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Safety, Efficacy and Direct/Indirect Cost Analysis of an Outpatient Antimicrobial Therapy Unit: A Prospective Cohort Study from Turkey

Ayaktan Antimikrobiyal Tedavi Ünitesinin Güvenlik, Etkinlik ve Direkt/İndirekt Maliyet Analizi: Türkiye'den Prospektif Kohort Çalışması

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Abstract

Introduction: Outpatient parenteral antimicrobial therapy (OPAT) is uncommon in Turkey and other developing countries, and its popularity has not increased at a satisfactory rate. We aimed to evaluate the direct and indirect cost analysis of an OPAT unit from the perspective of the Turkish health system using real-life data. Additionally, we aimed to investigate the clinical efficacy and safety of the OPAT unit and compare these parameters before and during the pandemic.
Materials and Methods: Patients admitted to the OPAT unit between January 2019 and February 2021 were included in the study. The patients' medical records were obtained from the hospital's electronic database. Real-life data were used for the direct and indirect cost analyses of the OPAT unit. This data were obtained via in-person interviews.
Results: In total, 307 patients were included in the study. The use of the OPAT unit saved 3040 bed days over 25 months. The end-of-treatment success rate was 92.2%. The presence of a urinary system infection, at least one comorbidity, and immunosuppressant administration were significantly higher in patients who were readmitted within 28 days for the same reason for which they were first admitted. The cost of OPAT was approximately 50% less than that incurred during hospitalization.
Conclusion: Outpatient parenteral antimicrobial therapy units are effective, safe, and cost-effective in the context of the Turkish national health system.
Keywords: Outpatient antimicrobial therapy unit, cost analysis, OPAT, safety

Öz

Giriş: Ayaktan parenteral antimikrobiyal tedavi (APAT) Türkiye'de ve diğer gelişmekte olan ülkelerde çok yaygın değildir ve yaygınlığı tatmin edici bir oranda artmamaktadır. Ayaktan parenteral antimikrobiyal tedavi biriminin direk ve indirek maliyet analizini Türk sağlık sistemi perspektifinden gerçek hayat verileriyle değerlendirmeyi amaçladık. Ayrıca APAT ünitesinin klinik etkinliğinin, güvenliğinin araştırılması ve pandemi öncesi-pandemi dönemlerinin karşılaştırılması amaçlandı.
Gereç ve Yöntem: Ocak 2019-Şubat 2021 tarihleri arasında APAT birimine başvuran hastalar çalışmaya dahil edildi. Hastaların tıbbi kayıtları hastanenin elektronik veri tabanından elde edildi. Ayaktan parenteral antimikrobiyal tedavi biriminin direk ve indirek maliyet analizi için gerçek hayat verileri kullanıldı. Maliyet analizi için kullanılan veriler hastalarla yüz yüze görüşülerek elde edildi.
Bulgular: Ocak 2019-Şubat 2021 tarihleri arasında toplam 307 hasta çalışmaya dahil edildi. Ayaktan parenteral antimikrobiyal tedavi ünitesi sayesinde 25 aylık süreçte 3040 yatak günü tasarrufu sağlandı. Ayaktan parenteral antimikrobiyal tedavi ünitesine başvuran hastalarda tedavi sonu başarı oranı %92,2 olarak tespit edildi. Yirmi sekiz gün içinde aynı nedenle tekrar başvuran hastalarda, üriner sistem enfeksiyonu varlığı, en az bir

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Öz

komorbidite varlığı ve immünsupresif tedavi alma durumu anlamlı olarak yüksek bulundu. Ayaktan parenteral antimikrobiyal tedavi ünitesinin maliyetinin, bu hastaların yatarak tedavi görmelerine durumuna göre yaklaşık %50 daha az olduğu tespit edildi.
Sonuç: Sonuç olarak, APAT biriminin Türk ulusal sağlık sistemi bağlamında etkili, güvenli ve maliyet etkin olduğu tespit edilmiştir.
Anahtar Kelimeler: Ayakta antimikrobiyal tedavi ünitesi, maliyet analizi, OPAT, güvenlik

Introduction

In recent years, with the increasing incidence of multidrug-resistant microorganism-induced infections, the widespread use of broad-spectrum parenteral antimicrobial drugs has increased dramatically[1]. This has resulted in the need for hospitalization of patients for the administration of antimicrobials. Outpatient parenteral antimicrobial therapy (OPAT) is a safe and effective alternative treatment option, especially in stable patients who do not require hospitalization other than for parenteral antibiotic administration.

