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Original article

Efficacy and safety of outpatient parenteral antibiotic therapy for infective endocarditis: a ten-year prospective study☆

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ABSTRACT

Background: The length of treatment of infective endocarditis (IE) with parenteral antibiotics varies from 2 to 6 weeks. Although several studies indicate that outpatient parenteral antibiotic treatment (OPAT) could be safe for uncomplicated viridans-group streptococci (VGS) IE, the experience in Spain is limited and data on other types of endocarditis and OPAT are scarce worldwide.
Methods: Prospective single center study of a cohort including all patients with IE admitted to the Hospital Clinic of Barcelona OPAT program from January 1997 to December 2006.
Results: During the study period, 392 consecutive episodes of IE in non-drug abusers were attended to. Of these, 73 episodes (42 native-valve, 23 prosthetic-valve, and 8 pacemaker-lead) were admitted to the OPAT program (19%). The percentage of inclusion was higher for viridans group streptococci (VGS) or *Streptococcus bovis (S. bovis)* IE (32% of all VGS or *S. bovis* IE episodes diagnosed *vs.* 14% of the remaining etiologies, *P*<.001). Twelve patients (16%) were readmitted due to complications, of which 3 died (4%). Glycopeptides use was the only predictor factor of hospital readmission (OR 4.5, 95% confidence interval 1.2; 16.8, *P*=.026). No differences in OPAT outcome were found between VGS plus *S. bovis* IE and *Staphylococcus aureus (S. aureus)* plus coagulase-negative staphylococci IE. Patients spent a median of 17 day on OPAT (interquartile range 11-26.5), which enabled 1,466 days of hospital stay to be saved.
Conclusions: These data suggest that OPAT for IE may be a safe and effective therapeutic approach in the treatment of selected patients with types of endocarditis other than uncomplicated VGS or *S. bovis* endocarditis, although patients taking glycopeptides need close clinical OPAT monitoring.

Eficacia y seguridad del tratamiento antibiótico parenteral a domicilio en la endocarditis infecciosa: estudio prospectivo de 10 años

Palabras clave:
Endocarditis infecciosa
Tratamiento antibiótico parenteral a domicilio
Estreptococo grupo viridans
Streptococcus bovis
Staphylococcus aureus
Estafilococo coagulasa negativo

RESUMEN

Antecedentes: La duración del tratamiento antibiótico endovenoso de la endocarditis infecciosa (EI) oscila entre 2 y 6 semanas. Aunque varios estudios indican que el tratamiento antibiótico a domicilio endovenoso (TADE) es seguro para el tratamiento domiciliario de la EI sobre válvula nativa no complicada por estreptococos del grupo viridans (EGV) la experiencia en España con TADE en la EI es limitada y los datos sobre otros tipos de endocarditis y TADE son escasos en todo el mundo.
Métodos: Estudio unicéntrico, prospectivo, de una cohorte de todos los pacientes con EI admitidos en el programa TADE en el Hospital Clínico de Barcelona entre enero de 1997 y diciembre de 2006.

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◊ The list of the members of the Hospital Clinic Endocarditis Study Group is shown in Appendix 1.

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Enterococcus faecalis
Endocarditis de válvula nativa
Endocarditis de válvula protésica
Infección de dispositivo intravascular
Glucopéptidos

