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RESEARCH

Outpatient parenteral antibiotic therapy in non-cystic fibrosis lung transplant recipients: characteristics, efficacy and safety

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Abstract

Purpose Bacterial isolation is associated with worse outcomes after lung transplantation (LTx), and successful bacterial eradication is shown to improve long-term survival and pulmonary function. Outpatient Parenteral Antibiotic Therapy (OPAT) may be an effective therapeutic modality for bacterial eradication post-LTx.

Methods A single-center, retrospective analysis of OPAT characteristics, efficacy, safety, and costs in non-cystic fibrosis LTx recipients.

Results A total of 156 OPAT courses (from June 2019 to December 2022) were evaluated in 108 distinct LTx recipients. OPAT mainly consisted of dual antibiotic therapy (69%) for pulmonary bacterial isolation (97%), mostly *Pseudomonas aeruginosa* (66%). Successful eradication at 3 months post-OPAT was achieved in 71%. Eradication rate was significantly higher in patients treated after the first post-operative year (79%), compared to patients within the first year (61%) ($p=0.017$). Eradication rate was similar for multidrug resistance (eradication rate 61%) versus no multidrug resistance (74%) ($p=0.116$). Spirometry remained stable at 90 days post-OPAT. A statistically significant, but clinically negligible, increase in serum creatinine at 90 days post-OPAT was observed (1.33 mg/dL vs. 1.39 mg/dL, $p<0.001$), yet unrelated to the antibiotic regimen used. OPAT-related hospital admissions occurred in 13% and line-related adverse events in 6%. Median number of hospitalization days saved per OPAT-course was 10 days (range 2–92), accounting for a total of 1841 avoided admission days and an estimated net cost reduction of 47% per treatment course.

Conclusion OPAT is an effective and safe therapeutic modality for bacterial eradication post-LTx, associated with a significant reduction in hospitalization days and treatment costs.

Keywords Outpatient parenteral antibiotic therapy · OPAT · Lung transplantation · Eradication · Efficacy · Safety

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Introduction

Lung transplantation (LTx) is a well-established, life-saving intervention in selected patients suffering from advanced lung disease such as emphysema, fibrotic lung diseases, cystic fibrosis (CF), and pulmonary hypertension. To date, however, long-term graft survival remains limited. Development of chronic lung allograft dysfunction (CLAD) is an important determinant affecting long-term graft survival after LTx [1, 2]. Respiratory infections with bacterial, viral, or fungal microorganisms, and bacterial chronic respiratory tract colonization, most notably by *Pseudomonas aeruginosa* (PsA), are known risk factors for CLAD onset and progression [3–11]. Conversely, PsA eradication was shown to preserve lung function and improve CLAD-free and graft

survival [12]. Implementation of antimicrobial eradication strategies faces significant hurdles. Many antibiotic regimens involve parenteral administration of (multiple) antibiotics, requiring extended (often up to 14 days) inpatient treatment, placing significant financial and logistical burden on the healthcare system [13, 14].

In 2019, a dedicated "Outpatient Parenteral Antibiotic Therapy" (OPAT) program was established at the University Hospitals Leuven (Belgium) to also cater tailored outpatient antibiotic treatment specifically for non-CF LTx recipients, similar to the OPAT program for CF patients established in our center since 2010. The OPAT program was designed to overcome the logistical challenges associated with antimicrobial eradication strategies and to provide personalized, high-quality patient care while pursuing swift initiation of eradication treatment upon bacterial isolation after LTx. In this study, we retrospectively assessed OPAT-related characteristics, outcomes, safety, and costs in non-CF LTx recipients at our center.

Patients and methods

Patient population and study design

All consecutive non-CF transplant recipients (bilateral lung, single lung, and heart-lung) in follow-up at the University Hospitals Leuven ($n=570$), who received OPAT between July 1st 2019 and December 31th 2022, were included in this single-center retrospective study. Transplanted CF patients in follow-up ($n=135$) were excluded from the current study because OPAT for these LTx recipients is coordinated by a separate dedicated CF team in our center, and because most of these patients receive long-term treatment with nebulized antibiotics (e.g., colistin, tobramycin) in case of bacterial respiratory tract colonization, which may bias analysis of OPAT efficacy. Patients with insufficient microbiological data (e.g., no bacterial identification at baseline) or lacking follow-up data (i.e., at least 3 months post-treatment follow-up required) were also excluded from the current analysis. The remaining LTx recipients were retrospectively evaluated using data extracted from their electronic medical records.

The primary aim of this study was a descriptive analysis of patient- and treatment-related characteristics (i.e., cohort demographics, type and duration of antibiotic treatment, type of bacterial isolation, time post-transplant, type of intravenous access for OPAT, etc.) and eradication efficacy (i.e. bacterial recurrence rate) of OPAT-treated patients. Secondary endpoints included OPAT-related hospital (re)admission rate, hospital stay (duration), adverse event rate (e.g., catheter-related complications, kidney function evolution), short term evolution of pulmonary function (FEV1, L/min) and renal function (serum creatinine, mg/dL) post-OPAT, avoided hospitalization days, and cost analysis compared to inpatient treatment.