Globally, patients have been treated with OPAT for over 40 years[2]. Approximately 250,000 people per year are treated with OPAT in the United States (US)[3]. Antimicrobial resistance among microorganisms has gradually increased in Turkey as well as in the rest of the world[4,5]. However, OPAT has not been widely used in Turkey; its popularity has been gradually increasing.

Outpatient parenteral antimicrobial therapy applications may be beneficial in terms of reducing the burden of hospital admissions and preventing the spread of multiresistant bacteria. The widespread use of OPAT has become more important than ever, especially during the Coronavirus disease-2019 (COVID-19) pandemic, due to the increased workload and need for beds.

Herein, we aimed to investigate the clinical effectiveness and analyze the direct and indirect costs of OPAT in the Turkish national health system. Additionally, we aimed to compare the OPAT status before and during the pandemic period at our hospital.

Materials and Methods

An OPAT unit was established in January 2013 at the University of Health Sciences Turkey, Ankara Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology. In May 2019, the OPAT unit did not provide services for four months due to relocation of the unit from the Ankara Numune Training and Research Hospital to the Ankara City Hospital in May 2019, the OPAT unit did not provide services for four months due to relocation of the Ankara Numune Training and Research Hospital to the Ankara City Hospital. After the completion of the relocation in October 2019, the six-bed daily infusion unit started to serve at the Ankara City Hospital with the same principles as that at the Ankara Numune Training and Research Hospital. Patients from both hospitals were included in our study because the same cost calculation and clinical efficacy assessment methods were used.

The study protocol was approved by the Ethics Committee of Ankara Training and Research Hospital (no: E-18-2137; date: 19.07.2018). Informed consents were obtained from all the patients who were referred to the OPAT unit. The following data were obtained from the hospital's electronic database: demographic data, clinical diagnoses, antibiotics used, antimicrobial resistance status, and laboratory results. Data used for cost analysis, such as patient's occupation, salary, mode of transportation to the hospital, daily travel expenses, and companion status, were obtained via in-person face-to-face interviews with the patients.

Only the first OPAT episode of each patient was included in the study. The treatment goal (cure or clinical improvement) of each patient to be treated with OPAT was determined before initiating treatment. Treatment success was determined based on "end-of-treatment success" and "28-day follow-up success". End-of-treatment success indicated that the initially set goal was achieved by the end of the therapy. Patients who clinically worsened during treatment, had to discontinue treatment due to the drug side effects, or refused to complete the treatment in the OPAT unit were considered as to have treatment failure. If the patient was readmitted to the hospital within 28 days for the same reason, it was considered as a treatment failure as well (Figure 1). The 28-day follow-up data of the patients was obtained from the hospital information system and national patient information system (E-Nabız) and via telephonic interviews with the patients. In the OPAT unit, antibiotics (such as ertapenem and teicoplanin) were administered once a day, and there was no limitation in the antimicrobial used.

We used real application data to determine OPAT costs. Furthermore, costs were calculated using models based on "hospitalization" instead of OPAT administration. The daily hospitalization cost was calculated using a model based on the Social Security Institution costs incurred if the patient was hospitalized for the same duration with the same diagnosis. Direct and indirect costs were the main components when calculating the OPAT cost; non-measurable intangible costs were excluded. The method developed for the World Bank and

World Health Organization was used to calculate the direct costs. The main total expenditure was calculated by multiplying the number of uses of each expenditure item by the percentage of cases using it and the unit costs. The "Human-Capital Approach" (HCA) method was used to calculate the indirect costs. The HCA was defined as the loss of production cost as a result of the early death of a person due to illness and disability. In our country, the Health Implementation Communiqué (HIC), which was officially announced by the government, is used for the reimbursement of health services. The reimbursement cost of all medical services was obtained from the HIC on December 30, 2020, to ensure standardization over time. The cost of the drugs used was included in the analysis by calculating the average cost of all existing commercial drugs containing the active ingredient. Pharmaceutical costs were obtained via Rx MediaPharma® 2021 (version 5.5.1; Update #18 Levent Üstünes, İzmir, Turkey) on March 1, 2021, considering the discounts applicable to drug procurement via the government. All costs were calculated in Turkish liras (TRY) and converted into US dollars (US$) according to the exchange rate (1 US$=5.68 TRY) at the Turkish Central Bank on July 1, 2019.

