Title: Outpatient Parenteral Antibiotic Treatment (OPAT) for Infective Endocarditis: a Prospective Cohort Study From the GAMES Cohort.

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Summary: The use of OPAT for treatment of IE patients using less restrictive criteria than those proposed by the IDSA was efficacious and safe.

The data presented in this study were reported in part at the 3rd Conference of the Spanish Society for Cardiovascular Infections (SEICAV), October 23-25 2014, Málaga, Spain, and at the 19th Conference of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC), May 26-28, Barcelona, Spain.

Abstract

Background: Outpatient parenteral antibiotic treatment (OPAT) has proven efficacious and safe for treating infective endocarditis (IE). However, the 2001 IDSA criteria for OPAT in IE are very restrictive. We aimed to compare the outcomes of OPAT with those of hospital-based antibiotic treatment (HBAT).

Methods: Retrospective analysis of data from a multicenter prospective cohort study of 2,000 consecutive IE patients in 25 Spanish hospitals from 2008 to 2012.

Results: A total of 429 patients (21.5%) received OPAT, and only 21.7% fulfilled IDSA criteria. Males accounted for 70.5%, median age was 68 years (IQR 56-76), 57% had native-valve IE, 27% had prosthetic-valve IE, and 19% had pacemaker/defibrillator IE. The most frequent causal microorganisms were viridans group streptococci (18.6%), *Staphylococcus aureus* (15.6%), and coagulase-negative staphylococci (14.5%). The median length of antibiotic treatment was 42 days (IQR 32-54), and 44% of patients underwent cardiac surgery. One-year mortality was 8% (42% for HBAT; P<0.001), 1.4% of patients relapsed, and 10.9% were readmitted during the first three months after discharge (no significant differences compared with HBAT). Charlson score (OR 1.21, 95%CI 1.04-1.42; P=0.01) and cardiac surgery (OR 0.24, 95%CI 0.09-0.63; P=0.04) were associated with one-year mortality, whereas aortic valve involvement (OR 0.47, 95%CI 0.22-0.98; P=0.007) was the only predictor of readmission at one year. Failing to fulfill IDSA criteria was not a risk factor for mortality or readmission.

Conclusions: OPAT provided excellent results despite the use of broader criteria than those recommended by IDSA; OPAT criteria should therefore be expanded.

Keywords: Infective endocarditis, outpatient parenteral antibiotic treatment, outcomes, hospitalization, relapses, readmission.

Introduction

Outpatient parenteral antibiotic treatment (OPAT) is a reliable alternative to conventional hospitalization in a wide range of infectious diseases owing to its efficacy, safety, and lower cost in well-selected patients [1-5].

In 2001, the Infectious Diseases Society of America (IDSA) established a set of criteria to select infective endocarditis (IE) patients who were potential candidates for safe completion of antibiotic treatment using OPAT [6]. These recommendations to assess OPAT candidates with IE remain in force and are included in both AHA and ESC guidelines for IE [7,8]. Briefly, the criteria are characterized by restrictive principles, namely, only considering as potential OPAT candidates those patients with non-complicated left-sided mitral or right-sided native-valve IE (NVIE) caused by non-aggressive, easy-to-treat streptococci (mostly from the viridans group) with neither indications for cardiac surgery nor clinical, echocardiographic, or microbiological complications [6]. However, a large proportion of patients included in available reports on OPAT programs from teams with extensive experience in OPAT and IE do not fulfill IDSA criteria [9-26]. As shown in **Table 2**, the results of these studies indicate that failing to follow IDSA criteria diligently does not lead to significantly worse outcomes.

Given the substantial changes in the epidemiology and clinical presentation of IE in recent decades [27] and the fact that the disease requires several weeks of antibiotic treatment, both the personal and the economic costs of long hospital stays for elderly patients pose a challenge to clinicians and policymakers in charge of health services and planning. OPAT is a good alternative for shortening the length of hospital admission while preserving

patients' safety and convenience of treatment. Expanding its use might lead to an improvement in the subjective wellbeing of patients, a reduction in nosocomial infections, and optimization of budget allocations [28].

This study describes the characteristics and outcomes of IE patients from the GAMES cohort included in OPAT programs during the period 2008-12 and compares them with those of patients who completed antibiotic treatment in hospitals in order to address whether the failure to fulfill IDSA criteria was associated with worse outcomes. We also propose a new set of criteria for indication of OPAT in IE patients.

Methods

Design: Multicenter prospective observational study including 25 Spanish centers between 2008 and 2012. The characteristics of the GAMES cohort, collection of data through a specific central registration depository, and definitions are described elsewhere [29]. Importantly, OPAT was defined as home administration of intravenous antibiotic therapy, with a daily visit by skilled nurses and at least two visits per week by the attending physician. Persistent bacteremia was defined as positive blood cultures beyond seven days of effective antibiotic therapy. Heart failure was categorized according to the NYHA scale (I-IV). These and other reported clinical complications occurred at admission or early in hospitalization. Sequelae at discharge or transfer to OPAT were considered moderate when they involved a significant reduction in patients' activity (e.g. partial hemiplegia or NYHA III heart failure) and severe when associated with almost complete invalidity (complete hemiplegia or dyspnea at rest). A relapse was a new episode of IE due to the same microorganism within the six months following the initial episode. Acute renal failure was defined in the data collection sheet as a decrease of ≥25% of serum creatinine or glomerular clearance within 72 hours.