Patients who underwent OPAT for non-respiratory infections were included for the purpose of safety and cost analysis but were not considered in the analysis of lung function evolution.

Treatment considerations

Antibiotic treatment was initiated at the discretion of the treating transplant physician, per protocol within a week after bacterial isolation. Historically, as in most European transplant centers (unlike to the USA or UK), there is no designated Infectious Diseases specialist involved in the antibiotic treatment of the solid organ or stem cell transplant recipients in our center. Choice of antibiotic regimen was guided by antibiotic susceptibility testing according to standard microbiological protocols, but dual antibiotic treatment was considered the standard approach in case of intermediary antibiotic susceptibility or multidrug resistance (MDR).

Pending antibiotic susceptibility, Piperacillin-tazobactam was the treatment of choice over ceftazidime in our OPAT program, as this allowed for continuous parenteral infusion over 24 h with once-daily renewal by the home care nurse. Ceftazidime, on the other hand, for reasons of drug stability only allows continuous infusions over 8–12 h, thus requiring more frequent manipulations by the homecare team (which may increase the risk of complications). Meropenem (intermittent parenteral administration only) was given in case antibiotic susceptibility testing did not allow an alternative treatment option. Antibiotics were intravenously infused via a computerised ambulatory delivery device (CADD) pump (for continuous and prolonged infusion) and/or via gravity administration sets (for single administration).

The decision for outpatient (as opposed to inpatient) parenteral treatment was made based on patient preference, patient condition (medical and social), availability of adequate venous access, and of an antibiotic regimen compatible with outpatient administration. Initiation of antibiotic therapy was always performed in hospital, after ensuring adequate venous access through a peripherally inserted central catheter (PICC), midline catheter, or through an existing port catheter (Porthacath).

Following hospital discharge, parenteral antibiotics administration was performed by an OPAT-trained home care nurse for the entire treatment duration (i.e., no "self-administered" OPAT, contrary to what is common practice for OPAT in CF patients). For this, collaboration with a specialized home healthcare provider was implemented (Remedus, Aartselaar, Belgium, https://www.remedus.be

/en/over-ons-eng/), which allowed remote monitoring of parameters related to patients' home treatment through an online platform (RemeCare, ISO 13485, CE). Direct communication between the treating physician and involved healthcare providers was facilitated by the RemeCare platform. When necessary for therapeutic drug monitoring (i.e., during aminoglycoside treatment), venous blood samples were obtained at home by the OPAT nurse, and subsequently shipped to the hospital's clinical lab for analysis of trough level and kidney function on the same day. In case of elevated aminoglycoside trough levels, subsequent dose reduction (e.g., if ≥ 0.5 mg/L for tobramycin) or drug cessation (i.e., if ≥ 1 mg/L for tobramycin or ≥ 3 mg/L for amikacin) were implemented within the next 24 h in all cases (via direct feedback to the patient's OPAT nurse).

Treatment definitions

Upon OPAT completion, all patients were clinically evaluated by the attending transplant pulmonologist. Spirometry, chest X-ray and venous blood sampling were repeated as part of routine care. Further follow-up visits were scheduled at 90 days (at the most) after OPAT cessation, earlier visits occurred upon clinical indication.

Successful eradication was defined as absence of the respective bacterial species that prompted initiation of antibiotic treatment in all samples obtained during the 3 months following treatment. Unsuccessful eradication was defined as persistence or recurrence of isolation of the same bacterial species in any sample collected within 3 months following treatment. Antibiotic MDR was defined in accordance with SET/GESITRA-SEIMC/REIPI recommendations, as an acquired non-susceptibility to at least 1 agent in 3 or more antibiotic categories [13].

Respiratory samples included sputum samples, bronchial aspirates, or bronchoalveolar lavage (BAL) fluid, either obtained during routine follow-up or upon indication by respiratory symptoms and/or lung function decline. Other samples (cerebrospinal fluid, blood cultures, urine cultures, wound swabs) were collected upon clinical indication.

Data collection

Data on all OPAT courses were retrospectively obtained from the electronic medical patient records. This included baseline demographics, microbiological data, longitudinal data on lung and renal function, therapeutic drug monitoring, type of IV access, type of antibiotic regimen, treatment duration, adverse events (i.e., catheter-related infections and venous thromboembolism, line-related adverse events, adverse drug events, readmission rate), and costs.

Cost estimations

Estimated net costs per treatment course were calculated by the difference in costs for inpatient antibiotic treatment (i.e. costs related to hospital stay (per-day hospital cost) and effective antibiotic costs) versus effective expenses for ambulatory treatment with OPAT (i.e., ambulatory antibiotic costs, nursing costs, costs for pumps/administration sets, disposables, venous blood sampling and shipping of blood samples not covered by healthcare insurance). For this, we considered that hospitalization beds vacated by OPAT can be used to admit other patients, for which at least a 50% stable bed occupancy was taken into account for the number of inpatient hospitalization days saved by OPAT. At the time of our study, OPAT was not reimbursed in Belgium. OPAT-related expenses were therefore covered by a dedicated patronage fund managed by the senior investigator (RV).