Statistical Analysis

This was a prospective single-center cohort study. Statistical analyses were performed using Statistical Package for the Social Sciences statistics for Windows (version 22.0; IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as mean±standard deviation, median [minimum (min)-maximum (max)], distribution, and percentage. The Pearson chi-squared test and Fisher's exact probability test were used to analyze the categorical variables. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov test) methods. The Student's t-test and Mann-Whitney U test were used to analyze the continuous variables. Statistical significance was set at $p<0.05$. The sample size was calculated using G-Power (version 3.1.9; HeinrichHeine-University, Dusseldorf, Germany). The sample size required for the study was calculated as 278 participants, which would provide a 95% confidence interval ($\alpha=0.05$) and 80% power ($\beta=0.20$) with a 30% effect size ($d=0.30$) for the t-test statistics.

Results

In our study, 311 patients who met the inclusion criteria and were referred to the OPAT unit between January 1, 2019 and February 1, 2021 were evaluated. Four patients who refused to participate in the study were excluded. Finally, 307 patients were included in the study.

Of the 307 patients, 169 (55%) were males. The median age of the patients was 58 years (min-max: 20-93 years). At least one comorbidity was detected in 237 (77.2%) patients, the commonest of which was diabetes mellitus, (n=100; 32.6%). Of the 307 patients, 252 (81.1%) were treated at Ankara City Hospital and 55 (17.9%) were treated at Ankara Numune Training and Research Hospital. Moreover, 175 (57%) patients were referred from outpatient polyclinics and 110 (35.9%) patients were referred from the Infectious Diseases and Clinical Microbiology Clinic to the OPAT unit (Table 1).

A urinary system infection was the most common infection (n=214, 69.7%), followed by chronic osteomyelitis (n=50, 16.3%). The treatment of 123 (40.1%) patients was started empirically, and 292 (95.1%) patients that were treated in the OPAT unit received monotherapy. The most frequently used antimicrobials in the OPAT unit were ertapenem (n=248; 80.8%), teicoplanin (n=35; 11.4%), and daptomycin (n=17; 5.5%). Fifteen patients (4.9%) were administered a combination therapy. The most commonly used drug combination was ertapenem and teicoplanin (n=11; 3.5%). Antifungal drugs were used in four patients (1.3%). Cultures yielded positive results

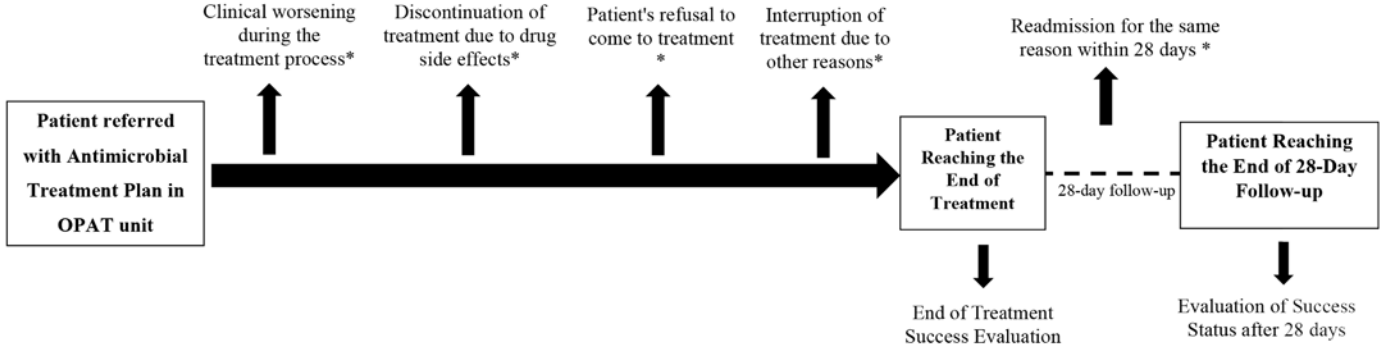

Figure 1. Treatment success follow-up in the OPAT unit
*Causes of failure in patients treated in the OPAT unit.
OPAT: Outpatient parenteral antimicrobial therapy

in 212 (69.1%) patients (Table 2). The most commonly isolated bacterium was *Escherichia coli* (n=139; 45.3%). Approximately 88.8% of isolated Gram-negative bacteria exhibited extended-spectrum beta-lactamase (ESBL) positivity. Carbapenemase was not detected in the Gram-negative microorganisms coltured from the study participants (Table 2). Methicillin resistance was detected in 14 (35%) of the 40 patients with a staphylococcal infection. Methicillin resistance was detected in 10 (52.6%) patients with an infection caused by *Staphylococcus aureus*. Ampicillin and vancomycin resistance was determined in one (9%) strain of *Enterococcus* spp.

