



Outpatient Parenteral Antimicrobial Therapy (OPAT) for Infective Endocarditis in a Belgian Tertiary Care Center

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Abstract

Aims: Treatment of infective endocarditis (IE) typically involves a long course of intravenous antibiotic therapy. Recognizing the increased emphasis on outpatient parental antibiotic therapy (OPAT) in the new 2023 ESC guidelines for IE, our aim is to evaluate our OPAT efficacy and safety in IE patients.

Methods and results: OPAT IE patients treated from July 2018 to December 2023 were included. Relevant demographic, clinical and microbiological data were collected. Outcomes were clinical cure at 3 months and OPAT- or IE-related readmission rates. A total of 70 OPAT episodes were performed in 69 patients with IE. Median age was 51.4 years (range 3-95 years), and 71% (n=49) of the patients were male. Prosthetic valve IE accounted for 50% of OPAT courses. Sixty-nine percent of patients needed cardiac surgery. Streptococci were the predominant causative organisms (63%), consequently, ceftriaxone was the most frequently used antibiotic (80%). Clinical cure 3 months after stopping OPAT was achieved in 67 of 70 episodes: two patients died unrelated to OPAT and one patient developed a reinfection one month after OPAT; readmission was necessary in 13 patients. Median duration of OPAT was 19 days (range 4-35), resulting in 1328 avoided hospitalization days.

Discussion: Consistent with previous studies, our OPAT program was effective and safe in selected patients. These data should be interpreted with caution given the stringent inclusion criteria, limited sample size, short OPAT duration and follow-up. In the future, we aim to provide a broader and earlier selection of patients, while maintaining a high clinical cure rate.

Keywords: Infective endocarditis; Outpatient parental antibiotic therapy; Valve surgery; Antibiotics

Introduction

Infective endocarditis (IE) is a complex and severe infectious disease that affects heart valves and potentially other cardiac structures, and that can lead to complications in other organs. Research has led to a better understanding of the pathophysiology and improved diagnostic and treatment modalities, but the incidence of IE continues to increase, and both morbidity and mortality remain high [1-4]. The treatment of IE typically requires a prolonged course of intravenous (IV) antibiotic therapy, and a significant number of patients also undergo cardiac surgery. Hospital stays are long and have important clinical and economic consequences [5].

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In recent decades, outpatient parenteral antimicrobial therapy (OPAT) has been implemented globally for a wide range of infections [6]. Since the beginning of the 21st century, its use in patients with IE has also become increasingly more common and confident [5,7-10]. Overall, OPAT has demonstrated effectiveness and safety in carefully selected patients, significantly reducing healthcare costs and alleviating the burden on healthcare resources across various cohorts [11-14]. OPAT enhances patients' quality of life by increasing their autonomy, allowing them to return home earlier, and reducing the transmission of multidrug-resistant organisms [15].

Over the years, the proposed criteria for switching to OPAT in IE have evolved: from very stringent (only uncomplicated native valve IE caused by low-virulence microorganisms, excluding *Staphylococcus aureus*) to more liberal (excluding only patients at high risk of complications), thus facilitating treatment outside the hospital [7,16]. The new 2023 ESC guidelines for the management of endocarditis recognize the potential of OPAT and include these broader criteria, providing considerations and guidance for timely switch to outpatient treatment [5]. The authors advocate for the use of OPAT once the patient is clinically stable, in the absence of critical infection-related complications or the expected need for surgery. The main remaining contraindications include neurological involvement, heart failure and renal impairment [5].

Until 2015, the overall experience with OPAT in Belgium was limited. However, in January 2017, OPAT was implemented at our tertiary hospital, and the first patient was treated with OPAT for IE in July 2018. In 2020, Quintens et al. [6] evaluated the OPAT program in general and reported

a high cure rate of 97.9% and a low incidence of adverse events at 14.5%, though only a few IE patients were included [6]. In the present study, we specifically reviewed all IE cases included in the OPAT program to determine the safety and outcomes of OPAT for IE.

Methods

Design, setting and patient population

This mono-centric, observational OPAT study was carried out at the University Hospitals Leuven (UHL), a 1738-bed tertiary care center [6]. The data were prospectively collected, and the aim of the study was determined retrospectively. Since 2000, all patients with IE at the UHL have been closely monitored by the endocarditis team consisting of cardiologists, cardiac surgeons and infectious disease specialists, in close collaboration with microbiologists, as recommended in all guidelines. IE was defined as definite or possible according to the ESC-modified Duke criteria [8]. Once IE is confirmed, patients are admitted to the Department of Cardiology or Cardiac Surgery. The eligibility of the patient for OPAT was discussed by the multidisciplinary OPAT team upon request by the treating physician. The OPAT team comprises a multidisciplinary collaboration between the infectious disease specialist, the microbiologist, clinical pharmacists, and home care nurses; the care is coordinated by three OPAT coordinators (all clinical pharmacists). Patients were included based on stringent criteria (Table 1). Details of the OPAT service and the prospectively maintained database used in the OPAT study have been published previously [6].