Statistical analysis

Patient characteristics and variables of interest/endpoints are summarized using descriptive statistics, and results are expressed as total value, proportions, or median (range), wherever appropriate. Proportions are compared using Chi-square testing. Groups are compared using Mann-Whitney test, or Wilcoxon matched-pairs signed-rank test for repeated measures. A p-value < 0.05 was considered significant. All statistical analyses were performed using IBM® SPSS® Statistics Standard Edition (saas-version).

Ethical approval and consent to participate

At listing for LTx, all patients provided signed informed consent to use their clinical data for scientific research purposes by affiliated researchers of University Hospitals Leuven. OPAT was initiated after oral consent of the LTx recipient following therapeutic proposal by their treating physician. The institutional Ethics Review Board waived approval for the current observational study (MP024367), which was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Study population

Between July 1st 2019 and December 31th 2022, a total of 159 OPAT courses were initiated in 110 individual LTx recipients. We excluded 1 patient who lacked sufficient microbiological data at baseline (accounting for 2 treatment

courses) and 1 patient who was lost to follow-up (accounting for 1 treatment course). Finally, 108 distinct patients were retained for analysis, with a total of 156 OPAT courses.

Transplant-related patient demographics

Transplant demographics are summarized in Table 1.

Median age at transplantation of the included patients was 58 years (interquartile range, IQR 50–62), most were male (56%), and most had undergone bilateral lung transplantation (SSLTx) (97%), except for three patients who underwent a combined heart-lung transplantation (HLTx). The most frequent indications for transplantation were chronic obstructive pulmonary disease (COPD)/emphysema (61%), interstitial lung disease (ILD) (27%) and pulmonary hypertension (4%). Most patients were treated with a tacrolimus (83%)/mycophenolate (68%)/steroid (99%)-based triple immunosuppressive regimen. At the time of OPAT, 85% of patients ($n=132$ treatment courses) were on a triple immunosuppressive regimen, while 15% ($n=24$ treatment courses) received dual immunosuppressive therapy.

Table 1 Transplant-related patient demographics

Variable		
Patients, *n*	108	
Age at LTx, years (IQR)	58	(50–62)
Sex, *n (%)*		
Male	61	(56)
Female	47	(44)
Type of transplant, *n (%)*		
SSLTx	105	(97)
HLTx	3	(3)
Underlying disease, *n (%)*		
Emphysema/COPD	66	(61)
ILD	29	(27)
PH	4	(4)
Other	9	(8)
Immunosuppressive therapy at start OPAT, *n (%)*		
Calcineurin blockers		
Tacrolimus	130	(83)
Cyclosporine	23	(15)
mTOR inhibitors		
Everolimus	2	(1)
Sirolimus	1	(1)
Cell cycle inhibitors		
Mycophenolate	106	(68)
Azathioprine	25	(16)
Corticosteroids	155	(99)

Abbreviations LTx: lung transplantation, SSLTx: sequential single (bilateral) lung transplantation, HLTx: heart-lung transplantation, COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, IQR: interquartile range, PH: pulmonary hypertension, mTOR: mammalian target of rapamycin, OPAT: outpatient parenteral antimicrobial therapy

OPAT-related demographics

OPAT demographics are summarized in Table 2.

Median age at inclusion was 60 years (IQR 53–65), with a median time since transplantation of 18 months (IQR 5–72, range 0-353). Following ensured vascular access and inpatient antibiotic treatment initiation, patients were subsequently discharged for continuation of antibiotic treatment at home. Median duration of hospitalization prior to discharge with OPAT was 3.5 days (IQR 3–5, range 1–32 days). Vascular access for OPAT was obtained through a temporary catheter, i.e., PICC ($n=143$ courses, 92%) or midline catheter ($n=2$, 1%), whereas in 11 courses (7%) a port catheter was used. Median antibiotic treatment duration was 14 days (IQR 14–15, range 7–99 days).

Isolation of a respiratory pathogen was the primary reason for OPAT initiation ($n=151$, 97%). Non-respiratory indications included central nervous system infections ($n=2$), post-ERCP sepsis ($n=1$), urinary tract infection ($n=1$) and soft tissue infection ($n=1$). In total, 47% ($n=73$) of respiratory samples were obtained from surveillance sampling during routine follow-up, whereas 53% ($n=78$) were obtained upon indication, guided by lung function decline, progressive respiratory symptoms, or overt respiratory infection.