Resultados: Durante el período de estudio se diagnosticaron 392 episodios consecutivos de EI en pacientes no consumidores de drogas, de los cuales 73 episodios (19%) fueron admitidos en el programa de TADE: 42 EI sobre válvula nativa, 23 EI sobre válvula protésica y 8 EI sobre cable de marcapasos. El porcentaje de inclusión en la TADE fue mayor para la EI por EGV o *Streptococcus bovis (S. bovis)* (32%) que para el resto de etiologías (14%; p < 0,001). Doce pacientes (16%) fueron reingresados debido a las complicaciones de los cuales tres fallecieron (4%). El uso de glucopéptidos fue el único factor predictor de reingreso hospitalario (OR [intervalo de confianza del 95%] 4,5 [1,2; 16,8] p = 0,026). No se observaron diferencias entre las EI por EGV y *S. bovis* y las EI estafilocócicas (*Staphylococcus aureus* y estafilococos coagulasa-negativos) incluidas en el TADE. Los pacientes incluidos estuvieron una mediana de 17 días en tratamiento domiciliario (rango intercuartílico de 11 a 26,5), lo que permitió un ahorro de 1.466 días de estancia hospitalaria.
Conclusiones: Estos datos sugieren que la TADE en la EI es una estrategia terapéutica segura y eficaz en el tratamiento domiciliario de pacientes seleccionados con EI por EGV y otras etiologías, aunque los pacientes que reciben glucopéptidos precisan un mayor control clínico.

Introduction

Outpatient parenteral antibiotic therapy (OPAT) has been shown to be efficacious, safe, and cost-effective for a wide variety of infectious diseases.[1] The indications for its use in infective endocarditis (IE) are supported by a small number of observational descriptions of short American[2–7] and European[8–10] series, and complete medical data are available only for uncomplicated viridans-group streptococci (VGS) native-valve endocarditis. However, experience with OPAT administered to treat IE in Europe is limited.[8–10]

Antibiotic regimens for IE require 2-6 weeks of parenteral treatment, as oral therapy is not recommended.[11] Thus, OPAT is a highly attractive option for reducing the length of hospital stay and the number of stay-related complications. Before considering outpatient therapy, most patients with IE should be evaluated and stabilized in hospital. Patients selected for home parenteral therapy should have a low risk for congestive heart failure and systemic emboli, which are the most frequent complications of endocarditis. The period of highest risk for systemic emboli is within the first 2 weeks of antimicrobial therapy.[12] The presence of congestive heart failure, neurological findings resulting from systemic emboli, cardiac conduction abnormalities, valve ring abscesses, persistent fever, and positive blood cultures should preclude home intravenous therapy.[11] Prosthetic-valve endocarditis was also excluded from OPAT in the American Heart Association guidelines,[11] as information regarding this issue is lacking. However, data from previous studies suggest that it is safe in selected patients with non-VGS IE.[10,13]

We describe the efficacy and safety —including patient outcome and requirement for readmission— of OPAT in patients with IE admitted to a specialized OPAT program in Spain between 1997 and 2006.

Methods

The Hospital Clinic Infective Endocarditis Study Group has been in existence since 1979. Its characteristics have been described elsewhere.[14,15] All patients with a diagnosis of IE were prospectively evaluated to be admitted to an OPAT program from 1997, when the OPAT unit was created,[16] to December 2006. Patients fulfilling the criteria for OPAT (see below) were included in the program. The 2 main functions of the program were to provide parenteral antimicrobial agents in an outpatient setting and clinical or analytical monitoring to achieve early hospital discharge or to control adverse-effects of antibiotics with a high risk of toxicity.[16] The diagnosis of IE was defined following the modified Duke criteria.[17] The inclusion criteria of patients with IE were adapted from those published by Andrews and von Reyn[18] and are summarized in Table 1. Briefly, patients living near the hospital with adequate family support, absence of intravenous drug use, and stable endocarditis treated in-hospital for at least 7 days, were eligible for inclusion once patient and family consent had been given. Prosthetic-valve IE did not preclude admission to OPAT. The OPAT program was physician-guided. All patients received antimicrobial therapy in their home or long-term care facility.

