

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

Juan M. Pericàs,^{1,2,a} Jaume Llopis,^{1,3,a} Patricia Muñoz,^{4,6} Víctor González-Ramallo,⁴ M. Eugenia García-Leoni,⁴ Aristides de Alarcón,⁵ Rafael Luque,⁵ M. Carmen Fariñas,⁶ Miguel Á. Goenaga,⁷ Marta Hernández-Meneses,¹ David Nicolás,¹ Antonio Ramos-Martínez,⁸ M. Ángeles Rodríguez-Esteban,⁹ Aroa Villoslada-Gelabert,¹⁰ and José M. Miró,^{1,11} on behalf of the GAMES Investigators^b

¹Hospital Clínic de Barcelona, Institut de Recerca Augusti Pi i Sunyer, Universitat de Barcelona, Barcelona, Spain, ²Liver Unit, Internal Medicine Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute for Research, CIBER Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain, ³Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain, ⁴Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain, ⁵Clinical Unit of Infectious Diseases, Microbiology and Preventive Medicine Infectious Diseases Research Group, Institute of Biomedicine of Seville (IBIS), University of Seville/CSIC/University Virgen del Rocío and Virgen Macarena, Seville, Spain, ⁶Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain, ⁷Hospital Donostia, San Sebastián, Spain, ⁸Unidad de Enfermedades Infecciosas, Servicio de Medicina Interna, Universitario Puerta de Hierro, Majadahonda, Madrid, Spain, ⁹Servicio de Medicina Intensiva, Hospital Central de Asturias, Oviedo, Spain, ¹⁰Servicio de Medicina Interna-Enfermedades Infecciosas, Hospital Son Llàtzer, Palma de Mallorca, Balearic Islands, Spain, and ¹¹CIBERINFECC. Instituto de Salud Carlos III, Madrid, Spain

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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^aEqual contribution.

^bMembers are listed in the Appendix.

Correspondence: José M. Miró, MD, PhD, Infectious Diseases Service, Hospital Clínic, Villarroel, 170. 08036 - Barcelona, Spain (jmmiro@ub.edu).

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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

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 <i>Staphylococcus aureus</i> 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 <i>Candida</i> spp.)
8. Active intravenous drug users

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

^aExcept 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.

^bTransfer 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.

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].