During the study, 16 adverse events were detected in patients treated in the OPAT unit. The most common side effects were hepatotoxicity (n=8) and allergic reactions (n=5). The drug had to be discontinued in only two patients due to an allergic reaction after the first antibiotic dose. Among these patients, one was being administered ertapenem and the other teicoplanin.

Table 1. Demographic characteristics of the patients treated in the OPAT unit

Characteristic	n (%)
Age (median, min-max)	58 (20-93)
Male gender	169 (55)
Presence of a comorbidity*	237 (77.2)
Diabetes mellitus	100 (32.6)
Chronic obstructive pulmonary disease	20 (6.5)
Malignancy	48 (15.6)
CKD	27 (8.8)
CKD requiring hemodialysis	7 (2.3)
Cerebrovascular disease	5 (1.6)
Hypertension	94 (30.6)
Cardiovascular disease	53 (17.3)
Benign prostatic hyperplasia	34 (11.1)
Renal transplantation	7 (2.3)
Immunosuppressive therapy†	49 (15.9)
Unit referring the patient for OPAT	
Emergency department	65 (21.2)
Polyclinics	175 (57)
Inpatient services	67 (21.8)
Clinic referring patients for OPAT	
Infectious diseases and clinical microbiology	110 (35.9)
Urology	52 (16.9)
Nephrology	20 (6.5)
Emergency department	64 (20.8)
Orthopedics and traumatology	21 (6.8)
Internal medicine	22 (7.2)
Other surgical clinics	16 (5.2)
Neurology	2 (0.7)

*Presence of at least one comorbidity. †Receiving immunosuppressive therapy in the past year.

OPAT: Outpatient parenteral antimicrobial therapy, min: Minimum, max: Maximum, CKD: Chronic kidney disease

The use of OPAT saved a total of 3040 bed days (25 months) during the study period. An average of 4.05 beds were saved per day. The diagnoses with the highest median bed days saved were chronic osteomyelitis and intra-abdominal infection (n=14 days) (Table 3). No patient was admitted to the OPAT unit for six months during the hospital transfer process and the first wave of the pandemic; patients were admitted to the unit over 19 months. Thus, on average, 5.33 bed days were saved per day.

A total of 283 (92.2%) patients reached their end-of-treatment goals. Twenty-four (7.8%) patients could not complete the treatment processes planned in the OPAT unit (Figure 2). Based on the 28-day follow-up results, 32 (10.4%) patients were readmitted for the same condition for which they had been admitted the first time (Figure 2).

Presence of at least one comorbidity and administration of immunosuppressants within the previous year were statistically significant causes of readmission within 28 days for the same condition (p=0.001). The readmission rate was higher in patients with urinary system infections than in those with other infections (p=0.001). The readmission rate was significantly higher in patients being referred from the nephrology clinic than in those being referred from other clinics (p<0.001). The readmission rate was significantly higher in patients with *Enterococcus* spp. infections than in those with infections caused by other microorganisms (p=0.018) (Table 4).

Among the patients with urinary tract infections, the readmission rates were statistically significantly higher in patients with a history of renal transplantation or urological intervention (p<0.001). Regression analysis revealed that immunosuppressive therapy in the preceding year was an independent risk factor for readmission (Table 5).

A total of 485,095 TRY (85,404.04 US$) was saved with OPAT. Of this total, 376,953.4 TRY (66,365 US$) was the direct cost saved and 108,141.6 TRY (19,039 US$) was the indirect cost saved. Approximately 1,580.114 TRY (278,18 $) was saved per patient in this study (Table 6).