The most frequently isolated pathogen was PsA (66%, $n=103$), followed by *Klebsiella pneumoniae* (6%, $n=9$), *Escherichia coli* (6%, $n=9$) and *Serratia marcescens* (5%, $n=8$). MDR bacteria were present in 28% ($n=44$) of OPAT courses. PsA constituted 5 of these 44 courses (11%), the remainder ($n=39$, or 89%) related to other gram-negative bacteria, i.e. *Klebsiella pneumoniae* ($n=8$), *Escherichia coli* ($n=8$), *Serratia marcescens* ($n=8$), and *Klebsiella aerogenes* ($n=3$). Antibiotic susceptibility per bacterial species revealed MDR in 5% (5 out of 103) of all PsA isolates. In contrast, 68% (36 out of 53) of the remaining non-PsA isolates were MDR. These included *Klebsiella pneumoniae* (8 out of 9 isolates, 89%), *Escherichia coli* (8 out of 9 isolates, 89%), *Serratia marcescens* (8 out of 8 isolates, 100%), and *Klebsiella aerogenes* (3 out of 4 isolates, 75%).

Surveillance samples prompting OPAT initiation included BAL ($n=65$, 89%) and sputum cultures ($n=8$, 11%), whereas indication samples (i.e., obtained because of symptomatic patient, lung function decline, or extrapulmonary infection) included BAL ($n=54$, 65%), sputum ($n=21$, 25%), pleural fluid ($n=2$, 2%), and bronchial aspirate ($n=1$, 1%), as well as samples of non-respiratory origin (6%): blood cultures ($n=2$, 2%), cerebrospinal fluid ($n=1$, 1%), wound swab ($n=1$, 1%), and urine culture ($n=1$, 1%).

Table 2 OPAT-related patient demographics

Variable		
Patients	108	
Age at OPAT, years (IQR)	60	(53–65)
Time since LTx, months (IQR)	18	(5–72)
Vascular access, type, n (%)	143	(92)
PICC	2	(1)
Midline		
Porth catheter	11	(7)
Days hospitalized, days (IQR)	3.5	(3–5)
Treatment duration, days (IQR)	14	(14–15)
Inpatient days saved, days (IQR)	10	(9–11)
Treatment courses, n	156	
Repeatedly treated patients, n (%)	29	(27)
Repeat treatment courses, n (%)	48	(31)
Repeat for same bacterium	37	(77)
Repeat for different bacterium	11	(33)
Microbiology of OPAT courses		
Pathogen, n (%)	156	
Pseudomonas aeruginosa	103	(66)
Klebsiella pneumoniae	9	(6)
Escherichia coli	9	(6)
Serratia marcescens	8	(5)
Klebsiella aerogenes	4	(3)
Burkholderia cepacia	3	(2)
Enterobacter cloacae	3	(2)
Nocardia nova	2	(2)
Serratia liquefaciens	2	(2)
Stenotrophomonas maltophilia	2	(2)
Other	11	(7)
Multidrug resistance, n (%)	44	(28)
Pseudomonas aeruginosa	5	(11)
Other	39	(89)
Focus, n (%)	156	
Pulmonary	151	(97)
Central nervous system	2	(1)
Bloodstream	1	(1)
Urinary tract	1	(1)
Soft tissue	1	(1)
Sampling of OPAT courses	**Indication**	**Surveillance**
Respiratory, n (%)	78 (94)	73 (100)
Bronchoalveolar lavage	54 (65)	65 (89)
Sputum	21 (25)	8 (11)
Pleural fluid	2 (2)	0
Bronchial aspirate	1 (1)	0
Non-respiratory, n (%)	5 (6)	0
Blood culture	2 (2)	0
Cerebrospinal fluid	1 (1)	0
Wound swab	1 (1)	0
Midstream urine	1 (1)	0

Abbreviations see main text or Table 1

Table 3 Characteristics of antibiotic therapy

Antibiotic regimen of OPAT courses		
Piperacillin-tazobactam based, n (%)	126	(81)
+ Aminoglycoside	73	(47)
+ Oral antibiotic	22	(14)
Monotherapy	31	(20)
Meropenem based, n (%)	16	(10)
+ Ceftazidime	1	(1)
+ Oral antibiotic	5	(3)
Monotherapy	10	(6)
Ceftazidime based, n (%)	10	(6)
+ Aminoglycoside	5	(3)
+ Oral antibiotic	2	(1)
Monotherapy	3	(2)
Other, n (%)	4	(3)
Therapeutic drug monitoring		
Aminoglycoside treatment courses, n (%)	79	(51)
Tobramycin, n (%)	75	(95)
Amikacin, n (%)	4	(5)
Aminoglycoside trough level at day 3, n (%)	76	(96)
Tobramycin trough level at day 3 (mg/L), median (range)	0.6	(0-2.3)
Toxic aminoglycoside trough level at day 3, n (%)	17	(22)
Aminoglycoside trough level at day 8, n (%)	75	(95)
Tobramycin trough level at day 8 (mg/L), median (range)	0.7	(0-3.9)
Toxic aminoglycoside trough level at day 8, n (%)	19	(25)
Any toxic aminoglycoside trough level, n (%)	27	(34)

Aminoglycoside trough levels are considered toxic in case of tobramycin ≥1mg/L and amikacin ≥3 mg/L

Antibiotic-related demographics

Characteristics of antibiotic therapy are summarized in Table 3.