Patients: Adult individuals with definite or possible IE diagnosed according to the modified Duke criteria [30] who survived the initial admission and had completed at least one year of follow-up. The decision to prescribe OPAT or hospital-based antibiotic treatment (HBAT) was taken independently by the attending physicians in each center according to the criteria shown in **Table 1,** which are in line with the recommendations for OPAT by the Spanish Society of Clinical Microbiology and Infectious Diseases [31]. The characteristics of 95

(22.1%) OPAT patients (70 and 25 patients out of 149 and 48 included, respectively, in both reports) have already been reported by Goenaga et al [22] and Pajarón et al [24].

Exclusion criteria: Intravenous drug users (IDUs) were excluded because they were not considered suitable candidates for OPAT: the IDSA criteria were not clear in this respect [6] and no conclusive evidence was published during the study period. Likewise, patients who died during the first admission of the IE episode were excluded from the analysis, as they could not be assessed for OPAT and did not receive a complete course of antibiotic treatment.

Fulfillment of IDSA criteria for OPAT (shown in **Supplementary Table 1**): This was evaluated as a binary variable (yes/no) in all patients receiving OPAT. A patient was considered to fulfill IDSA criteria if he/she (i) had non-aortic NVIE caused by viridans group streptococci (and other non-aggressive microorganisms upon consultation with an infectious-diseases expert), (ii) did not present heart failure (NYHA ≥2), periannular complications (perivalvular abscess, fistula, or pseudoaneurysm), septic shock, or major emboli, and (iii) did not have any indication for cardiac surgery at the time he/she was assessed for OPAT. The same criteria were applied during the review of articles from the literature reporting OPAT experiences in IE (**Table 2**).

Outcomes: Readmissions for any cause at 90 days, cardiac surgery within the first year after discharge, relapses, and one-year mortality.

Statistical analysis: Categorical variables were summarized as percentages and continuous variables as means and standard deviations. Categorical variables were compared using the chi-square test (or Fisher's exact test where necessary). Continuous variables were compared using the Kruskal-Wallis test.

A logistic regression model that included variables with P<0.30 in the univariate analysis was used for the analysis of risk factors of mortality and readmission. A two-sided P<0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, Illinois, USA).

Results

The study flowchart is shown in **Figure 1,** and the baseline characteristics of the 429 patients in the OPAT group and the 1,003 HBAT patients are shown in **Table 3**.

Comorbidities did not differ significantly between the two groups, with the exception of liver disease and long-term hemodialysis, which were more frequent in the HBAT group (3.6% vs. 1.4%; P=0.007, and 4.3% vs. 1.6%: P=0.003, respectively), and immunosuppressive therapy, which was more frequent in the OPAT group (4.1% vs. 7%; P=0.036). In the OPAT group, only 57.1% of cases were NVIE, while the percentage of cardiac implantable electronic device–related IE (CIED-IE) was significantly higher in the OPAT group than in the HBAT group. The most common causative agents were *S. aureus*, viridans group streptococci, and CoNS, enterococci. Enterococci were significantly more frequent among HBAT patients, as occurred with *S. agalactiae*, whereas IE caused by fungi and *Coxiella burnetii* was significantly more common among OPAT patients. Sources of acquisition did not differ between HBAT and OPAT patients, with community acquisition being the most common form in both groups.

Clinical complications and characteristics of therapy from admission to hospital discharge (HBAT) or transfer to OPAT are shown in **Table 4**. Only 21.7% of patients in the OPAT group fulfilled the criteria of the IDSA. In the hospital group, new-onset heart failure, hemorrhagic central nervous system (CNS) emboli, acute renal failure, severe aortic regurgitation, periannular complications, and leaflet perforation/rupture were significantly more frequent. However, these and other complications occurring during hospital admission

were not absent from the OPAT group, where, for instance, 29% presented new-onset heart failure, 9.8% perivalvular abscesses, 13.8% severe aortic regurgitation, 8.2% persistent bacteremia, and 8.4% CNS emboli. Significantly fewer patients in the OPAT group received vancomycin and gentamicin (26.2% vs. 20.7%, P=0.023, and 50.2% vs. 43.6%, P=0.02, respectively).

Although the rate of cardiac surgery was significantly higher in the HBAT group, a large proportion of OPAT (44.3%) patients did in fact undergo surgery. Patients from the HBAT group had significantly more severe sequelae at discharge than patients from the OPAT group at the time of transfer to home therapy and also presented significantly higher rates of poor heart function (NYHA class III or IV) at one year. No significant differences were observed between the groups for readmissions during the three months after discharge and relapses; however, mortality at one year was significantly higher in the HBAT group. The percentage of patients requiring cardiac surgery after discharge up to one year did not significantly differ between the two groups (**Table 4**). Median times to discharge from admission or cardiac surgery by native and prosthetic valve and type of microorganisms are shown in **Supplementary Table 2**. Although overall times were shorter for OPAT, when these subgroups were compared by microorganism, not all differences reached statistical significance, e.g., in cases due to *E. faecalis* and *S. aureus* in patients who did not undergo surgery. Causes of readmission and etiology of relapses are shown in **Supplementary Table 3**. Baseline characteristics, clinical and therapeutic features, and outcomes of prosthetic valve IE, CIED-IE, and patients undergoing cardiac surgery are shown separately in **Supplementary Tables 4, 5, and 6**, respectively.

Age-adjusted Charlson score was the only risk factor for one-year mortality found among OPAT patients in the multivariate model, whereas cardiac surgery was found to be a protective factor (**Table 5**). With regard to readmission, no risk factors were identified, whereas aortic valve involvement was shown to be a protective factor.