Discussion

Outpatient parenteral antimicrobial therapy units are an alternative to hospitalization in several countries to administer broad-spectrum antibiotics to patients who do not require hospitalization. Outpatient parenteral antimicrobial therapy units were established in Turkey in the early 2010s, and are gradually increasing. This study was conducted at the largest tertiary care hospitals in the capital city of Turkey. The fact

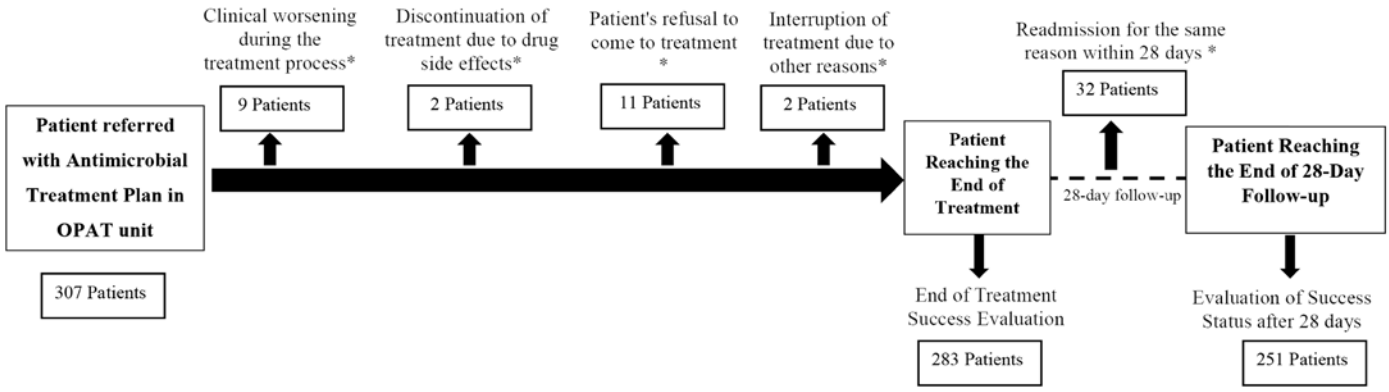

Figure 2. Treatment success results in the OPAT unit
*Causes of failure in patients treated in the OPAT unit.
OPAT: Outpatient parenteral antimicrobial therapy

Table 2. Diagnosis, treatment, and microbiological characteristics of the patients treated in the OPAT unit

Characteristics	n (%)
Diagnosis	
Urinary system infection	214 (69.7)
Bone and joint infection	50 (16.3)
Skin and soft tissue infection	15 (4.9)
Bloodstream infection	16 (5.2)
Intra-abdominal infection	9 (2.9)
Pneumonia	2 (0.7)
Mucormycosis	1 (0.3)
Treatment	
Causative treatment	184 (59.9)
Empirical treatment	123 (40.1)
Monotherapy	292 (95.1)
Combined therapy	15 (4.9)
Antimicrobial agents	
Ertapenem	248 (80.8)
Teicoplanin	35 (11.4)
Daptomycin	17 (5.5)
Ceftriaxone	6 (2)
Linezolid	6 (2)
Vancomycin	5 (1.6)
Voriconazole	2 (0.7)
Liposomal amphotericin B	2 (0.7)
Amikacin	1 (0.3)
Specimens isolated	
Urine	152 (49.5)
Wound	37 (12.1)
Blood	14 (4.6)
Abscess	8 (2.6)
Peritoneum	1 (0.3)

Table 2. Continued

Characteristics	n (%)
Microbiological features	
Patients with positive cultures	212 (69.1)
Gram-negative bacteria	170 (55.4)
ESBL-producing bacteria	151 (88.8)†
Gram-positive bacteria	40 (13)
Methicillin-resistant bacteria	14 (35)‡
Fungi	2 (0.7)
Microorganism	
Escherichia coli	139 (45.3)
Klebsiella pneumoniae	23 (7.5)
Staphylococcus aureus	19 (6.2)
Enterococcus spp.	11 (3.6)
Enterobacter spp.	5 (1.6)
Corynebacterium striatum	5 (1.6)
Coagulase negative Staphylococcus	5 (1.6)
Pseudomonas aeruginosa	1 (0.3)
Serratia marcescens	1 (0.3)
Morganella morganii	1 (0.3)
Candida krusei	1 (0.3)
Mucor spp.	1 (0.3)

†Percentage among Gram-negative bacteria. ‡Percentage among Gram-positive bacteria.

OPAT: Outpatient parenteral antimicrobial therapy, ESBL: Extended-spectrum beta-lactamase, spp.: Species

that only 307 patients were treated in the OPAT unit over approximately 25 months suggests that OPAT units are not yet used enough in Turkey indicates that the performance of OPAT units in Turkey remains unknown. Additionally, the home-based and nursing center-based OPAT models in Turkey need to be further developed.