For the present study, all patients with IE, treated between July 2018 and 31 December 2023 and with a minimum follow-up of 3 months were included. For all patients, the visiting-

Table 1: Inclusion criteria OPAT defined at the start of the University Hospitals Leuven OPAT program [6].

1. Medical infection related criteria
- Need of antimicrobial therapy
- Infection diagnostically proven
- Directed treatment: microorganism identified, including susceptibility to the prescribed antibiotic
- Administration of the antibiotic for at least one day in the hospital to avoid ADE (e.g. hypersensitivity reactions)
- Oral drug administration not possible or appropriate (e.g. no oral antibiotic with same spectrum and sufficient bioavailability)
- Biochemically and clinically stabilized infection with a predictable course:
o Declining CRP values (proven by at least 2 laboratory values)
o Afebrile for at least 48 h
- In case of vancomycin: at least 2 therapeutic plasma concentrations under continuous infusion
2. Other medical criteria
- No psychological or cognitive disease or disability
- No (IV) drug use or alcoholism
- No need for additional surgical or medical interventions which require hospitalization
3. Patient related criteria
- Able to cope independently
- Sufficient professional support at home
- Adequate social and home (hygienic) situation
- Informed consent (incl. financial feasibility)

nurse model at home was used. During OPAT, patients were followed daily by home care nurses and weekly by the OPAT coordinator, and a regular follow up with echocardiography and blood samples for inflammation markers was organised.

The OPAT study protocol was approved by the Ethics Committee Research University Hospitals Leuven, Belgium (study number S60847).

Data collection, outcome and definitions

All OPAT IE episodes were registered in a prospective database by the OPAT coordinators. Demographic data (age, sex) and IE or treatment specific data (involved valve, causative microorganism, need for surgery, specific antibiotic therapy, complications of IE and vascular access device used during OPAT) were collected from the electronic patient records. Patient data were pseudonymized.

The clinical outcome of IE treated with OPAT was registered as 'cure' or 'failure'. A cure was defined as successful treatment of endocarditis without relapse, reinfection, IE-related mortality, or the need for a prolonged new antibiotic therapy for the same episode of IE. Relapse

was defined as a new episode of IE caused by the same microorganism, while reinfection was characterized as a new episode of IE caused by a different microorganism [5]. The secondary outcomes were unplanned readmissions and OPAT-related adverse events (including line related adverse events (LRAEs) and adverse drug events (ADEs)). ADEs were defined as medical occurrences temporally associated with the use of the antibiotic, but not necessarily causally related [17,18]. LRAEs were classified as catheter malfunction, infection, drug extravasation, local problems, thrombosis or catheter injury.

Statistical analysis

Baseline categorical patient characteristics are described as counts (n) and percentages (%), while continuous characteristics are described as the means (+/- standard deviation, SD) or medians (+/- range), as appropriate.

Results

Between July 2018 and December 2023 a total of 70 OPAT episodes were performed in 69 patients with IE, grossly representing 13% of all IE cases treated at the UHL (Table 2).

Table 2: Clinical characteristics.

General IE episodes	N (%)	
2018-2023 all IE patients (estimated)*	515	
2018-2023 OPAT episodes	70** (13.4)	
Included OPAT episodes	N (%)	Median (range)
Clinical characteristics**	69	
Children	3 (4.3)	
Adults (>16 year)	66 (95.7)	
Male	49 (71)	
Female	20 (29)	
Age overall		51.4 (3-95)
Age adults		53.3 (17-95)
Medical history		
IE episodes in medical history	13 (18.8)	
Same microorganism, relapse <1 year	2 (2.9)	
Different microorganism and >1 year	11 (15.9)	
Pre-existing renal impairment#	5 (7.2)	
Liver cirrhosis Child Pugh b or c	1 (1.4)	
Valve involvement		
Aortic	26 (37.1)	
Mitral	27 (38.6)	
Aortic and mitral	3 (4.3)	
Tricuspid and aortic	1 (1.4)	
Tricuspid	1 (1.4)	