Discussion

More than one fifth of IE patients included in the GAMES cohort from 2008 to 2012 received OPAT. This is the largest study to date showing the safety and efficacy of OPAT in treating IE. However, it is not the first to describe the potential use of OPAT in patients who fail to meet the criteria proposed by Andrews and von Reyn more than 15 years ago [6]. Partridge et al, for instance, highlighted that more than two thirds of the patients included in their cohort would not have been deemed suitable for OPAT according to IDSA; however, more than 90% had successful outcomes [19]. The call for a broader use of OPAT in IE, which would require a modification of current guidelines, has gained support in the last decade [16-24,27].

In our study, worse outcomes were not associated with the type of IE (native valve–, prosthetic valve–, or CIED-related), valve involvement, presence of clinical and echocardiographic complications, specific comorbidities, or the type of microorganism causing the IE episode. Furthermore, there was a low incidence of causes of reinfection directly related to the performance of OPAT staff, such as catheter-related infections, issues associated with the intravenous line, urinary catheter–related infections, and antibiotic-related toxicity. Barely 22% of patients receiving OPAT in the GAMES cohort met IDSA criteria. Failing to fulfill IDSA criteria was not a risk factor for one-year mortality or readmission. Of note, 23.3% of HBAT patients also fulfilled the IDSA criteria. Therefore, a large proportion of patients traditionally considered to require hospitalization throughout the IE treatment period might not actually have required it. However, given that patients who were offered OPAT in our study had, in many ways, a less severe condition than those who continued to be treated at the hospital, the

better outcome for patients with OPAT does not necessarily mean that OPAT was the best solution for them.

Better-designed studies are required to clarify the causes and mechanisms leading to the outcomes observed in equivalent patients receiving either HBAT or OPAT. However, as a general rule, it seems reasonable to consider as candidates for OPAT all patients with endocarditis not caused by difficult-to-treat microorganisms requiring complex antibiotic combinations and not presenting clinical, echocardiographic, or post-surgical complications that have not resolved shortly after onset. Naturally, an individualized assessment of each patient performed by OPAT-skilled physicians might lead to rejection of OPAT for more specific reasons. General recommendations apply only to centers with established OPAT programs meeting all appropriate requirements, including a well-organized multidisciplinary team, excellent communication and monitoring systems, and proper physical and support conditions in the patients' homes or outpatient clinic [4,6,32-34].

Professionals should be aware of any evidence that enables better strategies and less severe criteria for OPAT in areas that are not assessed in this study. For example, we did not include IDUs, since the lack of relevant information led us to be cautious in order to avoid losses to follow-up or the use of the intravenous route to inject illicit drugs. However, recent studies have shown contradictory findings [26, 27], and well-selected and properly followed IDUs with endocarditis (i.e. by multidisciplinary teams including addiction specialists) might actually be safely treated with OPAT. This is particularly important in the USA owing to the recent increase in cases of endocarditis among IDUs associated with the opioid crisis [35]. We did not evaluate current strategies for

improved catheter care that reduce the risk of catheter-associated infection and other catheter-related complications [36].

A recently published randomized clinical trial (POET) [37] showed that selected IE patients can complete the latter part of their treatment with oral antimicrobials. This strategy should be incorporated into future studies of outpatient therapy for IE (vs. OPAT). Another area of interest in OPAT for endocarditis is the use of long-acting antimicrobials. Several anti–Gram-positive agents with specific pharmacokinetic and pharmacodynamic parameters allowing weekly administration are available, although they are not FDA- or EMA-approved for endocarditis. Such is the case of oritavancin and dalbavancin. Although specific evidence on IE remains scanty, a recent report including 27 patients with Gram-positive endocarditis using dalbavancin as both primary and sequential treatment showed promising results [38].

Appropriate interpretation of our results is subject to a series of limitations other than those presented above. First, the design did not allow for the matching of HBAT and OPAT patients. Second, there is remarkable heterogeneity with regard to OPAT experience among GAMES participating centers. Third, for some of these centers, a referral bias might have influenced the profile of HBAT patients in terms of severity and prognosis at admission and of the likelihood of cardiac surgery (not all GAMES participating centers have cardiac surgery departments). Fourth, the GAMES central registry was not designed to collect data specifically for OPAT, e.g., causes of readmission were not entered for all cases. Fifth, straightforward extrapolation of the results to other geographic areas is hampered by epidemiological aspects (e.g. rates of MRSA or non-nosocomial healthcare-associated acquisition compared with those reported in

North America). Sixth, the percentage of cases due to *S. aureus* is remarkably lower than in most general series owing to the exclusion of a large number of cases because of in-hospital mortality or intravenous drug use. Finally, the performance of early and late cardiac surgery as a prognostic factor was not assessed separately.

More than one fifth of patients in the GAMES cohort received OPAT during the period 2008-2012. Outcomes were excellent, in terms of both efficacy and safety. Consequently, the IDSA recommendations proposed more than 15 years ago should be replaced by less restrictive criteria.

Authorship: 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.

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References

1. Williams DN, Baker CA, Kind AC, Sannes MR. The history and evolution of outpatient parenteral antibiotic therapy (OPAT). Int J Antimicrob Agents **2015**; 46:307-12.