Antibiotics were administered in 3 ways: *1)* Standard treatment: Daily visits and gravity-based diluted antibiotic bolus administration by a nurse; *2)* Self-administration: Administration by the patient or a family member of the night-dose in the case of twice-daily administered antibiotic or occasional self-administration of ceftriaxone (1 or 2 doses). Only those patients with full autonomy or close support by relatives were allowed to use self-administration of antibiotics; and *3)* Portable infusion-pump system: To administer antibiotics with 2 or more doses/day and adequate stability (24 hours or more) in solution, we used an electronic portable infusion-pump system (CADD-Legacy™ PLUS, Deltec Inc., St. Paul, Minnesota, USA) programmed for intermittent pulses (ampicillin or cloxacillin). Ampicillin was diluted in 500 milliliters of 0.9% sodium chloride, as at this concentration this antibiotic is stable for 24 hours (antibiotic concentrations 24 hours after the ampicillin solution preparation of 90% by HPLC and 76% by bioassay).[19] The dilution of cloxacillin was considered stable for 24 hours following the IDSA guidelines.[1]

Variables were collected prospectively using a specific MS-Access database. Age, gender, underlying chronic diseases, microbiological characteristics, type of endocarditis, antibiotic treatment, days on OPAT, and outcome measures (hospital readmission and mortality) were collected. All patients had at least 1 year

Table 1
Eligibility criteria for inclusion of patients with endocarditis in an OPAT program

Logistic criteria:
- Patient and family consent
- Autonomy or family support
- Residence in the metropolitan area of the hospital
- Telephone contact
- Absence of intravenous drug addiction

Endocarditis criteria:
- Native-valve IE by VGS, *S. bovis*, *S. aureus*, *Enterococcus spp*, coagulase-negative staphylococci or HACEK
- Late prosthetic-valve IE
- Control of infection: negative blood cultures (3 d) and apyrexia (7 d)
- Hemodynamic and electrophysiological stability
- Absence of cardiac abnormalities (severe valve regurgitation, paravalvular abscess by TTE/TEE)
- Absence of extracardiac abnormalities
- At least 7 days of in-hospital treatment

Source: modified from Andrews and von Reyn[18].
HACEK, *Haemophillus* spp., *Actinobacillus* spp., *Cardiobacterium* spp., *Eikenella* spp. and *Kingella* spp.; IE, infective endocarditis; TTE/TEE, transthoracic echocardiography/transesophageal echocardiography; VGS, viridans-group streptococci.

Table 2
Cases of endocarditis diagnosed at the Hospital Clinic in Barcelona (total number and those admitted to the OPAT program) during the study period, stratified by type of endocarditis and etiologic agent. Intravenous drug use–associated endocarditis was not included in the analysis as it was a contraindication for admission to the program

	Native-valve	Prosthetic-valve	Pacemaker-lead	Total	Percentage of patients included in OPAT**	Median days of admission (IQR)
*IE diagnosed during the study period**						
VGS + *S. bovis*	71 (31%)	26 (25%)	3 (5%)	100 (26%)	32%	25 (17-36)
S. aureus	60 (26%)	19 (18%)	16 (28%)	95 (24%)	13%	36.5 (25-53)
CoNS	27 (12%)	21 (20%)	27 (47%)	75 (19%)	13%	30.5 (19.5-47)
Enterococcus spp	22 (10%)	14 (14%)	2 (4%)	38 (10%)	16%	38.5 (21-51.5)
Other	51 (22%)	24 (23%)	9 (16%)	84 (21%)	15%	32 (19-41)
IE admitted to OPAT program during the study period						
VGS + *S. bovis*	22 (52%)	9 (39%)	1 (13%)	32 (44%)	NA	18 (11.5-27)
S. aureus	8 (19%)	2 (9%)	2 (24%)	12 (16%)	NA	16.5 (6-25.5)
CoNS	3 (7%)	3 (13%)	4 (50%)	10 (14%)	NA	18 (13-26)
Enterococcus spp	2 (5%)	4 (17%)	0	6 (8%)	NA	24 (16-35)
Other***	7 (17%)	5 (22%)	1 (13%)	13 (18%)	NA	15 (11-17)

CoNS, coagulase-negative staphylococci; IE, infective endocarditis; IQR: Interquartile range; NA, not applicable; VGS, viridans-group streptococci.
*Excluding endocarditis associated with intravenous drug use; **Patients treated by OPAT/number of IE diagnosed during the study period by type of microorganism; ***Other etiologies admitted to OPAT included: *Haemophilus* spp. (2 cases), *Streptococcus pneumoniae* (2 cases), *Abiotrophia* spp. (1 case), *S. agalactiae* (1 case), *Alcaligenes xylosoxidans* (1 case), *Actinobacillus actinomycetemcomitans* (1 case) and *Aspergillus* spp. (1 case). In 4 cases there was no microbiological isolation.

of follow-up since the diagnosis of IE. All patients with IE associated to intravenous drugs abuse were excluded from the analysis.