Dual antibiotic therapy (either by adding an aminoglycoside or an oral alternative, such as a quinolone) was the treatment of choice over monotherapy in case of reduced ('intermediary') antibiotic susceptibility, or in case of MDR. As a result, OPAT consisted of dual antibiotic therapy in 69% of cases, i.e., administration of two parenteral antibiotics in 51% ($n=79$), and of one parenteral *plus* one oral antibiotic in 19% ($n=29$), while 31% consisted of parenteral antibiotic monotherapy. The most frequently used antibiotic was therefore piperacillin-tazobactam (126 of 156 cases, 81%), given in combination with aminoglycosides ($n=73$, 47%), an oral antibiotic ($n=22$, 14%, usually levofloxacin) or as a stand-alone therapy ($n=31$, 19%). Alternative treatments were meropenem-based (16 of 156 cases, 10%), ceftazidime-based (10 of 156 cases, 6%), or other (3%).

Therapeutic drug monitoring during aminoglycoside treatment, both for tobramycin ($n=75$) and for amikacin ($n=4$), was performed on day 3 after treatment initiation (mostly in-hospital) and on day 8 of treatment (at home).

Serum aminoglycoside trough levels on day 3 and day 8 were available in 76 and 75 (out of 79) patients, respectively. Median tobramycin trough level was 0.6 mg/L (range 0-2.3) on day 3 and 0.7 mg/L (range 0-3.9) on day 8. Potentially nephrotoxic trough levels (i.e., ≥1 mg/L for tobramycin and ≥3 mg/L for amikacin) were seen in 22% (17 out of 76 samples) on day 3, in 25% (19 out of 75 samples) on day 8, and at any time during treatment in 34% of cases (27 out of 79 samples).

Treatment outcomes

Microbiological outcomes are summarized in Table 4 and determinants of bacterial eradication in Table 5.

Successful eradication, defined as negative cultures during 3 months of follow-up post-OPAT, was achieved in 71% (110 out of 156 OPAT courses). The same percentage was seen in the respiratory subgroup (107/151, 71%). In patients who underwent repeated OPAT courses, i.e., in case of persistent or repeated bacterial isolation, similar success rates were noted upon each subsequent OPAT course.

No significant difference was seen in eradication rates regarding underlying disease (chronic obstructive pulmonary disease vs. interstitial lung disease vs. other, $p=0.137$), or treatment regimen (dual parenteral antibiotic therapy vs. parenteral plus oral antibiotic therapy vs. parenteral monotherapy, $p=0.762$). The same was true when only the subgroup of PsA was considered ($p=0.236$). Eradication rates were, however, significantly higher in patients beyond the first post-operative year (79%), compared to patients treated within the first year (61%) ($p=0.017$). Eradication rates tended to be non-significantly higher in non-MDR cases (74%), compared to MDR cases (61%) ($p=0.116$), especially in non-MDR PsA (76%) vs. MDR PsA (40%) ($p=0.08$).

Graft function and kidney function at the start of OPAT were compared to corresponding values 90 days before and 90 days after OPAT, respectively. Evolution of FEV1 and serum creatinine levels is depicted in Fig. 1.

FEV1 increased prior to start of OPAT, from 2.15 L/min (0.55–4.92) to 2.17 L/min (0.51–4.93) ($p=0.008$). At 90 days post-OPAT, FEV1 further increased, yet not significantly, to 2.21 L/min (0.5–4.96) ($p=0.43$). Serum creatinine levels significantly increased prior to start of OPAT, from 1.23 mg/dL to 1.33 mg/dL ($p=0.043$), and further increased at 90 days post-OPAT to 1.39 mg/dL ($p=0.035$), indicating a slight, but clinically negligible, decrease in renal function after OPAT.

Table 4 Microbiology outcomes

Eradication characteristics of OPAT courses		
Eradication rate, *n(%)*		
Eradication at 3 months	110	(71)
Respiratory only	107	(71)
Dual IV therapy	56	(70)
Combined IV-Oral	22	(76)
Monotherapy	32	(68)
Eradication rate in repeat OPAT, n (%)		
1st episode	76	(70)
2nd episode	20	(69)
3rd episode	9	(69)
4th episode	4	(80)
5th episode	1	(100)

Abbreviations IV: intravenous, OPAT: outpatient parenteral antimicrobial therapy

Table 5 Determinants of bacterial eradication

Variables for successful eradication			*p*
Antibiotic modality, n (%)			0.762
Dual IV	56	(70)	
IV - oral combination	22	(76)	
IV monotherapy	32	(68)	
Antibiotic modality - PsA only, n (%)			0.236
Dual IV	53	(72)	
IV - oral combination	16	(89)	
IV monotherapy	7	(64)	
Diagnosis, n (%)			0.137
Emphysema	65	(69)	
ILD	28	(65)	
Other	17	(89)	
Time since Tx			0.017
≤12 months	44	(61)	
>12 months	66	(79)	
Multidrug resistance, n (%)			0.116
MDR	27	(61)	
Non-MDR	83	(74)	
Multidrug resistance - PsA only, n (%)			0.08
MDR	2	(40)	
Non-MDR	74	(76)	
Multidrug resistance - non-PsA, n (%)			0.99
MDR	25	(64)	
Non-MDR	9	(64)	

Abbreviations IV: intravenous, PsA: Pseudomonas aeruginosa, ILD: interstitial lung diseases, MDR: multidrug resistant

Adverse events

A summary of all recorded adverse events is given in Table 6.