Pulmonalis	10 (14.3)	
Unknown	1 (1.4)	
Pacemaker, lead vegetation	1 (1.4)	
Type of endocarditis		
Prosthetic valve IE	35 (50)	
Native valve IE	34 (48.6)	
CDRIE, only lead vegetation	1 (1.4)	
Causative microorganism		
Abiotrophia spp.	2 (2.9)	
Aggregatibacter aphrophilus	2 (2.9)	
Cardiobacterium hominis	1 (1.4)	
Cutibacterium acnes	1 (1.4)	
Culture negative	3 (4.3)	
Haemophilus parainfluenzae	3 (4.3)	
All staphylococcus spp.	14 (20)	
Staphylococcus aureus	11 (15.7)	
Streptococcus spp. ^	44 (62.9)	
Surgery		
Cardiac surgery during admission	48 (68.6)	
Surgery indicated but risk too high	1 (1.4)	
Septic emboli		
Septic emboli due to IE^^	24 (34.2)	
Cerebral emboli	13 (18.5)	
Septic arthritis	5 (7.1)	
Spondylodiscitis	4 (5.7)	
Septic emboli to kidney, spleen or lung	9 (12.9)	
Muscle emboli	7 (10)	
Skin emboli	2 (2.9)	
Retinal emboli or endophthalmitis	2 (2.9)	
Antibiotic used for OPAT		
Ceftriaxone	56 (80)	
Flucloxacillin	13 (18.6)	
Cefazolin	1 (1.4)	
Type of infusion		
Continuous infusion	13 (18.5)	
Intermittent	57 (81.4)	
Type of vascular access device		
Tunnelled central venous catheter	1 (1.4)	
Midline	7 (10)	
PICC	62 (88.6)	
<p>*This number is estimated based on case registrations of the endocarditis team.</p> <p>**70 episodes, in 69 patients</p> <p>#CKD chronic kidney disease category \geqG3a–G5, and albuminuria</p> <p>^^Some patients had multiple septic emboli to different locations.</p> <p>^No enterococci species were includedcategory A2–A3 [19]</p> <p>IE infective endocarditis, AB antibiotic therapy, MO microorganism, OPAT outpatient parental antibiotic therapy, CDRIE cardiac device related infective endocarditis.</p>		

Patient characteristics (Table 2)

Sixty-six patients (96%) were adults ≥ 16 years, 71% (n=49) of whom were male. The median age of the patients in the cohort was 51 years (range 3-95). Thirteen patients (19%) had a previous IE episode in their medical history, 2 patients were treated for an IE relapse with the same microorganism as the previously documented episode.

All patients lived at home before hospitalization and were discharged home for OPAT. Median duration of hospital stay before discharge with OPAT was 23 days (range 5-64).

Disease and treatment related characteristics (Tables 2 and 3)

The aortic (n=30) and mitral valve (n=30) were most commonly involved. Only one patient had a cardiac device-related IE. Prosthetic valve IE accounted for 50% (n=35) of the 70 OPAT episodes. Streptococci were the predominant causative organism (n=44, 63%), followed by staphylococci (20%, n=14), the majority of which were *S. aureus* (n=11). Ceftriaxone was the most frequently used antibiotic (n=56, 80%). Sixty-nine percent (n=48) of patients required cardiac surgery. The median time between surgery and initiation of OPAT was 18.2 days (range 7-62). During hospitalization, septic embolic complications were registered in 24 of 70 IE episodes (34%), 13 of which involved cerebral emboli.

Outcomes (Table 3 and Table 4)

Clinical cure at 3 months after stopping of OPAT was achieved in 67 of 70 episodes (96%). Two patients died before completing the follow-up period, and both deaths were unrelated to OPAT (one during OPAT due to gram-negative abdominal sepsis and one during OPAT due to a witnessed cardiac arrest 2 days after a reassuring clinical check-up by the cardiac surgeon). One patient developed a new episode of IE with a different microorganism one month after completing OPAT.

Unplanned readmissions were observed in 13 out of 70 episodes (19%) up to 3 months after OPAT. Two patients were readmitted during OPAT because of antibiotic related problems (one case of nonallergic intolerance to ceftriaxone and one case of high anion gap metabolic acidosis (HAGMA) with 5-oxoproline accumulation, which could be attributed to flucloxacillin, but also to starvation, paracetamol use and renal insufficiency). The reasons for readmission after the end of OPAT are listed in Table 4.

The median duration of OPAT was 19 days (range 4-35); the median total duration of antibiotic treatment was 42 days (range 28-82). Overall, OPAT resulted in 1328 avoided hospitalization days.