2. Petrak RM, Skorodin NC, Fliegelman RM, Hines DW, Chundi VV, Harting BP. Value and Clinical Impact of an Infectious Disease-Supervised Outpatient Parenteral Antibiotic Therapy Program. Open Forum Infect Dis **2016**; 3:ofw193.

3. Ross Nolet B. Update and overview of outpatient parenteral antimicrobial therapy regulations and reimbursement. Clin Infect Dis **2010**; 51 Suppl 2:S216-9.

4. Paladino JA, Poretz D. Outpatient parenteral antimicrobial therapy today. Clin Infect Dis **2010**; 51 Suppl 2:S198-208.

5. González-Ramallo VJ, Mirón-Rubio M, Mujal A, et al. Costs of outpatient parenteral antimicrobial therapy (OPAT) administered by Hospital at Home units in Spain. Int J Antimicrob Agents **2017**; 50:114-8.

6. Andrews MM, von Reyn CF. Patient selection criteria and management guidelines for outpatient parenteral antibiotic therapy for native valve infective endocarditis. Clin Infect Dis **2001**; 33:203-9.

7. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J **2015**; 36:3075-128.

8. Baddour LM, Wilson WR, Bayer AS, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A

Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation **2015**; 132:1435-86.

9. Kind AC, Williams DN, Persons G, Gibson JA. Intravenous antibiotic therapy at home. Arch Intern Med **1979**; 139:413–5.

10. Rehm SJ, Weinstein AJ. Home intravenous antibiotic therapy: a team approach. Ann Intern Med **1983**; 99:388–92.

11. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. Rev Infect Dis **1991**; 13:S160-3.

12. Francioli P, Etienne J, Hoigné R, Thys JP, Gerber A. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks. Efficacy and outpatient treatment feasibility. JAMA **1992**;267:264-7.

13. Graninger W, Presterl E, Wenisch C, Schwameis E, Breyer S, Vukovich T. Management of serious staphylococcal infections in the outpatient setting. Drugs **1997**; 54 Suppl 6 :S21–28.

14. Sexton DJ, Tenenbaum MJ, Wilson WR, et al. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible streptococci. Endocarditis Treatment Consortium Group. Clin Infect Dis **1998**; 27:1470–4.

15. Lopardo G. Management of endocarditis: outpatient parenteral antibiotic treatment in Argentina. Chemotherapy **2001**; 47 Suppl 1:24-32.

16. McMahon JH, O'Keeffe JM. Is hospital-in-the-home (HITH) treatment of bacterial endocarditis safe and effective? Scand J Infect Dis **2008**; 40:40–3.

17. Larioza J, Heung L, Girard A, Brown RB. Management of infective endocarditis in outpatients: Clinical experience with Outpatient Parenteral Antibiotic Therapy. South Med J **2009**; 102:575–9.

18. Cervera C, del Río A, García L, et al. Efficacy and safety of outpatient parenteral antibiotic therapy for infective endocarditis: a ten-year prospective study. Enferm Infecc Microbiol Clin **2011**; 29:587-92.

19. Partridge DG, O'Brien E, Chapman AL. Outpatient parenteral antibiotic therapy for infective endocarditis: a review of 4 years' experience at a UK centre. Postgrad Med J **2012**; 88:377-81.

20. Duncan CJ, Barr DA, Ho A, Sharp E, Semple L, Seaton RA. Risk factors for failure of outpatient parenteral antibiotic therapy (OPAT) in infective endocarditis. J Antimicrob Chemother **2013**; 68:1650-4.

21. Htin AK, Friedman ND, Hughes A, et al. Outpatient parenteral antimicrobial therapy is safe and effective for the treatment of infective endocarditis: a retrospective cohort study. Intern Med J **2013**; 43:700-5.

22. Goenaga MA, Kortajarena X, Ibarguren O, et al. Outpatient parenteral antimicrobial therapy (OPAT) for infectious endocarditis in Spain. Int J Antimicrob Agents **2014**; 44:89-90.

23. Lacroix A, Revest M, Patrat-Delon S, et al. Outpatient parenteral antimicrobial therapy for infective endocarditis: a cost-effective strategy. Med Mal Infect. **2014**;44:327-30.

24. Pajarón M, Fernández-Miera MF, Allende I, et al. Self-administered outpatient parenteral antimicrobial therapy (S-OPAT) for infective endocarditis: a safe and effective model. Eur J Intern Med **2015**; 26:131-6.

25. Kortajarena X, Goenaga MA, Ibarguren M, et al. Outpatient parenteral antimicrobial therapy for infective endocarditis in patients over 80 years. Rev Esp Quimioter **2017**; 30:276-9.

26. Buehrle DJ, Shields RK, Shah N, Shoff C, Sheridan K. Risk Factors Associated With Outpatient Parenteral Antibiotic Therapy Program Failure Among Intravenous Drug Users. Open Forum Infect Dis. **2017**;4(3):ofx102.

27. Suzuki J, Johnson J, Montgomery M, Hayden M, Price C. Outpatient Parenteral Antimicrobial Therapy Among People Who Inject Drugs: A Review of the Literature. Open Forum Infect Dis. **2018** 7;5:ofy194.

28. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet **2016**; 387:882-93.

29. Pericás JM, Aibar J, Soler N, López-Soto A, Sanclemente-Ansó C, Bosch X. Should alternatives to conventional hospitalization be promoted in an era of financial constraint? Eur J Clin Invest **2013**; 43:602-15.

30. Muñoz P, Kestler M, De Alarcon A, et al. Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. Medicine (Baltimore) **2015**; 94:e1816.

31. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633-8.

32. Spanish Society of Infectious Diseases and Clinical Microbiology and Spanish Society of Domiciliary Hospitalization. [Consensus statement on OPAT by SEHAD-SEIMC]. 2017.

33. Tice AD, Rehm SJ, Dalovisio JR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis **2004**; 38:1651-72.

34. Chapman AL, Seaton RA, Cooper MA, et al. Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement. J Antimicrob Chemother **2012**; 67:1053-62.

35. Deo SV, Raza S, Kalra A, et al. Admissions for Infective Endocarditis in Intravenous Drug Users. J Am Coll Cardiol. **2018**;71:1596-1597.

36. Lam PW, Volling C, Chan T, et al. Impact of Defaulting to Single-Lumen Peripherally Inserted Central Catheters on Patient Outcomes: An Interrupted Time Series Study. Clin Infect Dis. **2018**;67:954-957.

37. Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med. **2018** Aug 28. doi: 10.1056/NEJMoa1808312 [Epub ahead of print].

38. Tobudic S, Forstner C, Burgmann H, et al. Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna. Clin Infect Dis. **2018**;67:795-798

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Figure Legends

Figure 1. Flowchart of patient treatment.

Table 1. Criteria Used to Indicate OPAT in IE Patients by GAMES Investigators in the Present Cohort.

Type of IE	Recommendation	Indications	Requirements
Native valve IE	**Rapid transfer to OPAT (as of 10 days after admission/surgery)**	1. IE by any causative agent-except highly difficult-to-treat microorganisms (HDTTM)* 2. Patients not presenting severe clinical complications 3. Patients undergoing or not undergoing cardiac surgery.	1. Negative blood cultures at 72 h. 2. No severe clinical complications or post-surgical complications. 3. No anticoagulation issues. 4. TEE ruling out severe aortic regurgitation and prosthetic dysfunction.
	Postponed transfer (at least 3 weeks after admission/surgery)	1. Patients presenting severe complications at onset. 2. Very fragile patients or patients with severe comorbidities receiving cardiac surgery or other treatment.	1. Identical criteria plus: 2. No severe sequelae or clinical complications 3. Need for frequent and/or complex cures.
Prosthetic valve IE	**Rapid transfer to OPAT (as of 10 days after admission)**	1. All cases caused by viridans or bovis group streptococci or *Enterococcus faecalis* and 2. Not undergoing cardiac surgery.	Same as for rapid transfer in NVIE
	Postponed transfer (at least 3 weeks	1. Cases of IE undergoing	Same as for postponed

	after admission/surgery)	cardiac surgery and 2. Not caused by HDTTM or 3. Presenting severe complications.	transfer in NVIE.
CIED IE	**Rapid transfer to OPAT (as of 1 week after device reimplantation)**	1. Cases with no severe clinical complications by any causative agent except from HDTTM. and 2. Cases with non-complicated early lead extraction (within first week from admission).	1. Normal function of the newly implanted device checked by the electrophysiology team. 2. No signs of infection in the pocket. 3. Negative blood cultures at 72 h after reimplantation. 4. Normal TEE.
	Postponed transfer (as of 2 weeks after device reimplantation)	1. Associated right-sided IE with large vegetations (>2 cm) 2. Left-sided IE. 3. Clinical complications. 4. Late or complicated lead extraction.	Identical plus the same criteria as for postponed transfer in NVIE.
Not candidates for OPAT*		1. Patients with Child B or C liver cirrhosis. 2. Severe CNS emboli (multiple >3, large >2 cm, hemorrhagic, or with fixed neurologic deficits). 3. Not drained large splenic or renal abscess. 4. Vertebral abscesses requiring neurosurgery. 5. Periannular complications or other severe conditions requiring surgery when this is contraindicated**	

	6. Severe post-surgical complications. 7. HDTTM. 8. IDUs.

CIED: cardiac implantable electronic devices; CNS: central nervous system; IDUs: intravenous drug users; PCM/DF: pacemaker/defibrillator; PVE: prosthetic valve endocarditis; TEE: transesophageal echocardiography; *Highly difficult-to-treat microorganisms (HDTTM): 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 (e.g. MRSA 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*, etc.); **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.

Table 2. Summary of Main Results of Previous Reports on OPAT in Infective Endocarditis.

First author	Year	Country	n	Fulfillment of IDSA criteria *	One-year mortality	Readmissions	Comments
Kind [9]	1979	U.S.	37	59%	3%	5%	Patients with osteomyelitis also included.
Rehm [10]	1983	U.S.	36	69%	3%	3%	Patients with bone and skin and soft tissue infections
Stamboulian [11]	1991	Argentina	27	100%	0%	4%	All had penicillin-susceptible streptococcal IE.
Francioli [12]	1992	Belgium, France, and Switzerland	23	100%	0%	7%	Study design: 4 weeks of single-dose ceftriaxone for streptococcal IE (59 patients in total, 36 HBAT).
Graninger [13]	1997	Austria	10	0%	ND	20%	All were staphylococcal IE treated with teicoplanin.
Sexton [14]	1998	U.S.	51	94%	4%	4%	RCT comparing ceftriaxone alone for 4 weeks vs. 2 weeks of ceftriaxone + gentamicin for 2 weeks and 2 weeks of ceftriaxone alone for penicillin-susceptible