Table 3. Number of bed days saved in the OPAT unit according to the diagnoses

	Number of bed days saved	Median of the number of bed days saved (min-max)
Urinary system infection	1675	7 (1-14)
Bone and joint infection	932	14 (1-65)
Skin and soft tissue infection	144	10 (4-19)
Intra-abdominal infection	140	14 (10-21)
Bloodstream infection	116	6.5 (1-20)
Mucormycosis	30	30 (30-30)
Pneumonia	3	1.5 (1-2)
Total	3040	8 (1-65)

OPAT: Outpatient parenteral antimicrobial therapy, min: Minimum, max: Maximum

Table 4. Readmission rates within 28 days according to the clinical, microbiological and laboratory characteristics of the patients

Characteristics	Readmission within 28 days		p
	Yes (n=32) n (%)	No (n=251) n (%)	
Male sex	18 (56.3)	137 (54.6)	0.858[c]
Age (median, min-max)	63 (20-86)	58 (20-93)	0.322[m]
Presence of comorbidity*	32 (100)	186 (74.1)	**0.001**[c]
Diabetes mellitus	11 (34.4)	82 (32.7)	0.847[c]
Chronic obstructive pulmonary disease	1 (3.1)	17 (6.8)	0.704[f]
Malignancy	8 (25)	33 (13.1)	0.104[f]
Chronic kidney disease	3 (9.4)	21 (8.4)	0.742[f]
Hypertension	13 (40.6)	76 (30.3)	0.235[c]
Cerebrovascular disease	0 (0)	5 (2)	1.000[f]
Cardiovascular disease	2 (6.3)	50 (19.9)	0.060[c]
Immunosuppressive therapy[†]	12 (37.5)	30 (12)	**0.001**[f]
Charlson Comorbidity Index	3 (0.1)	2(0.7)	0.228[m]
Median Charlson Comorbidity Index (estimated 10-year survival <53%)	9 (28.1)	54 (21.5)	0.397[c]
Hospitalization in the past year	18 (56.3)	120 (48)	0.379[c]
Diagnoses			
Urinary system infection	31 (96.9)	171 (68.1)	**0.001**[c]
Skin and soft tissue infection	0 (0)	13 (5.2)	0.374[f]
Bone and joint infection	1 (3.1)	44 (17.5)	**0.036**[c]
Bloodstream infection	0 (0)	12 (4.8)	0.372[f]
Pneumonia	0 (0)	1 (0.4)	1.000[f]
Intra-abdominal infection	0 (0)	9 (3.6)	0.604[f]
Unit referring the patient for OPAT			
Emergency department	4 (12.5)	55 (21.9)	0.217[c]
Polyclinics	23 (71.9)	136 (54.2)	0.057[c]
Inpatient services	5 (15.6)	60 (23.9)	0.229[c]
Clinic referring the patient for OPAT			
Emergency department	4 (12.5)	55 (21.9)	0.440[c]
Infectious diseases and clinical microbiology	8 (25)	97 (38.6)	0.132[c]
Urology	8 (25)	38 (15.1)	0.155[c]
Nephrology	10 (31.3)	10 (4)	**<0.001**[f]

Table 4. Continued

Characteristics	Readmission within 28 days		p
	Yes (n=32) n (%)	No (n=251) n (%)	
Clinic referring the patient for OPAT			
Orthopedics and traumatology	0 (0)	18 (7.2)	0.239[f]
Internal medicine	2 (6.3)	17 (6.8)	1.000
Surgical clinics	8 (25)	71 (28.3)	0.696[c]
Microorganism			
Culture positivity	27 (84.4)	171 (68.1)	0.059[c]
Escherichia coli	19 (59.4)	115 (45.8)	0.148[c]
Klebsiella pneumoniae	5 (15.6)	18 (7.2)	0.158[f]
Staphylococcus aureus	0 (0)	16 (6.4)	0.231[f]
Enterococcus spp.	3 (9.4)	5 (2)	**0.018**[f]
Treatments			
Empirical treatment	8 (25)	104 (41.4)	0.073[c]
Monotherapy	32 (100)	240 (95.6)	0.620[f]
Ertapenem	29 (90.6)	194 (77.3)	0.082[c]
Teicoplanin	1 (3.1)	27 (10.8)	0.223[f]
Daptomycin	2 (6.3)	14 (5.6)	0.699[f]
Ceftriaxone	0 (0)	5 (2)	1.000[f]
Vancomycin	0 (0)	3 (1.2)	1.000[f]
Laboratory values[ǂ] (median, min-max)			
C-reactive protein (mg/l)	26 (1-255)	34 (1-279)	0.757[m]
Glomerular filtration rate (ml/min/1.73 m^2)	73.5 (22-132)	84 (5-172)	0.210[m]
White blood cell count (x10^6/l)	8200 (3600-23550)	8950 (3270-28300)	0.217[m]
Leukocyte count (x10^6/l)	5800 (1290-21080)	5950 (1200-25400)	0.537[m]

