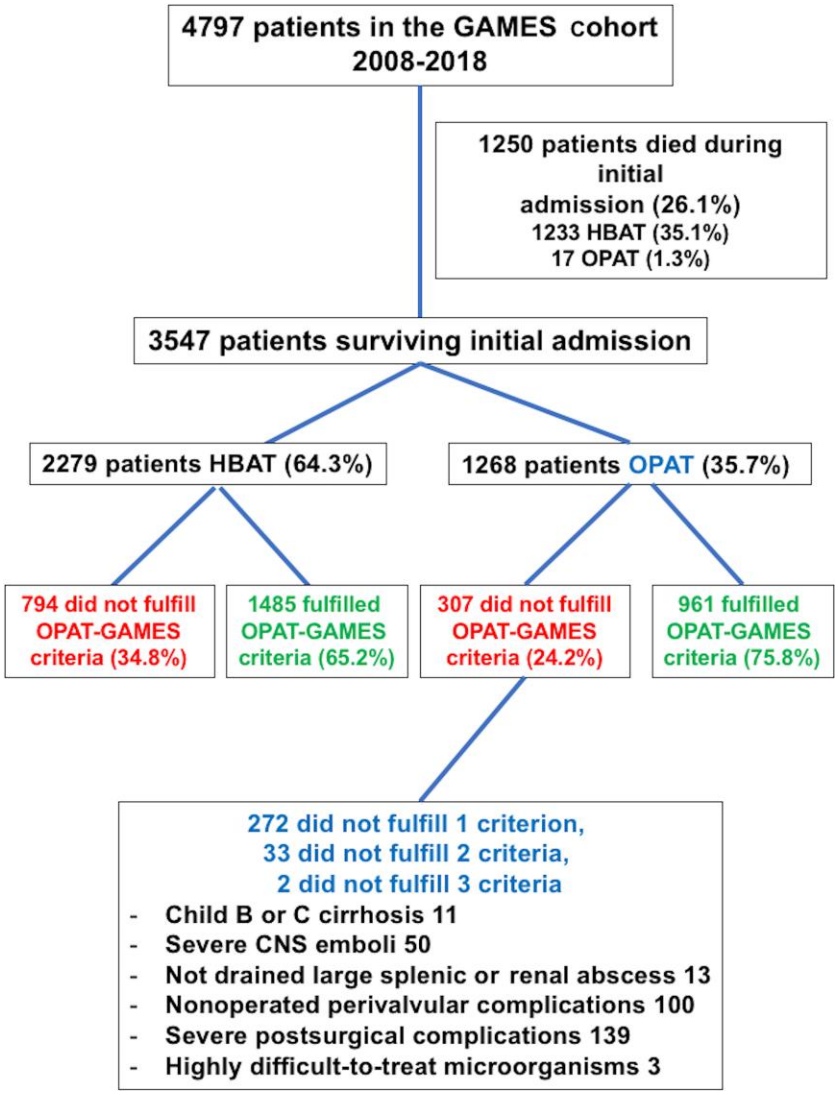

Figure 1. Flowchart of patients' dispositions. Abbreviations: CNS, central nervous system; GAMES, Grupos de Apoyo al Manejo de la Endocarditis en ESpaña; HBAT, hospital-based antibiotic treatment; OPAT, outpatient parenteral antibiotic treatment.

conduction abnormality, paravalvular complications, etc.) or belonging to a high-risk group (acute IE, aortic valve disease, prosthetic valve, or IE caused by *S. aureus* or other virulent organisms) [6]. Although it seems reasonable that such patients should remain at the hospital during the initial treatment phase, our findings suggest that this may not be the case for many patients after the critical phase. It is worth noting that a large proportion of patients who did fulfill OPAT-GAMES criteria would have been declined OPAT according to current guidelines for various reasons, for example, prosthetic IE (31% of patients), aortic valve involvement (46%), heart failure (23%), or staphylococcal etiologies (35%). Our findings indicate that none of these should constitute an exclusion criterion in isolation. Moreover, we found that 65.2% of patients who were fully treated at the hospital fulfilled OPAT-GAMES criteria, suggesting that a substantial proportion of these patients could have been safely transferred to OPAT at some point.

OPAT-GAMES criteria are based on the lack of resolution of complications or the difficulties in treating certain microorganisms or managing patients such as active intravenous drug users to rule out OPAT. Not fulfilling OPAT-GAMES criteria was significantly associated with a higher risk of readmission among OPAT patients in the multivariable analysis. Although these findings warrant further investigation, they appear to accurately identify those patients at higher risk of poor outcomes. Of note, contemporary cohorts of endocarditis patients in Western countries [20, 23, 24] widely differ from those of the late nineties; the criteria of Andrews and von Reyn were proposed in 2001. Moreover, hospital-at-home units and OPAT

Table 2. Logistic Regression Analysis of Risk Factors for Readmission Among OPAT Patients