							streptococci. 27.5% received cardiac surgery.
Lopardo [15]	2001	Argentina	48	77%	0%	0%	10% received cardiac surgery
McMahon [16]	2008	Australia	40	<40%	7%	7%	16 staphylococci, 11 streptococci, 4 other, 9 culture-negative. 25% PVE; 52.5% aortic.
Larioza [17]	2009	U.S.	43	78%	0%	33%	35% staphylococci
Cervera [18]	2011	Spain	73	45%	4%	16%	32% PVE and 11% PCM IE; no differences in outcomes were found between VGS plus *S. bovis* IE and staphylococcal IE
Partridge [19]	2012	England	36	29%	6%	11%	A successful outcome was achieved in 22/24 episodes (91.7%) deemed by IDSA to be less suitable for OPAT owing to a higher risk of complications.
Duncan [20]	2013	Scotland	80	30%	4%	26%	45% PVE, and 42.5% streptococcal. On multivariate analysis, heart or kidney failure and teicoplanin therapy were independently associated with increased OPAT

							failure.
Htin [21]	2013	Australia	68	43%	3%	4%	Only 43% NVE; 42% staphylococcal. 37% underwent cardiac surgery.
Goenaga [22]	2014	Spain	149	50%	1%	20%	29.5% PVE and 9.4% PCM-IE; 27.5% staphylococci
Lacroix [23]	2014	France	18	80%	5.5% (at 3 months)	33.3%	50% PVE, 44.4% aortic, 27.8% received cardiac surgery, 16.7% caused by staphylococci.
Pajarón [24]	2015	Spain	48	<25%	10%	13%	31% streptococcal IE and 37.5% PVE. Self-administered antibiotics in all patients. 35.4% cardiac surgery.
Kortajarena [25]	2017	Spain	194	<30%	0.5%	18%	No significant differences in mortality or readmissions were found between patients younger or older than 80 years.
Buerhle [26]	2017	U.S.	35	-	-	-	All IDUs. Treatment failed in 61% (worsening or ongoing infection requiring readmission to hospital within 30 days, worsening or ongoing infection resulting in prolonged

							antibiotic therapy, non-adherence to antibiotic therapy, non-adherence to follow-up clinic appointments, or death during treatment).
Suzuki [27]	2018	U.S., Australia, Canada, Singapore	133	-	-	0-30%	Review including only IDUs receiving OPAT for a variety of ID. Readmissions refer to all ID pooled together.

* Approximation from data available in each of the studies consulted works.

HBAT: hospital-based antibiotic treatment; ID: infectious diseases; IDUs: intravenous drug users; IE: infective endocarditis; PCM: pacemaker; PVE: prosthetic valve endocarditis; RCT: randomized clinical trial; VGS: viridans group streptococci.

Table 3. Baseline Characteristics of Patients and Endocarditis Episodes.

	HBAT (N=1,003)	OPAT (N=429)	*P*
Fulfillment of IDSA criteria for the use of OPAT [6]	234 (23.3%)	93 (21.7%)	0.465
Median age, years (IQR)	68.6 (56.6-76.3)	67.8 (55.9-76.4)	0.805
Male sex (%)	702 (70%)	303 (70.6%)	0.808
Comorbidities			
• Diabetes mellitus	250 (24.9%)	113 (26.3%)	0.576
• Chronic lung disease	156 (15.6%)	75 (17.5%)	0.372
• Ischemic heart disease	224 (22.3%)	97 (22.6%)	0.908
• Congestive heart failure	290 (28.9%)	118 (27.5%)	0.587
• Moderate/severe liver disease	36 (3.6%)	6 (1.4%)	0.007
• Moderate/severe chronic renal failure	142 (14.2%)	48 (11.2%)	0.114
• Hemodialysis	43 (4.3%)	7 (1.6%)	0.003
• Neoplasm	146 (14.6%)	72 (16.8%)	0.294
• Transplantation	15 (1.5%)	8 (1.9%)	0.626
• Immunosuppressive therapy	41 (4.1%)	30 (7%)	0.036
• HIV	10 (1%)	4 (0.9%)	0.908
• Previous IE	88 (8.8%)	35 (8.2%)	0.700
• Congenital cardiac abnormality	69 (6.9%)	26 (6.1%)	0.559
• Non-congenital valve disease	439 (43.8%)	183 (42.7%)	0.697
• Median age-adjusted			

Charlson score (IQR)	4.0 (3.0-6.0)	4.0 (2.0-6.0)	0.353
Type of endocarditis			
• Native	658 (65.6%)	245 (57.1%)	0.003
• Prosthetic	262 (26.1%)	117 (27.3%)	0.653
• PCM/DF	117 (11.7%)	80 (18.6%)	0.001
Valve involvement*			
• Aortic	490 (48.9%)	188 (43.8%)	0.080
• Mitral	437 (43.6%)	170 (39.6%)	0.164
• Tricuspid	54 (5.4%)	17 (4%)	0.229
• Pulmonary	13 (1.3%)	4 (0.9%)	0.535
Etiology			
• S. *aureus*	185 (18.4%)	67 (15.4%)	0.186
- MSSA	158 (15.8%)	56 (13.1%)	0.176
- MRSA	27 (2.7%)	11 (2.6%)	0.889
• Viridans group streptococci	164 (16.4%)	80 (18.6%)	0.300
• Coagulase-negative staphylococci	166 (16.6%)	62 (14.5%)	0.309
• Enterococci	157 (15.7%)	40 (9.3%)	<0.001
• Negative blood culture	122 (12.2%)	58 (13.5%)	0.486
• Bovis group streptococci	75 (7.5%)	40 (9.3%)	0.258
• *S. agalactiae*	26 (2.6%)	4 (0.9%)	0.015
• Non-HACEK Gram-negative rods	20 (2%)	15 (3.5%)	0.130
• HACEK	16 (1.6%)	8 (1.9%)	0.724
• *S. pneumoniae*	11 (1.1%)	4 (0.9%)	0.773
	11 (1.1%)	5 (1.2%)	0.911