Categorical variables were summarized as percentages and compared using the χ^2 test (or Fischer exact test when appropriate). Quantitative variables were expressed as the mean (SD) or median (interquartile range [IQR]) depending on their homogeneity. Quantitative variables were compared using the Student *t* test. All analyses were performed using SPSS version 12.0 (SPSS Inc, Chicago, Illinois, USA).

Results

During the study period, 392 episodes of IE in non-drug abusers were attended to at Hospital Clinic in Barcelona Of these, OPAT was initiated for 73 (19%) episodes. (Table 2). Most patients treated by OPAT had native-valve endocarditis (42 episodes, 58%), 23 (31%) had prosthetic-valve endocarditis, and 8 had (11%) pacemaker-lead endocarditis. Although most of the cases were diagnosed at our hospital, a reference center for the treatment of infective endocarditis, we received 98 patients (25% of the cohort) from other hospitals in Catalonia.

Table 2 also shows the main characteristics of the cohort, the type of endocarditis and the microbiological diagnosis. The most frequent type of IE included were community-acquired native-valve IE, and the most frequent microbiological diagnosis was VGS (including *Streptococcus bovis [S. bovis]*) IE. Thirty two percent of all VGS or *S. bovis* IE episodes diagnosed were admitted, compared with only 14% of the remaining etiologies (P<.001).

Fourteen patients had complicated IE before admission to the program (10 with valve rupture and 4 with perivalvular abscess). Of these 14 patients, 9 required surgical correction during admission (7 valve replacement,1 aortic root graft and 1 aortic root graft plus valve replacement) with a median of 32 days (range: 23-74 days)admission prior to OPAT. Of the 9 patients requiring surgery due to complicated IE, 2 patients required readmission during OPAT and 1 of these 2 patients died during hospital readmission. Fifteen patients were admitted to the program to complete antibiotic

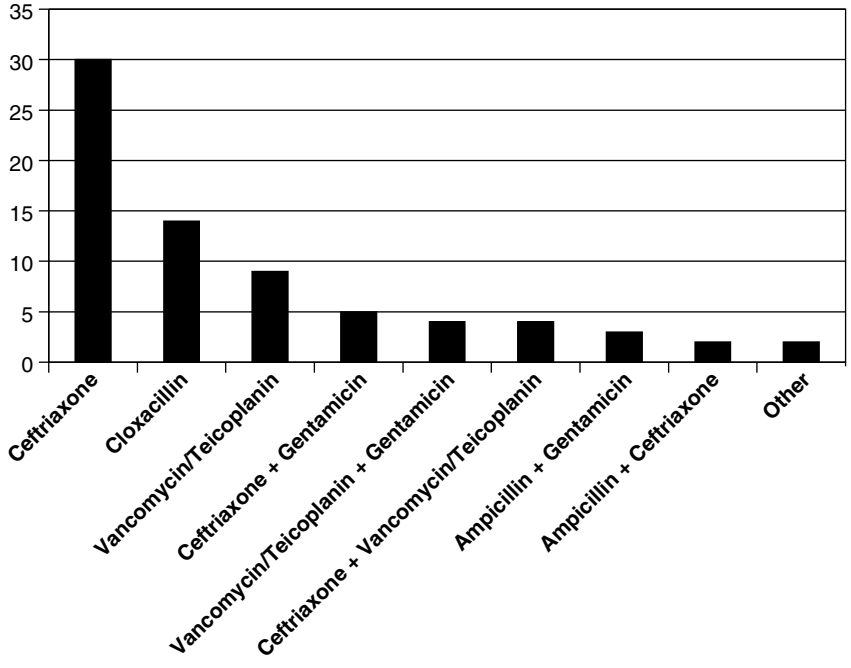

Figure 1. Antibiotics administered for the treatment of IE (number of episodes). The use of ceftriaxone plus glycopeptides in 4 patients was sequential in time.