Readmission (for any reason) within 3 months after OPAT occurred in 24% (38 out of 156 OPAT courses). Of these, 21 events (87% of all readmissions, or 13% of all OPAT courses) were possibly OPAT-related: 2 patients were admitted due to treatment failure (1 empyema initially

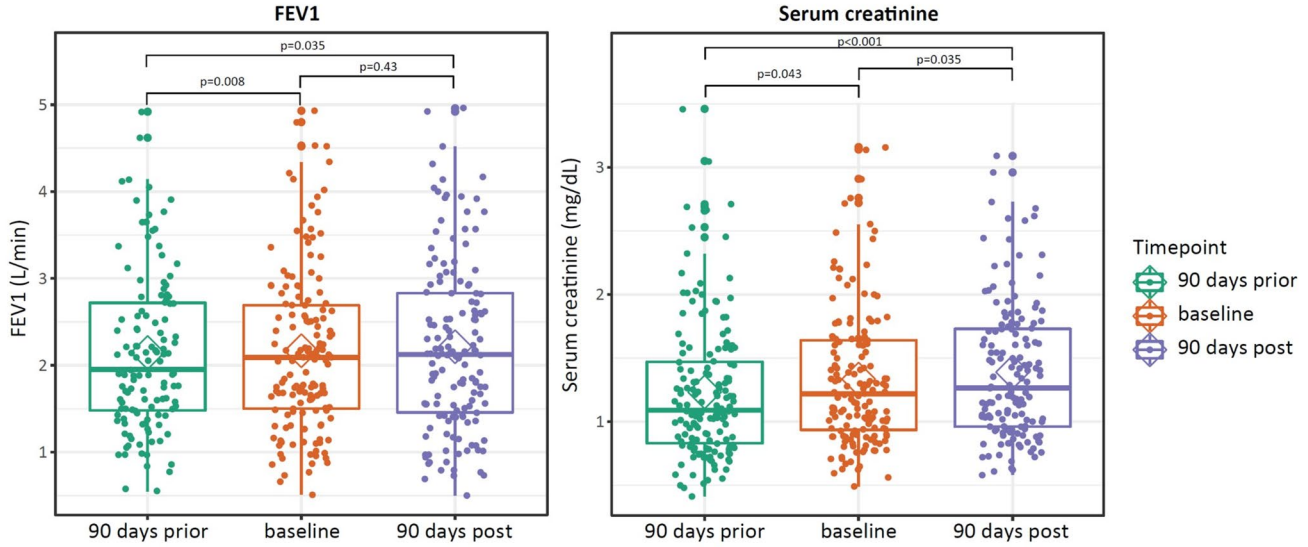

Fig. 1 Evolution of FEV1 and serum creatinine. Boxplots (median and interquartile range) representing FEV1 (L/min) and serum creatinine values (mg/dL) 90 days prior to OPAT, at start of OPAT (baseline) and 90 days post-OPAT. *Abbreviations* FEV1: forced expiratory volume in 1 second, OPAT: outpatient parenteral antimicrobial therapy

Table 6 Adverse events

Adverse events of OPAT courses	*n*	(%)
Readmissions within 3 months	38	(24)
OPAT-related readmissions	21	(87)
Unrelated readmissions	17	(13)
Catheter-related infection	0	(0)
Line-related adverse event	9	(6)
Venous thromboembolism		
Deep venous thrombosis	1	(1)
Pulmonary embolism	3	(2)
Adverse drug events		
Diarrhea	16	(10)
CTCAE Grade 1	7	(4)
CTCAE Grade 2	6	(4)
CTCAE Grade 3	3	(2)
Acute Kidney Injury	12	(8)
KDIGO Grade 1	8	(5)
KDIGO Grade 2	4	(3)

Abbreviations OPAT: outpatient parenteral antimicrobial therapy, CTCAE: Common Terminology Criteria for Adverse Events, KDIGO: Kidney Disease Improving Global Outcomes

managed conservatively, but eventually requiring surgical source control; 1 *Burkholderia cepacia* pneumonia with insufficient clinical response), 6 due to recurrent bacterial isolation requiring novel treatment initiation, 1 for ultrasound-proven catheter-associated venous thromboembolism, and 3 patients with pulmonary embolism (imaging of catheter site not available, but clinically not likely line-related). The remaining 9 patients were admitted due to acute kidney injury ($n=7$) or general asthenia ($n=2$).