Table 3: Outcome.

Duration of admission, treatment and OPAT	Mean (+/-SD)	Median (range)
Duration admission	23.1 (8.7)	23 (5-64)
Duration of antibiotic therapy	41.5 (7.2)	42 (28-82)
Days between admission and CS	6.8 (6.0)	5.0 (0-27)
Days between CS and OPAT	16 (8.1)	18.2 (7-62)
Duration of OPAT	19 (7.5)	19 (4-35)
Avoided hospital days (in total)	1328 days	
Outcome 30 days after stop OPAT	N (%)	
Cure	69 (98.6)	
Dead [^]	1 (1.4)	
Readmission	10 (14.3)	
- Due to complication of IE	3 (4.3)	
- Due to complication of AB (ADE)	2 (2.9)	
- Other not OPAT/AB/IE related	5 (7.1)	
Outcome 3 months after stop OPAT	N (%)	
Cure	67 (95.7)	
Dead [^]	2 (2.9)	
Readmission	13 (18.6)	
- Due to complication of IE	5 (7.1)	
- Due to complication of AB (ADE)	2 (2.9)	
- Other not OPAT/AB/IE related	6 (8.6)	
- Reinfection with different MO	1 (1.4)	
[^] unrelated to IE CS cardiac Surgery, IE infective endocarditis, AB antibiotic therapy, MO microorganism, OPAT outpatient parental antibiotic therapy, ADE adverse drug event		

Table 4: Readmission reasons (during OPAT and follow up).

Related to IE / AB (n=7)	Other (n= 6)
Reinfection (n=1)	Atrial fibrillation (n=1)
Redo valve surgery (unplanned) (n=2)	COVID infection (n=2)
Heart failure (n=2)	Gram-negative sepsis (n=1)
Intolerance of Ceftriaxone (n=1)	Kidney failure due to diuretics (n=1)
HAGMA with 5-oxoproline accumulation due to flucloxacillin (n=1)	Malignancy (n=1)

Discussion

Consistent with the findings of previous studies, our findings indicate that our OPAT program is both effective and safe for treating IE in patients who meet the selected criteria. The cure rate was high, and the incidence of unplanned readmissions due to OPAT was low.

A key factor contributing to the positive outcomes observed in our study was the effective collaboration between the multidisciplinary endocarditis team and the formalized, centralized OPAT service. This service includes clear protocols and close patient follow-up by an OPAT coordinator [6,14,18].

We included patients considered to be at increased risk of complications during OPAT, specifically a high proportion of patients with prosthetic valve IE, a few patients with *Staphylococcus aureus* IE, patients with preexisting renal impairment [19,20], and those with a medical history of IE [21,22]. Due to the prevalence of these high-risk groups (Table 2), compared to the findings of other studies (14% [22], 28% [11], 27% [20], 44% [10], 23% [23], 0% [24], a large proportion (69%) of our patients underwent valve surgery during hospitalization, usually within the first week. Durojaiye et al. [20] and Pericas et al. [16] both concluded that early surgery is associated with favourable long-term outcomes and serves as a protective factor during OPAT [10]. Early surgery can have contributed to the relatively low rate of unplanned readmissions and adverse events we observed.

Another noteworthy fact is the inclusion of a high percentage (34%) of patients with septic emboli, especially cerebral emboli (19%). The OPAT GAMES criteria suggest to excluding patients from OPAT if they have multiple (more than 3), large (more than 2 cm) or hemorrhagic emboli, or if they have fixed neurologic deficits [10]. According to these criteria, 10 out of 13 patients with emboli in our cohort would not have been eligible for OPAT, yet they still experienced favorable outcomes. Interestingly, the new ESC guidelines also exclude patients with neurological involvement and renal impairment, although no firm definitions are provided [5].

Based on the positive outcomes observed in this study, we believe that the exclusion criteria may need to be reconsidered for selected patients, and further research seems warranted.

Most studies have reported a higher incidence of adverse events, up to 27%, including drug- or line-related complications [9,10,20,22,23]. We observed very few drug-related events and no line-related complications. This could be attributed at least partly to our use of single-agent antibiotic therapy and the fact that no patients received glycopeptide therapy, factors that are known to carry a higher risk for adverse events [6,18].

The all-cause readmission rate in our study was relatively low (19%) compared to that in earlier studies, in which readmission rates reached 50% [11,20,21,23]. Early surgery, as previously mentioned, may have contributed to the low readmission rate, but the rather late switch to OPAT could also be a factor. Pericas et al. [16] reported a 3 month readmission rate of only 10-16%, especially when patients met the OPAT GAMES criteria and had very intensive follow-up (daily nurse visits, and twice-weekly consultations with the attending physician) [10].