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,

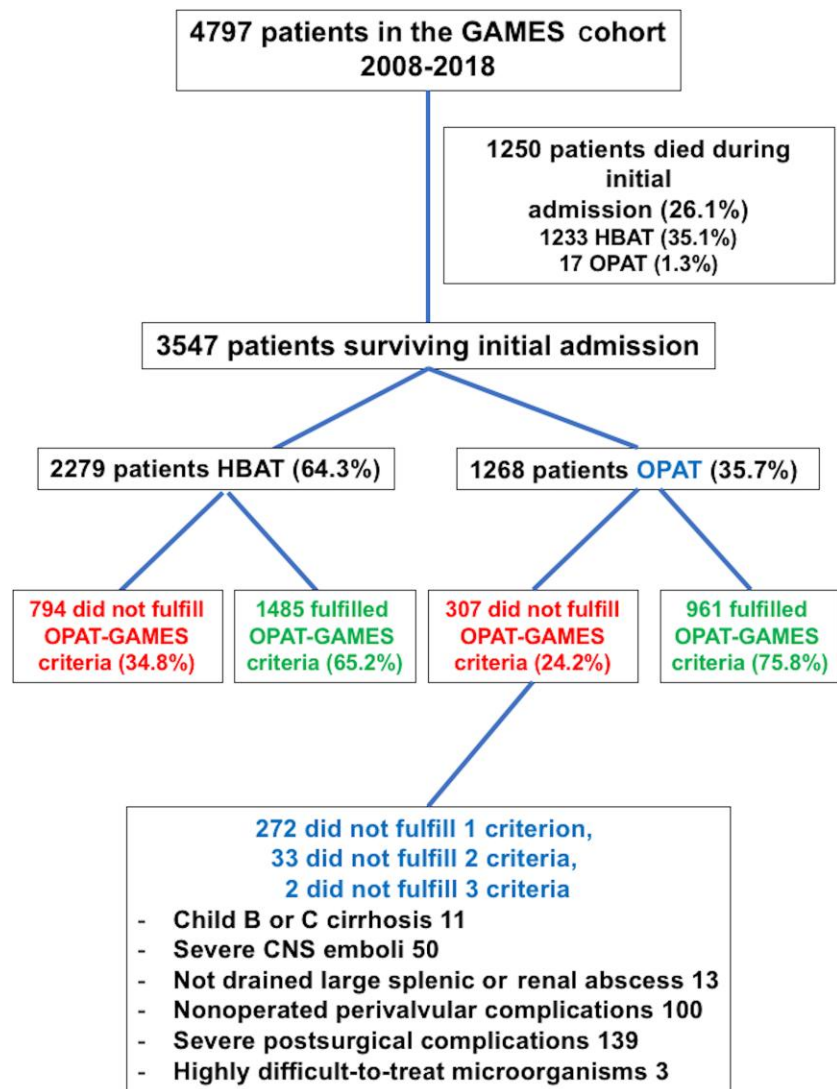


Figure 1. Flowchart of patients' dispositions. Abbreviations: CNS, central nervous system; GAMES, Grupos de Apoyo al Manejo de la Endocarditis en España; HBAT, hospital-based antibiotic treatment; OPAT, outpatient parenteral antibiotic treatment.

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

Variables	Univariate Model		Multivariable Model	
	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		
<i>Staphylococcus aureus</i>	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			
<i>S. aureus</i>	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
<i>Candida</i> 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

GAMES investigators. Hospital Costa del Sol (Marbella): Fernando Fernández Sánchez, Mariam Noureddine, Gabriel Rosas, Javier de la Torre Lima; Hospital Universitario de Cruces (Bilbao): Elena Bereciartua, Roberto Blanco, María Victoria Boado, Marta Campaña Lázaro, Alejandro Crespo, Laura Guio Carrión, Mikel Del Álamo Martínez de Lagos, Gorane Euba Ugarte, Josune Goikoetxea, Marta Ibarrola Hierro, José Ramón Iruetagoiena, Josu Irurzun Zuazabal, Leire López-Soria, Miguel Montejo, Javier Nieto, David Rodrigo, Regino Rodríguez, Yolanda Vitoria, Roberto Voces; Hospital Universitario Virgen de la Victoria (Málaga): M^a Victoria García López, Radka Ivanova Georgieva, Guillermo Ojeda, Isabel Rodríguez Bailón, Josefa Ruiz Morales; Hospital Universitario Donostia-Poliklinika Gipuzkoa-IIS Biodonostia (San Sebastián): Harkaitz Azkune Galparsoro, Elisa Berritu Boronat, M^a Jesús Bustinduy Odriozola, Cristina del Bosque Martín, Tomás Echeverría, Alberto Eizaguirre Yarza, Ana Fuentes, Miguel Ángel Goenaga, Muskilda Goyeneche del Río, Ángela Granda Bauza, José Antonio Iribarren, Xabier Kortajarena Urkola, José Ignacio Pérez-Moreiras López, Ainhoa Rengel Jiménez, Karlos Reviejo, Alberto Sáez Berbejillo, Elou Sánchez Haza, Rosa Sebastián Alda, Itziar Solla Ruiz, Irati Unamuno Ugartemendia, Diego Vicente Anza, Iñaki Villanueva Benito, Mar Zabalo Arrieta; Hospital General Universitario de Alicante (Alicante): Rafael Carrasco, Vicente Climent, Patricio Llamas, Esperanza Merino, Joaquín Plazas, Sergio Reus; Complejo Hospitalario Universitario A Coruña (A Coruña): Nemesio Álvarez, José María Bravo-Ferrer, Laura Castelo, José Cuenca,