• Group C and G streptococci	8 (0.8%)	12 (2.8%)	0.018
• Fungi	4 (0.4%)	1 (0.2%)	0.589
• *C. acnes*	3 (0.3%)	13 (3%)	0.001
• *C. burnetii*	5 (0.5%)	2 (0.5%)	0.935
• *Gemella spp*	5 (0.5%)	4 (0.9%)	0.399
• Gram-positive anaerobes	5 (0.5%)	3 (0.7%)	0.662
• *Abiotrophia/Granulicatella*	0	3 (0.7%)	0.082
• Mycobacteria	2 (0.2%)	3 (0.7%)	0.241
• *Bartonella spp*	0	1 (0.2%)	0.317
• *Brucella spp*	0	1 (0.2%)	0.317
• *T. whipplei*	18 (1.8%)	3 (0.7%)	0.060
• Other			
Acquisition			
• Community	610 (60.8%)	265 (61.8%)	0.734
• Nosocomial	270 (26.9%)	118 (27.5%)	0.820
• Non-nosocomial healthcare-associated	89 (8.9%)	28 (6.5%)	0.116
• Unknown	33 (3.3%)	18 (4.2%)	0.419

HBAT: hospital-based antibiotic treatment; HIV: human immunodeficiency syndrome; IQR: interquartile range; MSSA: methicillin-susceptible *S. aureus;* MRSA: methicillin-resistant *S. aureus*; PCM/DF: pacemaker/defibrillator

* The sum does not reach 100% because the cases affecting only PCM/DF leads are not counted.

Table 4. Clinical Complications, Echocardiographic and Therapeutic Characteristics, and Outcomes

	HBAT (N=1,003)	OPAT (N=429)	*P*
Clinical complications			
• New-onset or worsening heart failure	376 (37.5%)	107 (29%)	<0.001
- NYHA I	31 (8.2%)	9 (8.4%)	0.917
- NYHA II	65 (17.3%)	24 (22.4%)	0.028
- NYHA III	137 (36.4%)	51 (47.7%)	<0.001
- NYHA IV	143 (38%)	32 (29.9%)	0.003
• Persistent bacteremia	81 (8.1%)	35 (8.2%)	0.958
• CNS emboli	142 (14.2%)	36 (8.4%)	0.086
- Hemorrhagic	65 (45.8%)	24 (66.7%)	<0.001
- Extensive (>2 cm)	10 (7%)	5 (13.9%)	0.056
- Multiple (>3)	12 (8.5%)	5 (13.9%)	0.135
• Other major emboli	220 (21.9%)	76 (17.7%)	0.062
• Pulmonary emboli	15 (1.5%)	8 (1.9%)	0.626
• Vertebral osteomyelitis	26 (2.6%)	19 (4.4%)	0.099
• Non-vertebral osteomyelitis	11 (1.1%)	7 (1.6%)	0.441
• Renal abscess	28 (2.8%)	21 (4.9%)	0.071
• Splenic abscess	42 (4.2%)	10 (2.3%)	0.055
• Heart conduction abnormality	66 (6.6%)	30 (7%)	0.777
• Acute renal failure	340 (33.9%)	104 (24.2%)	<0.001
• Septic shock	59 (5.9%)	18 (4.2%)	0.167

Echocardiographic findings			
• TEE	774 (77.2%)	361 (84.1%)	0.002
• Median ejection fraction (IQR)	60 (55-66)	60 (55-66.5)	0.642
• Median vegetation size (IQR)	10.0 (6.6-16.6)	10.0 (5-15)	0.012
• Severe aortic regurgitation	212 (21.1%)	59 (13.8%)	<0.001
• Severe mitral regurgitation	193 (19.2%)	81 (18.9%)	0.873
• Perivalvular abscess	126 (12.6%)	42 (9.8%)	0.119
• Intracardiac fistula	29 (2.9%)	4 (0.9%)	0.005
• Pseudoaneurysm	52 (5.2%)	10 (2.3%)	0.005
• Leaflet perforation/rupture	131 (13.1%)	38 (8.9%)	0.016
Treatment characteristics			
• Antibiotics properly indicated	968 (96.5%)	408 (95.1%)	0.239
• Median length of antibiotic treatment, days (IQR)	42.0 (29-45)	42.0 (32-54)	<0.001
• Most used antibiotics			
- Cloxacillin	181 (18%)	76 (17.7%)	0.881
- Vancomycin	263 (26.2%)	89 (20.7%)	0.023
- Ceftriaxone	321 (32%)	149 (34.7%)	0.318
- Ampicillin	212 (21.1%)	67 (15.6%)	0.011
- Gentamicin	504 (50.2%)	187 (43.6%)	0.020
- Daptomycin	84 (8.4%)	35 (8.2%)	0.891
- Rifampin (po)	141 (14.1%)	55 (12.8%)	0.526
• Cardiac surgery			
- Indicated	622 (62%)	237 (55.2%)	0.018
- Performed	519 (51.7%)	190 (44.3%)	0.009