	Univariate Model		Multivariable Model	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Male sex	0.81 (0.60–1.09)	.60		
Age, y	1.01 (1.00–1.02)	.02	1.01 (0.99–1.02)	.30
Age-adjusted Charlson score	1.07 (1.01–1.12)	.01	1.04 (0.98–1.10)	.21
Prosthetic endocarditis	1.40 (1.05–1.88)	.02	1.26 (0.93–1.71)	.13
Aortic valve involvement	0.82 (0.62–1.08)	.16		
Perivalvular abscess	1.11 (0.75–1.66)	.14		
Staphylococcus aureus	0.99 (0.69–1.43)	.96		
Persistent bacteremia	1.59 (1.05–2.42)	.03	1.35 (0.86–2.10)	.19
Central nervous system emboli	0.97 (0.63–1.50)	.89		
Other emboli	1.48 (1.07–2.06)	.02	1.41 (0.97–2.06)	.07
Septic shock	0.91 (0.48–1.72)	.76		
Splenic abscess	2.07 (1.10–3.90)	.02	1.49 (0.73–3.05)	.27
Renal abscess	1.09 (0.40–2.95)	.86		
Cardiac surgery during admission	0.69 (0.52–0.92)	.01	0.72 (0.53–0.98)	.03
Not fulfilling OPAT-GAMES criteria	1.51 (1.11–2.05)	.009	1.43 (1.03–1.97)	.03

Abbreviations: GAMES, Grupos de Apoyo al Manejo de la Endocarditis en ESpaña; OPAT, outpatient parenteral antibiotic treatment; OR, odds ratio.

programs in general have gained experience and increasingly showed better outcomes for a variety of serious infectious diseases.

Remarkably, a large proportion of OPAT patients not fulfilling OPAT-GAMES criteria did not fulfill the criteria because they had paravalvular complications such as periannular abscesses, fistulas, or pseudoaneurysms and did not receive cardiac surgery, and therefore a palliative rather than curative approach was adopted. This is likely one important reason why cardiac surgery was associated with lower risk of readmission in the multivariable analysis. According to OPAT-GAMES criteria, transfer to OPAT (either at the patient's home or a long-term care facility) for palliative purposes is also possible after careful discussion and agreement with the patient and/or relatives. Remarkably, another reason for not fulfilling the OPAT-GAMES criteria in our cohort was severe complications after cardiac surgery, such as mediastinitis or ventilator-related pneumonia.

While further evidence is gathered to elucidate which criteria should be applied for the more complex, fragile, or severe patients, we advocate for the use of less restrictive criteria than those of Andrews and von Reyn for deciding OPAT in IE, including more liberal recommendations to be included in the coming versions of international IE guidelines. Of course, in order to ensure that the new set of criteria is safely applied, OPAT programs should comply with the necessary requirements such as experienced medical and nursing staff, daily visits, follow-up supported by telehealth tools, etc., and patients

Table 3. Propensity Score Analysis 2:1 Comparing Patients Fully Treated at the Hospital (HBAT) vs Patients Transferred to OPAT

	HBAT (n = 1116)	OPAT (n = 558)	*P*
Median age (IQR), y	68 (55–77)	69 (57–77)	.456
Male sex, No. (%)	765 (68.5)	376 (67.4)	.631
Comorbidities			
Diabetes mellitus	276 (24.7)	164 (29.4)	.045
Chronic lung disease	213 (19.1)	99 (17.7)	.502
Ischemic cardiomyopathy	317 (28.4)	144 (25.8)	.257
Congestive heart failure	367 (32.9)	193 (34.6)	.488
Moderate/severe liver disease	26 (2.3)	12 (2.2)	.814
Moderate/severe chronic renal failure	157 (14.1)	69 (12.4)	.328
Neoplasm	146 (13.1)	99 (17.7)	.015
Transplantation	19 (1.7)	10 (1.8)	.896
Immunosuppressant therapy	49 (4.4)	47 (8.4)	.002
HIV	9 (0.8)	6 (1.1)	.600
Previous IE	90 (8.1)	38 (6.8)	.350
Congenital heart disease	101 (9.1)	36 (6.5)	.054
Natural valve disease	487 (43.6)	244 (43.7)	.972
Median age-adjusted Charlson score (IQR)	4 (3–6)	4 (3–6)	.729
Type of endocarditis			
Native	663 (59.4)	325 (58.2)	.648
Prosthetic	309 (27.7)	149 (26.7)	.669
CIED	176 (15.8)	101 (18.1)	.235
Valve involvement			
Aortic	528 (47.3)	254 (45.5)	.488
Mitral	422 (37.8)	211 (37.8)	1.000
Tricuspid	66 (5.9)	28 (5.0)	.441
Pulmonary	26 (2.3)	4 (0.7)	.005
Causative microorganism			
S. aureus	214 (19.2)	101 (18.1)	.593
Coagulase-negative staphylococci	216 (19.4)	90 (16.1)	.010
Enterococci	170 (15.2)	65 (11.6)	.046
Streptococci	307 (27.5)	177 (31.7)	.077
Candida spp.	8 (0.7)	9 (1.6)	.129
Unknown	104 (9.3)	41 (7.3)	.161
Acquisition			
Community	681 (61.0)	347 (62.2)	.644
Health care associated			
Nosocomial	292 (26.2)	143 (25.6)	.813
Non-nosocomial health care associated	111 (9.9)	40 (7.2)	.049
Complications			
Persistent bacteremia	96 (8.6)	56 (10.0)	.347
Central nervous system emboli	131 (11.7)	45 (8.1)	.015
Other major emboli	199 (17.8)	101 (18.1)	.893
Pulmonary emboli	41 (3.7)	19 (3.4)	.778
Vertebral osteomyelitis	24 (2.2)	25 (4.5)	.017
Nonvertebral osteomyelitis	12 (1.1)	16 (2.9)	.020
Renal abscess	12 (1.1)	8 (1.4)	.544
Splenic abscess	39 (3.5)	15 (2.7)	.359
TEE performed	900 (80.6)	471 (84.4)	.052
New-onset or worsening heart failure	337 (30.2)	142 (25.4)	.039
Septic shock	51 (4.6)	23 (4.1)	.669
Perivalvular abscess	94 (8.4)	43 (7.7)	.609