Pedro Llinares, Enrique Miguez Rey, María Rodríguez Mayo, Efrén Sánchez, Dolores Sousa Regueiro; Complejo Hospitalario Universitario de Huelva (Huelva): Francisco Javier Martínez; Hospital Universitario de Canarias (Canarias): M^a del Mar Alonso, Beatriz Castro, Teresa Delgado Melian, Javier Fernández Sarabia, Dácil García Rosado, Julia González González, Juan Lacalzada, Lissete Lorenzo de la Peña, Alina Pérez Ramírez, Pablo Prada Arrendo, Fermín Rodríguez Moreno; Hospital Regional Universitario de Málaga (Málaga): Antonio Plata Ciezar, José M^a Reguera Iglesias; Hospital Universitario Central Asturias (Oviedo): Víctor Asensi Álvarez, Carlos Costas, Jesús de la Hera, Jonnathan Fernández Suárez, Lisardo Iglesias Fraile, Víctor León Arguero, José López Menéndez, Pilar Mencía Bajo, Carlos Morales, Alfonso Moreno Torrico, Carmen Palomo, Begoña Paya Martínez, Ángeles Rodríguez Esteban, Raquel Rodríguez García, Mauricio Telenti Asensio; Hospital Clínic-IDIBAPS, Universidad de Barcelona (Barcelona): Manuel Almela, Juan Ambrosioni, Manel Azqueta, Mercè Brunet, Marta Bodro, Ramón Cartañá, Guillermo Cuervo, Carlos Falces, Guillermina Fita, David Fuster, Cristina García de la Mària, Delia García-Pares, Marta Hernández-Meneses, Jaume Llopis Pérez, Francesc Marco, José M. Miró, Asunción Moreno, David Nicolás, Salvador Ninot, Eduardo Quintana, Carlos Paré, Daniel Pereda, Juan M. Pericàs, José L. Pomar, José Ramírez, Irene Rovira, Elena Sandoval, Marta Sitges, Dolors Soy, Adrián Téllez, José M. Tolosana, Bárbara Vidal, Jordi Vila; Hospital General Universitario Gregorio Marañón (Madrid): Iván Adán, Juan Carlos Alonso, Ana Álvarez-Uría, Javier Bermejo, Emilio Bouza, Gregorio Cuerpo Caballero, Antonia Delgado Montero, Ana González Mansilla, M^a Eugenia García Leoni, Esther Gargallo, Víctor González Ramallo, Martha Kestler Hernández, Amaia Mari Hualde, Marina Machado, Mercedes Marín, Manuel Martínez-Sellés, Patricia Muñoz, María Olmedo, Álvaro Pedraz, Blanca Pinilla, Ángel Pinto, Cristina Rincón, Hugo Rodríguez-Abella, Marta Rodríguez-Créixems, Antonio Segado, Neera Toledo, Maricela Valerio, Pilar Vázquez, Eduardo Verde Moreno; Hospital Universitario La Paz (Madrid): Isabel Antorrena, Belén Loeches, Mar Moreno, Ulises Ramírez, Verónica Rial Bastón, María Romero, Sandra Rosillo; Hospital Universitario Marqués de Valdecilla (Santander): Hospital Universitario Marqués de Valdecilla (Santander): Jesús Agüero Balbín, Cristina Amado, Carlos Armiñanzas Castillo, Ana Arnaiz, Francisco Arnaiz de las Revillas, Manuel Cobo Belaustegui, María Carmen Fariñas, Concepción Fariñas-Álvarez, Marta Fernández Sampedro, Iván García, Claudia González Rico, Laura Gutierrez-Fernandez, Manuel Gutiérrez-Cuadra, José Gutiérrez Díez, Marcos Pajarón, José Antonio Parra, Ramón Teira, Jesús Zarauza; Hospital Universitario Puerta de Hierro (Madrid): Jorge Calderón Parra, Marta Cobo, Fernando Domínguez, Alberto Fortaleza, Pablo García Pavía, Jesús González, Ana Fernández Cruz, Elena Muñoz, Antonio Ramos, Isabel Sánchez Romero; Hospital Universitario Ramón y Cajal (Madrid): Tomasa Centella, José Manuel Hermida, José Luis Moya, Pilar Martín-Dávila, Enrique Navas, Enrique Oliva, Alejandro del Río, Jorge Rodríguez-Roda Stuart, Soledad Ruiz; Hospital Universitario Virgen de las Nieves (Granada): Carmen Hidalgo Tenorio; Hospital Universitario Virgen Macarena (Sevilla): Manuel Almendro Delia, Omar Araji, José Miguel Barquero, Román Calvo Jambriña, Marina de Cueto, Juan Gálvez Acebal, Irene Méndez, Isabel Morales, Luis Eduardo López-Cortés; Hospital Universitario Virgen del Rocío (Sevilla): Aristides de Alarcón, Emilio García, Juan Luis Haro, José Antonio Lepe, Francisco López, Rafael Luque; Hospital San Pedro (Logroño): Luis Javier Alonso, Pedro Azcárate, José Manuel Azcona Gutiérrez, José Ramón Blanco, Antonio Cabrera Villegas, Lara García-Álvarez, Concepción García García, José Antonio Oteo; Hospital de la Santa Creu i Sant Pau (Barcelona): Natividad de Benito, Mercè Gurguí, Cristina Pacho, Roser Pericas, Guillem Pons; Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña): M. Álvarez, A. L. Fernández, Amparo Martínez, A. Prieto, Benito Regueiro, E. Tijeira, Marino Vega; Hospital Santiago Apóstol (Vitoria): Andrés Canut Blasco, José Cordo Mollar, Juan Carlos Gainzarain Arana, Oscar García Uriarte, Alejandro Martín López, Zuriñe Ortiz de Zárate, José Antonio Urturi Matos; Hospital SAS Línea de la Concepción (Cádiz): Sánchez-Porto Antonio, Úbeda Iglesias Alejandro;