treatment after surgery for IE: 9 patients had had a valve replacement (2 with the implantation of an allograft aortic root), 5 patients underwent pacemaker extraction, and 1 patient received an allograft aortic root without valve replacement.

The most frequent venous access was a peripherally-inserted central venous catheter (41 patients, 56%), followed by a short catheter (19 patients, 26%), and a jugular or subclavian central venous catheter (13 patients, 18%). The most frequent antibiotic regimen was ceftriaxone monotherapy (30 patients, 41% of the treatments), followed by cloxacillin monotherapy (9 patients, 12%), and ceftriaxone plus gentamicin (5 patients, 7%) (Fig. 1). These three regimens represented 60% of the treatments. Seventeen patients received glycopeptides (vancomycin [8 cases] or teicoplanin [9 cases]) and 14 gentamicin. Eighteen patients (25%) received treatment via an electronic portable infusion pump system (Table 3), of which 12 received cloxacillin (7 *Staphylococcus aureus [S. aureus]* and 5 coagulase-negative staphylococci), 5 ampicillin (1 ampicillin plus gentamicin for VGS, 2 ampicillin plus gentamicin for *Enterococcus faecalis [E. faecalis]* and 2 ampicillin plus ceftriaxone for *E. faecalis*) and 1 penicillin (penicillin plus vancomycin for coagulase-negative staphylococci plus VGS).

The median days of hospital admission prior to OPAT were 21 days (interquartile range 13-29 days). There were no differences in the days of hospital admission prior to OPAT according to the presence of native valve endocarditis or *S. aureus* endocarditis. Patients requiring surgery had longer hospital stays prior to OPAT (median hospital stay, 29 and 17 days respectively, *P*<.001). Patients spent a median of 17 days (range: 2-90 days) on OPAT, which enabled 1,466 days of hospital stay to be saved.

We compared the main features, the incidence of complications and the OPAT characteristics between streptococcal and staphylococcal IE in Table 3. Patients with staphylococcal IE admitted to OPAT had a trend of higher rates of intracardiac prosthetic-device infections and health-care associated IE and needed more often antibiotic treatment by infusion pump (*P*<.001) and central catheters (*P*=0.009) than patients with VGS or *S. bovis* admitted to OPAT (Table 3). No deaths during OPAT were registered in patients with VGS, *S. bovis* or *S. aureus* IE.

Twelve patients had complications requiring readmission. Of these, 9 were non-fatal complications (heart failure 2 cases and catheter-related sepsis, variceal hemorrhage, abdominal pain, dizziness, lower-back pain, fever of unknown origin, and hypersensitivity reaction in one case each) and 3 patients had fatal complications. The patient with catheter-related sepsis suffered a coagulase-negative staphylococci bacteremia and was not under self-administration of antibiotic. Of the 12 patients requiring

Table 3
Main characteristics of patients with endocarditis admitted to the OPAT program