Table 3. Continued

	HBAT (n = 1116)	OPAT (n = 558)	*P*
Intracardiac fistula	16 (1.4)	2 (0.4)	.014
Pseudoaneurysm	43 (3.9)	11 (2.0)	.022
Leaflet perforation/rupture	104 (9.3)	36 (6.5)	.035
Treatment characteristics			
Median length of stay (IQR), d			
Total	40 (26–51)	45 (38–58)	<.001
OPAT		18 (13–30)	-
Median length of antibiotic treatment (IQR), d	40 (28–44)	42 (32–50)	<.001
Cardiac surgery			
During admission	529 (47.4)	235 (42.1)	.040
After discharge up to 1 y	40 (3.6)	30 (5.4)	.105
EuroScore, median (IQR)	9 (6–12)	9 (6–11)	.122
LogEuroScore, median (IQR)	14.8 (6.8–29.8)	13.1 (5.9–27.2)	.136
Outcomes			
Readmissions	156 (14.0)	86 (15.4)	.438
1-y mortality	92 (8.2)	45 (8.1)	.899
IE-related	33 (3.0)	15 (2.7)	.752
Non-IE related	59 (5.3)	30 (5.4)	.939
Recurrences	22 (2.0)	14 (2.6)	.475
Relapses	13 (1.2)	7 (1.3)	.875
Reinfections	9 (0.8)	7 (1.3)	.409

Three hundred sixty-nine patients (24.8%) fulfilling OPAT-GAMES criteria in the HBAT group were not included in the propensity score analysis, whereas 403 (41.9%) of the OPAT patients fulfilling OPAT-GAMES criteria were not included because no matching with HBAT patients was found. Variables used for matching: age, sex, type of endocarditis (native, prosthetic, and cardiovascular implantable electronic devices) and OPAT-GAMES exclusion criteria (Child B or C liver cirrhosis, severe central nervous system, not drained large splenic or renal abscess, vertebral abscesses requiring neurosurgery, periannular complications or other severe conditions requiring surgery when this is contraindicated, severe postsurgical complications, highly difficult-to-treat microorganisms).

Abbreviations: CIED, cardiovascular implantable electronic devices; GAMES, Grupos de Apoyo al Manejo de la Endocarditis en ESpaña; HBAT, hospital-based antibiotic treatment; IE, infective endocarditis; IQR, interquartile range; OPAT, outpatient parenteral antibiotic treatment; TEE, transesophageal echocardiography.

presenting clinical complications should be kept at the hospital for at least the time necessary to restore organic function and rule out early recurrences. These decisions should take place as part of endocarditis teams' [7, 25–27] routine in each site.

This study is constrained by several limitations. First, it was not randomized, and the OPAT-GAMES criteria were not systematically applied. The use of a propensity analysis tries to partially overcome this design shortcoming. Second, a notable proportion of patients in the OPAT group not fulfilling OPAT-GAMES criteria did not receive cardiac surgery when indicated because they were deemed unfit for aggressive therapeutic measures, therefore constituting a "palliative care" subgroup that might have biased the outcomes of this subgroup of patients. Third, as most of the GAMES centers are reference hospitals for cardiac surgery, there could be a reference bias. In addition, most GAMES centers have extensive experience treating IE through OPAT programs using hospital-at-home units, which might limit the external validity of our findings. The nationwide scope of the GAMES cohort, the first nationwide experience on OPAT for IE, at least partially overcomes these limitations.

In conclusion, OPAT can be safely administered using less restrictive criteria than those currently recommended in a substantial proportion of patients with IE. The OPAT-GAMES criteria allow identification of those patients at higher risk of long-term complications. International guidelines for IE should adopt more liberal criteria for indicating OPAT in upcoming versions.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All the authors listed in the contributors' affiliations meet the ICMJE Authorship Criteria; that is, they substantially contributed to conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

APPENDIX

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