Hospital Clínico Universitario Virgen de la Arrixaca (Murcia): José M^a Arribas Leal, Elisa García Vázquez, Alicia Hernández Torres, Ana Blázquez, Gonzalo de la Morena Valenzuela; Hospital de Txagorritxu (Vitoria): Ángel Alonso, Javier Aramburu, Felicitas Elena Calvo, Anai Moreno Rodríguez, Paola Tarabini-Castellani; Hospital Virgen de la Salud (Toledo): Eva Heredero Gálvez, Carolina Maicas Bellido, José Largo Pau, M^a Antonia Sepúlveda, Pilar Toledano Sierra, Sadaf Zafar Iqbal-Mirza; Hospital Rafael Méndez (Lorca-Murcia):, Eva Cascales Alcolea, Ivan Keituqwa Yañez, Julián Navarro Martínez, Ana Peláez Ballesta; Hospital Universitario San Cecilio (Granada): Eduardo Moreno Escobar, Alejandro Peña Monje, Valme Sánchez Cabrera, David Vinuesa García; Hospital Son Llàtzer (Palma de Mallorca): María Arrizabalaga Asenjo, Carmen Cifuentes Luna, Juana Núñez Morcillo, M^a Cruz Pérez Seco, Aroa Villoslada Gelabert; Hospital Universitario Miguel Servet (Zaragoza): Carmen Aured Guallar, Nuria Fernández Abad, Pilar García Mangas, Marta Matamala Adell, M^a Pilar Palacián Ruiz, Juan Carlos Porres; Hospital General Universitario Santa Lucía (Cartagena): Begoña Alcaraz Vidal, Nazaret Cobos Triguero, María Jesús Del Amor Espín, José Antonio Giner Caro, Roberto Jiménez Sánchez, Amaya Jimeno Almazán, Alejandro Ortín Freire, Monserrat Viqueira González; Hospital Universitario Son Espases (Palma de Mallorca): Pere Pericàs Ramis, M^a Àngels Ribas Blanco, Enrique Ruiz de Gopegui Bordes, Laura Vidal Bonet; Complejo Hospitalario Universitario de Albacete (Albacete): M^a Carmen Bellón Munera, Elena Escribano Garaizabal, Antonia Tercero Martínez, Juan Carlos Segura Luque; Hospital Universitario Terrassa: Cristina Badía, Lucía Boix Palop, Mariona Xercavins, Sónia Ibars; Hospital Universitario Dr. Negrín (Gran Canaria): Xerach Bosch, Eloy Gómez Nebreda, Ibalia Horcajada Herrera, Irene Menduñía Gallego, Imanol Pulido; Complejo Hospitalario Universitario Insular Materno Infantil (Las Palmas de Gran Canaria): Héctor Marrero Santiago, Isabel de Miguel Martínez, Elena Pisos Álamo; Hospital Universitario 12 de Octubre (Madrid): Eva M^a Aguilar Blanco, Mercedes Catalán González, María Angélica Corres Peiretti, Andrea Eixerés Esteve, Laura Domínguez Pérez, Santiago de Cossío Tejido, Francisco Galván Román, José Antonio García Robles, Francisco López Medrano, M^a Jesús López Gude, M^a Ángeles Orellana Miguel, Patrick Pilkington, Yolanda Revilla Ostalaza, Juan Ruiz Morales, Sebastián Ruiz Solís, Ana Sabín Collado, Marcos Sánchez Fernández, Javier Solera Rallo, Jorge Solís Martín; Hospital Universitari de Bellvitge (L'Hospitalet de Llobregat): Francisca Escrihuela-Vidal, Jordi Carratalá, Inmaculada Grau, Sara Grillo, Carmen Ardanuy, Dámaris Berbel, José Carlos Sánchez Salado, Oriol Alegre, Alejandro Ruiz Majoral, Fabrizio Sbraga, Arnau Blasco, Laura Gracia Sánchez, Iván Sánchez-Rodríguez; Hospital Universitario Fundación Jiménez Díaz (Madrid): Beatriz Álvarez, Alfonso Cabello Úbeda, Ricardo Fernández Roblas, Miguel Ángel Navas Lobato, Ana María Pello; Hospital Basurto (Bilbao): Mireia de la Peña Triguero, Ruth Esther Figueroa Cerón, Lara Ruiz Gómez; Hospital del Mar (Barcelona): Mireia Ble, Juan Pablo Horcajada Gallego, Antonio José Ginel, Inmaculada López, Alexandra Mas, Antoni Mestres, Lluís Molina, Ramón Serrat, Núria Ribas, Francisca Sánchez, Ana Silverio, Marina Suárez, Luisa Sorlí, Lluís Recasens, Manuel Taurón.

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