Variable	All cases	VGS or *S. bovis*	*S. aureus* or CoNS	p
Number of patients	73	32	22	
Male sex	55 (75%)	23 (72%)	19 (86%)	0.320
Mean age (SD), years	59.5 (18.7)	61.0 (19.2)	61.5 (16.8)	0.924
Diagnosis of endocarditis				
Pathologic	14 (19%)	2 (6%)	6 (27%)	
Definite	36 (49%)	16 (50%)	11 (50%)	
Probable	17 (23%)	10 (31%)	3 (14%)	
Possible	6 (8%)	4 (13%)	2 (9%)	0.138
Valve affected				
Pacemaker-lead	8 (11%)	1 (3%)	6 (27%)	
Mitral	34 (47%)	15 (47%)	9 (41%)	
Aortic	24 (33%)	11 (34%)	6 (27%)	
Mitral + aortic	3 (4%)	1 (3%)	1 (5%)	
Unknown	4 (6%)	4 (13%)	0	0.043
Type of endocarditis				
Native-valve	42 (58%)	22 (69%)	11 (50%)	
Prosthetic-valve	23 (32%)	9 (28%)	5 (23%)	
Pacemaker-lead	8 (11%)	1 (3%)	6 (27%)	0.051
Origin				
Community	63 (86%)	31 (97%)	17 (77%)	
Nosocomial	6 (8%)	1 (3%)	3 (14%)	
Healthcare-related	4 (6%)	0	2 (9%)	0.066
Chronic underlying diseases				
Diabetes	10 (14%)	5 (23%)	3 (9%)	0.248
Chronic renal failure:	6 (8%)	1 (3%)	2 (9%)	0.560
Dialysis	5 (7%)	1 (3%)	1 (5%)	–
Liver cirrhosis	7 (10%)	1 (3%)	1 (5%)	1.000
Neoplasm	4 (6%)	1 (3%)	2 (9%)	0.560
Other	12 (16%)	6 (19%)	5 (23%)	0.743
Antibiotic treatment				
Ceftriaxone monotherapy	30 (41%)	22 (69%)	0	<0.001
Glycopeptides	17 (23%)	4 (12%)	9 (41%)	0.016
Gentamicin	14 (19%)	7 (22%)	1 (4%)	0.122
Treatment with 2 i.v. antibiotics	24 (33%)	8 (25%)	6 (27%)	0.851
Treatment by infusion pump	18 (25%)	2 (6%)	12 (55%)	<0.001
Type of catheter used				
Short catheter	19 (26%)	14 (44%)	2 (9%)	
Peripherally inserted central venous catheter	41 (56%)	15 (47%)	13 (59%)	
Central catheter (jugular or subclavian)	13 (18%)	3 (9%)	7 (32%)	0.009
Complications				
Re-admission	12 (16%)	4 (13%)	6 (27%)	0.285
Death	3 (4%)	0	2 (9%)	0.161

Table 4
Predictive factors for OPAT complications leading to hospital readmission

	No readmission (n=61)	Hospital readmission or death (n=12)	p
Mean age (SD)	60.9 (18.7)	52.2 (17.8)	0.139
Male gender	47 (77%)	8 (67%)	0.474
Community-acquired IE	53 (87%)	10 (83%)	0.665
Left-sided IE	53 (87%)	12 (100%)	0.409
Aortic valve IE	20 (33%)	6 (50%)	0.330
Native valve IE	34 (56%)	8 (67%)	0.484
Liver cirrhosis	3 (5%)	1 (8%)	0.521
Neoplasm	3 (5%)	1 (8%)	0.521
Chronic renal failure	3 (5%)	1 (8%)	0.521
VGS IE	28 (46%)	4 (33%)	0.347
Staphylococcal endocarditis	16 (27%)	6 (46%)	0.192
Ceftriaxone monotherapy	28 (46%)	2 (17%)	0.106
Treatment with infusion pump	16 (26%)	2 (17%)	0.718
*Treatment with glycopeptides**	11 (18%)	6 (50%)	0.026
Treatment with gentamicin	12 (20%)	2 (16%)	1.000
Treatment with 2 i.v. antibiotics	19 (31%)	5 (42%)	0.513
Treatment by short catheter	17 (28%)	2 (17%)	0.720

IE, infective endocarditis; VGS, viridans-group streptococci.
*Vancomycin 9; Teicoplanin 8.

readmission, all had left-sided endocarditis, 2 had previous endocarditis surgery, and 8 had native valve IE and 4 prosthetic valve IE.