Importantly, no catheter-related infections occurred. There were 9 cases (6%) of non-thromboembolic line-related adverse events, consisting of issues at the insertion site (bleeding, numbness, pain), catheter obstruction (managed either by aspiration, flushing or local thrombolysis instillation), or partial catheter dislocation. In all, but one, cases these issues were managed in the outpatient clinic, allowing further utilization of the catheter. Catheter replacement was required in 1 case. None of these line-related adverse events resulted in hospital admission or discontinuation of OPAT.

A total of 28 (18%) possible adverse drug events associated with antibiotic treatment were recorded, including diarrhea ($n=16$), acute kidney injury ($n=12$), or a combination of both. Of the patients presenting with acute kidney injury, 9 were being treated with aminoglycosides (all tobramycin), 6 of whom had toxic trough levels during treatment. In general, there was no statistically significant association between receiving aminoglycoside treatment and occurrence of acute kidney injury ($p=0.079$). However, in the subgroup of patients reaching toxic aminoglycoside trough levels ($n=27$), a significant association with acute kidney injury was seen ($p=0.028$). Overall, the most frequently reported adverse drug event was diarrhea ($n=16$), limited to grade 1 ($n=7$) or grade 2 ($n=6$) in most cases, but requiring hospitalization (grade 3) in 3 patients.

Cost analysis

Median antibiotic treatment duration was 14 days (IQR 14–15, range 7–99 days), and the median number of inpatient hospitalization days saved by OPAT was 10 (IQR 9–11, range 2–92) days per treatment course, resulting in a cumulative number of 1841 hospitalization days saved in 156

OPAT courses, which corresponds to a total number of 3214 antibiotic treatment days with OPAT.

Estimated costs for inpatient antibiotic treatment (instead of OPAT) totaled €432,832.83, or on average €2,774.60 per treatment course. Effective OPAT-related expenses totaled €229,455.87, or on average €1,470.87 per OPAT course. Net estimated cost savings for the healthcare budget through OPAT vs. inpatient treatment thus totaled €203,376.96, or on average €1,303.73 per treatment course, thus a cost reduction of 47%.

Discussion

In recent years, OPAT implementation has found its way into standard clinical practice, yet mainly in the USA and UK and to a lesser extent in Europe, where it has been proven to be efficacious as well as safe and cost-effective for various conditions [15–17]. However, OPAT in immunocompromised LTx recipients is not the standard of care in most transplant centers, due to logistical (i.e. geographical distance) or health insurance or reimbursement restrictions, and the risk of adverse events. In this retrospective single-center study we describe our real-word experience with OPAT for the management of infections in non-CF LTx recipients, a population particularly prone to infectious problems given their severely immunocompromised condition, often harboring difficult-to-treat micro-organisms. We demonstrated OPAT in this specific setting to be effective, safe, and likely cost-effective.

Successful bacterial eradication was achieved in 71% of cases, which is in line with previous data from our center, in a cohort which also included CF LTx recipients, mostly receiving inpatient treatment and at a later stage after LTx, in whom eradication rates up to 80% were noted, specifically for PsA [12]. No significant difference in treatment efficacy (eradication rate) was seen across various treatment strategies. This is likely due to the personalized OPAT regimen used, based on preceding antibiotic susceptibility testing and best-possible targeted therapy ('antibiotic stewardship') [13, 14]. Of note, it is common practice in our LTx center to preferably treat (intermediary sensitive) PsA with dual antibiotic therapy and for a minimum of 14 days, to avoid development of antibiotic resistance, and because of the lack of nebulized antibiotics for additional treatment due to local reimbursement restrictions in these non-CF LTx recipients. Overall, the prevalence of MDR in the PsA group was relatively low (5%), which may explain the high rate of successful eradication – yet again, noting that no CF patients were included in our study, in whom MDR rates may be higher. In the non-PsA group, on the other hand, MDR was present in 68% of cases, yet this did not appear to be associated with worse eradication rates, likely because of our susceptibility-directed antibiotic therapy avoiding the use of ineffective antibiotic therapies. Interestingly, the most important determinant of successful eradication was time since transplantation, with a higher eradication rate in patients beyond the first post-LTx year. This may be due to the use of more intensive immunosuppressive therapy during the first year post-LTx, hence leading to less potent innate and the adaptive immune responses to clear bacterial infections in this period.

Another finding indicative of a successful treatment strategy is the fact that lung function did not decline in the months following OPAT, which is in line with previous findings from our group [12]. However, longer follow-up is needed to assess the possible beneficial effects on later CLAD development in these patients.