The median duration of hospitalization prior to discharge with OPAT was 23 days, with a wide range (5 to 64 days), due to two specific patients. One patient was a child with congenital heart disease who was discharged after only 5 days of in hospital antibiotic treatment because of social considerations. The other patient was an adult who had an in hospital stay of 64 days for *S. aureus* IE due to persistent positive blood cultures, required two valve surgeries, and was discharged with OPAT for the remaining 19 days of a total 82-day antibiotic course.

The majority of our patients were treated before the publication of the 2023 ESC revised guidelines for the management of endocarditis. When comparing our cohort to these guidelines, we could have initiated OPAT earlier after the start of antibiotic treatment, and particularly earlier after valve surgery [5]. In contrast with the guidelines' recommendations, we did not routinely perform transoesophageal echocardiography (TOE) before deciding to switch to OPAT. The advantages of TOE may include visual confirmation of stable disease without new surgical indications. During the follow-up of stable IE patients, we relied on weekly transthoracic echocardiography. We believe that the absence of TOE did not affect outcomes in our cohort because the time to OPAT initiation was longer than anticipated in the new guidelines, and our study was strictly observational.

We consider it a strength of our study that it is monocentric and that we have an endocarditis team in place since 2000, leading to homogeneous treatment of all our patients.

This study has several limitations. First, this was a retrospective analysis, but the data were originally collected

prospectively, which reduces the risk of missing data. Second, the cohort was small. The selection of IE patients for OPAT was not systematic, as the decision for and timing of OPAT mainly depended on the treating physician's request. Therefore, and due to the observational design of the study, there may have been selection bias, resulting in the inclusion of a relatively healthy group with few comorbidities. Two additional considerations are the choice we made to offer only monotherapy in OPAT, which led to treating a more selective and potentially less complex group of patients, and the relatively short follow-up period.

The results of the present study identified several opportunities for improving our OPAT program. OPAT reduced the hospital length of stay by a median of 19 days, thereby avoiding 1328 hospitalization days in 5.5 years. However, the duration of OPAT was relatively short (range 17-27 days) compared to that of other studies and as suggested in the ESC guidelines [5,10,20,22,23]. Moreover, OPAT were used for approximately 1 out of the 10 hospitalized IE patients, whereas other studies have reported the possibility of continuing treatment with OPAT for up to 50% of their IE population [10,11,23]. This could be improved by increasing awareness among treating physicians about the possibility of OPAT. Additionally, the COVID-19 pandemic, which started in 2020, contributed to reduced OPAT usage due to logistical problems, reorganization, and a shift toward other hospital workloads. This is reflected in the inclusion of only one patient in 2020 and 15 patients in both 2021 and 2022. Since 2023, there has been a marked increase in inclusions.

Therefore, we aim to implement a broader and earlier selection of patients according to the GAMES criteria and new ESC criteria in the near future. We believe that a structured selection would allow substantially more patients to benefit from OPAT, further reducing hospital LOS while maintaining the quality of care we strive to provide.

Oral therapy is a promising new option for treating IE and plays a prominent role in the newest guidelines; however, identifying the advantages of continuing IV therapy is important [5]. First, the same antibiotic used in the hospital is continued, ensuring appropriate tissue levels and guaranteed bioavailability. Moreover, IV therapy, involving daily contact between the patient and home care nurse, offers better control over adherence which is crucial for managing a life-threatening disease. Research on and development of antibiotics with a better stability profile for prolonged IV treatment are needed to expand treatment options (e.g. IV amoxicillin is currently not feasible in OPAT due to its instability for prolonged IV infusion). Furthermore, patients' experiences with continuing IV treatment seem generally positive, allowing them to resume their daily activities and even return to work while continuing a treatment with proven efficacy [13,15].

In conclusion, OPAT for IE was found to be safe and

effective at our center. As the ESC guidelines state, we confirm that OPAT helps to alleviate the effects of infection and prolong hospitalization.

Statements and Declarations

Funding: This study was not funded.

Conflict of interest: All the authors declare that they have no competing interests.

Data access: The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee for Research, University Hospitals Leuven, Belgium; S60847) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Contribution

IS, LE and CQ initiated the OPAT study and wrote the protocol, LH and HH initiated the sub study of IE patients and all remaining authors reviewed them. HH analyzed the data under the supervision of LH. HH wrote the first draft of the manuscript, which was reviewed by all the authors.

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