Three patients died during OPAT. The first was a 37-year-old man with acute leukemia (AML-5) who had been in remission for the last 5 years. He was admitted to the OPAT program due to a native-mitral-valve IE caused by coagulase-negative staphylococci. He died of health-care related pneumonia. The second was a 71-year-old diabetic woman with prosthetic-aortic-valve IE caused by *E. faecalis*. She died of a sudden and massive cerebral hemorrhage due to the rupture of a mycotic aneurysm just two days after finishing OPAT. The third patient was a 56-year-old man with aortic and prosthetic–mitral-valve nosocomial IE caused by coagulase-negative staphylococci. During the course of OPAT with vancomycin, he developed lower-back pain and acute renal failure, requiring readmission. During his stay, he developed a fatal pulmonary edema and died.

Table 4 shows the predictive factors associated with hospital readmission. Patients treated with glycopeptides had a higher incidence of complications requiring readmission (6 of 17 patients [35%]) (OR 4.5, 95% confidence interval 1.2; 16.8, *P*=.026). Of the 12 cases of *S. aureus* IE, 8 were treated with cloxacillin and 4 with glycopeptides due to allergy to betalactams. Fifty percent of all readmissions were patients receiving glycopeptides (3 vancomycin and 3 teicoplanin). The reasons for readmission of these six patients were: abdominal pain, lower-back pain, fever, catheter-related sepsis, health-care related pneumonia and lower-back pain and renal failure in one case each. Two of these patients died (see above). Eight patients receiving glycopeptides were treated with monotherapy (5 teicoplanin and 3 vancomycin). The rest received combination therapy, of whom 5 received gentamicin.

Discussion

Almost 19% of patients in our cohort of patients with IE received antibiotic treatment on a physician-guided OPAT program specially designed for infectious diseases. As Hospital Clinic is a reference center for the treatment of complicated IE in Catalonia (Spain), almost 25% of all cases were referred from other centers. These cases are more frequently complicated IE and often required surgery. For this reason, the incidence of OPAT could be higher in other centers based on our eligibility criteria. Although uncomplicated native-valve IE was the most frequent diagnosis, we also included a high number of complicated IE, post-surgery IE, and prosthetic-valve IE. Our OPAT unit brings together a multidisciplinary team made up of infectious diseases specialists, cardiovascular surgeons, and microbiologists. The active search for potential OPAT candidates may explain the high number of IE included. In two recent series in the USA and New Zealand, 66% and 47% of patients with IE, respectively, completed antibiotic treatment on an outpatient basis.[20,21]

Previous studies suggest that OPAT for uncomplicated native-valve VGS IE is safe and efficacious.[4,8,9] In this regard, the review of 14 studies of OPAT for IE by Monteiro and Cobbs included 223 patients available for clinical assessment at the end of therapy.[22] The main conclusion of this study was that outcome was good for stable patients with uncomplicated penicillin-susceptible VGS endocarditis. None of our patients with VGS or *S. bovis* endocarditis (6 with prosthetic-valve and 1 with pacemaker-lead IE) died. Although a previous study suggested that early hospital discharge is safe in native-valve VGS endocarditis,[9] all our patients received at least 7-10 days of in-hospital treatment. In fact, 2 previous studies reported an incidence ranging from 10% to 23% of patients treated entirely on an outpatient basis.[4,8,9] Our data, however, suggest that, at least, a one-week period of hospital evaluation and treatment prior to OPAT is preferable. In the case of IE by *S. aureus*, the period of inpatient evaluation and treatment should be probably extended to at least 2 weeks, due to its more aggressive course and its high ability to produce systemic emboli and septic metastases.[23]