Sequelae at the time of hospital discharge or transfer to OPAT	166 (16.6%)	59 (13.8%)	0.169
- Mild	75 (45.2%)	35 (59.3%)	0.061
- Moderate	73 (43.9%)	23 (39%)	0.505
- Severe	18 (10.8%)	1 (1.7%)	0.029
Clinical and echocardiographic status at one year*			
• Neurological sequelae			
- Mild	22 (17.5%)	5 (15.6%)	0.805
- Moderate	11 (8.7%)	3 (9.4%)	0.908
- Severe	9 (7.1%)	1 (3.1%)	0.404
• Heart function			
- Asymptomatic	577 (74.3%)	284 (79.3%)	0.034
- Symptomatic	200 (25.7%)	74 (20.7%)	0.034
○ NYHA I	48 (24%)	23 (31.1%)	0.019
○ NYHA II	102 (51%)	37 (50%)	0.965
○ NYHA III	50 (25%)	14 (20.3%)	0.047
○ NYHA IV	10 (5%)	0	<0.001
Outcomes			
• Readmissions during first 3 months after discharge	101 (10%)	47 (10.9%)	0.614
- IE-related	58 (57.4%)	20 (42.5%)	0.091
- Catheter/antibiotic-related	5 (4.9%)	5 (10.6%)	0.199
- Other complications	38 (37.6%)	22 (46.8%)	0.289
• Surgery within first year after discharge	80 (8%)	45 (10.5%)	0.142
• Relapse	32 (3.2%)	6 (1.4%)	0.053
• Mortality at 1-year	125 (12.5%)	33 (7.7%)	0.004

CNS: central nervous system; HBAT: hospital-based antibiotic treatment; IQR: interquartile range; OPAT: outpatient parenteral antibiotic treatment; TEE: transesophageal echocardiography; VGS: viridans group streptococci.

* Sample sizes were as follows: Patients assessed for neurological sequelae at one year, 126 of the 142 (88.7%) receiving HBAT and 32 of the 36 (88.9%) patients receiving OPAT presenting with CNS emboli during hospital admission; Patients assessed for heart function, 777 (88.5%) receiving HBAT and 358 (90.4%) receiving OPAT.

Table 5. Analysis of Risk Factors for One-Year Mortality and Readmission for 429 Patients Receiving OPAT.

	One-year mortality				Readmission			
	Univariate		*Multivariate*		*Univariate*		*Multivariate*	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Male sex	0.99 (0.44, 2.41)	0.99			0.92 (0.50, 1.72)	0.76		
Age (years)	1.03 (1.00, 1.06)	0.02			1.00 (0.99, 1.03)	0.27		
Diabetes mellitus	1.22 (0.55, 2.77)	0.60			0.87 (0.43, 1.67)	0.68		
Moderate-severe liver disease	2.49 (0.51, 23.17)	0.39			1.15 (0.02, 10.57)	0.89		
Age-adjusted Charlson score	1.25 (1.10, 1.43)	0.001	1.21 (1.04, 1.42)	0.01	1.06 (0.96, 1.17)	0.26		
Community acquisition	0.62 (0.33, 1.44)	0.23			0.79 (0.41, 1.55)	0.36		
Prosthetic IE	0.84 (0.32, 1.98)	0.67			1.30 (0.69, 2.39)	0.37		
Aortic valve involvement	1.76 (0.82, 3.83)	0.11			0.51 (0.27, 0.93)	0.04	0.47 (0.22, 0.98)	0.007
Staphylococcus aureus	1.38 (0.48, 3.50)	0.48			0.70 (0.27, 1.60)	0.38		
Viridans group streptococci	0.44 (0.08, 1.50)	0.18			0.79 (0.32, 1.74)	0.54		
Periannular complications	0.52 (0.06, 2.25)	0.39			1.64 (0.64, 3.82)	0.22		

Vegetation size ≥ 10mm	1.01 (0.99, 1.02)	0.32			1.01 (0.99, 1.02)	0.35		
New-onset heart failure	1.49 (0.63, 3.32)	0.29			1.45 (0.76, 2.67)	0.20		
Persistent bacteremia	1.57 (0.52, 4.73)	0.43			1.22 (0.44, 4.22)	0.66		
CNS emboli	1.87 (0.53, 5.33)	0.22			0.67 (0.17, 1.99)	0.46		
Other emboli	0.93 (0.30, 2.40)	0.88			1.05 (0.48, 2.15)	0.87		
New heart conduction abnormality	1.33 (0.24, 4.70)	0.65			1.85 (0.64, 4.72)	0.17		
Acute renal failure	1.81 (0.78, 3.99)	0.11			1.76 (0.93, 3.25)	0.07		
Septic shock	0.65 (0.02, 4.36)	0.67			0.31 (0.01, 2.02)	0.23		
Inappropriate initial antibiotics	0.71 (0.02, 5.04)	0.74			0.77 (0.08, 3.44)	0.72		
Cardiac surgery	0.20 (0.06, 0.55)	0.001	0.24 (0.09, 0.63)	0.004	1.00 (0.56, 1.77)	0.99		
Logistic EuroSCORE	1.02 (0.99, 1.04)	0.08			1.01 (0.99, 1.03)	0.10		
Fulfillment of IDSA criteria	1.80 (0.42, 5.64)	0.29			0.85 (0.21, 2.56)	0.77		
Non-fulfillment of IDSA criteria	0.55 (0.17, 5.88)	0.29			1.17 (0.39, 4.76)	0.77		

Figure 1