OPAT-related adverse events are an important consideration in this immunocompromised population, yet overall prevalence of adverse events was rather low in our study. OPAT-related readmissions occurred in 13%, line-related adverse events in 6%, and severe (grade $\geq$ 2) drug-related events in 6% (mainly diarrhea and/or acute kidney injury, no case of allergic reaction). These events are not entirely unexpected from a clinical perspective, as most of these would likely also have occurred during inpatient treatment. Given the high prevalence of chronic kidney disease in solid organ transplant patients - and in LTx recipients in particular - close monitoring of renal function is crucial. Our observation of mild renal function decline over 6 months of follow-up (from 90 days prior to 90 days after OPAT) underscores the importance of strict renal surveillance. Nevertheless, we noted generally no association between the use of aminoglycosides and occurrence of acute kidney injury after OPAT, likely due to close therapeutic drug monitoring avoiding potentially harmful trough levels in most patients. In the few cases with toxic trough levels, however, a significant association with acute kidney injury was seen. This finding underlines that aminoglycoside treatment is safe, providing that adequate care is given to meticulous therapeutic drug monitoring and swift dose adjustments. Finally, the threshold for outpatient assessment or inpatient observation in the event of any medical issues in our LTx patients is low, and rightfully so, which may have led to a higher documentation of grade $\geq$ 2 adverse events.

Estimated treatment cost savings per OPAT course appear to be considerable, and favorable for the overall healthcare budget, which thus may advocate for reimbursement and/or health insurance coverage of OPAT in this vulnerable population in other LTx centers in Belgium or abroad. However, to safely allow venous line manipulation and antibiotic administration, adequate staffing is crucial; and remote monitoring of OPAT-treated patients (e.g., therapeutic drug

monitoring, drug- or line-related adverse events) by the lung transplant team is key to ensure patient safety with OPAT. Furthermore, personnel costs for remote monitoring during OPAT by the LTx team were not considered in our OPAT cost calculations, as these healthcare workers would also have been involved in the inpatient treatment of our LTx patients, yet wages may differ between inpatient and outpatient nurses. Also, costs of unscheduled hospital visits during OPAT were not taken into account for our cost estimation, because we were unfortunately unable to retrieve the exact costs related to these events. As a result, the *actual* cost of OPAT may be higher than what was estimated. Overall, however, cost studies for OPAT in this population are generally lacking, and OPAT costs may be highly variable between different countries and/or scenarios [18–20].

The descriptive nature of our study is an obvious limitation. Despite systematic 3-monthly follow-up of our LTx patients and careful monitoring of respiratory symptoms and lung function, retrospective analysis may have confounded results. CF patients are not represented in our study, which is important because infections in these patients often prove more difficult to successfully eradicate due to high prevalence of MDR organisms. Also, patient-reported outcomes and satisfaction with OPAT were not systematically documented. Questionnaires of quality-of-life parameters could contribute to further optimize patient-centered OPAT care. Also, add-on or prolonged use of nebulized antibiotics was not included in our study but could further increase treatment success. Finally, unlike our center's policy, not all transplant centers may aim to eradicate pathogens found on surveillance bronchoscopy, despite their associated risk for CLAD development, which may limit generalizability of our findings.

Conclusion

In summary, we provide real-world data on OPAT in non-CF LTx recipients, demonstrating that this approach is effective, safe, and could reduce costs for the healthcare budget. Aggressive eradication strategies of specific bacteria, such as PsA, which have been proven to be harmful in terms of pulmonary function evolution and CLAD-free survival after LTx, can be facilitated by implementation of an OPAT program. Higher eradication rates in patients after the first post-transplant year suggest that the level of immunosuppressive therapy may contribute to eradication failure, which warrants further investigation. Adverse events are an important consideration given this vulnerable patient population, yet prevalence was low in our experience. Our findings may therefore facilitate implementation of OPAT for treating infections in LTx and in other solid organ transplant recipients, given that OPAT is properly governed, uses the principles of antimicrobial stewardship, and that early discharge and admission avoidance is supported.

Abbreviations

SSLTx	Bilateral Lung Transplantation
BAL	Bronchoalveolar Lavage
CLAD	Chronic Lung Allograft Dysfunction
COPD	Chronic Obstructive Pulmonary Disease
CF	Cystic Fibrosis
HLTx	Heart-Lung Transplantation
FEV1	Forced Expiratory Volume in 1 second
ILD	Interstitial Lung Disease
LTx	Lung Transplantation
MDR	Multidrug Resistance
OPAT	Outpatient Parenteral Antimicrobial Therapy
PICC	Peripherally Inserted Central Catheter
PsA	Pseudomonas Aeruginosa

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Author contributions FB data collection, data curation, analysis, final draft preparation, review, and editing. SV methodology, data collection, analysis, review, and editing. SI methodology, data collection, review, and editing. QC methodology, data collection, analysis, review, and editing. DS data collection, review, and editing. BS data collection, review, and editing. VBP review, and editing. LN review, and editing. DSL review, and editing. GL review, and editing. DLJ review, and editing. VR conceptualization, deign, methodology, data collection, analysis, data curation, final draft preparation, review, editing, funding.

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Data availability The datasets generated during and/or analyzed during the current study are available upon reasonable request to the corresponding author (RV).

Declarations

Ethical approval The University Hospitals Leuven Ethics Review Board waived approval for the current study (MP024367), which was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Generative AI AI was not used to create or adjust any part of the current work.

Competing interests The authors declare no competing interests.

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