The safety of OPAT for other types of IE is unknown. This is a key issue, as *S. aureus* is currently the leading cause of IE.[23] Although a 2-week inpatient regimen of nafcillin plus gentamicin for uncomplicated *S. aureus* right-sided endocarditis, which usually occurs in intravenous drug users, has been shown to be effective, outpatient therapy for this population may be problematic because of adherence difficulties. There is little information regarding OPAT for the treatment of left-sided *S. aureus* IE. Of the 7,800 patients recorded in the OPAT Outcomes Registry from 1996 to 2002 at 24 centers around the United States, 198 had a diagnosis of bacterial endocarditis (44 of these cases were caused by *S. aureus*).[24] Treatment was discontinued early in 30 patients (15%), 2 of whom died. However, the authors provide no information on the type of valve affected, the etiologic agent, or the treatment administered. One of the main difficulties in treating *S. aureus* IE in the outpatient setting is the pharmacokinetics of cloxacillin. This drug must be administered via an electronic infusion pump system, usually connected to a central venous access. The poor availability of these devices may limit inclusion. Moreover, the use of second-line drugs for the treatment of methicillin-susceptible *S. aureus* IE could be associated with poorer outcome. In our series, none of the 12 cases of *S. aureus* IE, which included 2 prosthetic-valve and 2 pacemaker-lead infections, had a fatal outcome. A recent series from Australia reported more treatment failures of *S. aureus* IE treated with an OPAT program in comparison with other etiologies (*P*=.046), the mean in-hospital treatment being 23.5 days, and all treatment failures in this series were IE due to *S. aureus*.[25] Coagulase-negative staphylococci endocarditis deserves additional comments. Two of the three patients who died had a coagulase-negative staphylococci endocarditis and the use of glycopeptides, the drug of choice for the treatment of methicillin-resistant coagulase-negative staphylococci endocarditis, was a predictor of complications during OPAT. Based on our results, cases of coagulase-negative endocarditis should be carefully evaluated prior to OPAT inclusion.

Twelve patients (16%) in our study required hospital readmission or died during OPAT due to IE complications in only 4 cases. The hospitalization rate was similar to other OPAT series published[13,20,21,25] and ranged between 7.5%[25] and 23%.[20] Three patients developed fatal complications during OPAT. This outcome was unpredictable before discharge, and a careful review of the medical history revealed that none of these complications were

related to OPAT. Interestingly, treatment with glycopeptides was the only predictive factor of hospital readmission. However, we must note that in only 2 patients the reason for readmission was directly related to the drug (renal failure and catheter-related infection). New drugs, such daptomycin, could emerge as an alternative to glycopeptides, especially vancomycin, due to their lack of nephrotoxicity and better pharmacokinetic profile, allowing once-daily administration and less catheter overuse.[26] To reduce complications, the inclusion criteria for admission to the program play a key role. When the patient is stable, OPAT is associated with a low incidence of complications, regardless of the type of endocarditis, the etiologic agent, or the antibiotic treatment used. In a large series of endocarditis, more than two-thirds of patients with IE had a serious complication during treatment.[27] In our series, 18% of the patients had a complication requiring readmission, a percentage that is clearly lower than that reported in the hospital setting.

Our study has several limitations. The low number of cases included makes it impossible to draw firm conclusions on the safety of OPAT for IE, other than in uncomplicated VGS native-valve IE. In the case of *S. aureus* IE in particular, more studies are needed to evaluate the safety of OPAT. We must remember that the setting of our study is a tertiary-care university hospital with a cardiovascular surgery service. Therefore, in order to apply OPAT as a standard therapeutic method, the same conditions would be needed to obtain similar results.

In conclusion, our data suggest that OPAT for IE could be a safe and efficacious therapeutic option for very carefully selected patients with IE other than uncomplicated VGS or *S. bovis* endocarditis. Patients with uncomplicated native valve endocarditis due to VGS can be discharged early to OPAT after 7 days of in-hospital treatment. Glycopeptides use was the only predictive factor of hospital readmission and therefore close clinical monitoring of OPAT is recommended for patients taking vancomycin or teicoplanin. However, further studies investigating OPAT in these types of endocarditis or antibiotic use are warranted.

Conflict of interests

The authors declare no conflicts of interest related to this study.

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Appendix 1.

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