*Presence of at least one comorbidity. †Receiving immunosuppressive therapy in the past year. ǂValues at the time of admission.

[f]: Fisher's exact test, [c]: Pearson's chi-squared test, [m]: Mann-Whitney U test.

OPAT: Outpatient parenteral antimicrobial therapy, min: Minimum, max: Maximum

Table 5. Univariate analysis of the risk factors for readmission within 28 days

Variables	B	OR (CI)	p
Age (>65 years)	0.161	1.175 (0.524-2.636)	0.696
Male sex	0.087	1.091 (0.496-2.401)	0.896
Immunosuppressive therapy	1.365	3.917 (1.715-8.948)	**0.001**
Culture positivity	0.776	2.172 (0.784-6.021)	0.136
Clinic referring patients for OPAT (surgical clinics)	0.280	1.323 (0.538-3.255)	0.542

B: Coefficient of variation, OR: Odds ratio, CI: Confidence interval, OPAT: Outpatient parenteral antimicrobial therapy

OPAT units in Turkey are reportedly cost-effective, based on direct cost analyses and considering the Turkish health system and reimbursement conditions[6,7]. To the best of our knowledge, this is the first prospective study to analyze the direct and indirect costs of OPAT units, treatment success, and reasons for treatment failure in detail, as well as compare these parameters during the pre- and post-pandemic periods.

The median age of the patients in our study was 58 (range 20-93) years. Our finding is similar to that of previous studies that have reported median ages of 53.5 and 60 years[8,9]. The criteria for admission to the OPAT unit include clinically stable patients who do not require close follow-up or hospitalization. Additionally, especially in the hospital-based OPAT model, the patients need to visit the hospital or be brought to the hospital

Table 6. Comparison of the direct and indirect cost components between OPAT and inpatient antimicrobial therapy

Cost components	OPAT ($) Mean / min-max	IPAT ($) Mean / min-max
Direct medical costs		
Bed charges	11.5 / 1.16-75.5	76.6 / 7.74-503.5
Laboratory and radiologic evaluation	2.69 / 0-17.18	36.39 / 3.67-239.17
Antimicrobials	244.4 / 2.48-7,354.7	
Auxiliary medical supplies (infusion solutions)	32 / 2.78-296.9	140.3 / 14.1-922.3
Interventions (intravenous access/cannula)	11.5 / 1.17-76.67	29.9 / 3.02-196.8
Average direct medical cost per patient	**302.3 / 10.89-7,527.5**	**527.69 / 32.4-8,214**
Total direct medical cost (n=307)	**92,820.1**	**162,001.0**
Direct non-medical costs		
Transport	11.6 / 0-80.1	2.42 / 0-5.28
Accommodation	-	-
Average direct non-medical cost per patient	**11.6 / 0-80.1**	**2.42 / 0-5.28**
Total direct non-medical cost (TRY) (n=307)	**3,562.2**	**745.42**
Total direct cost	**96,381.3**	**162,746.4**
Indirect costs		
Early retirement	-	-
Disability pension	-	-
Permissions and reports (accompanying)	-	62.02 / 0-978.48
Early deaths	-	-
Average indirect cost per patient		**62.02**
Total indirect cost	**-**	**19,039.0**
Total unit cost	**96,381.3**	**181,758.44**

OPAT: Outpatient parenteral antimicrobial therapy, IPAT: Inpatient parenteral antibiotic therapy, min: Minimum, max: Maximum. TRY: Turkish liras

by his/her companion every day. Thus, hospital-based OPATs are preferred for relatively young patients. The home-based or nursing center-based model is a more suitable option for older patients.

In the present study, urinary system infection was the most common diagnosis, followed by bone and joint infections. This finding is comparable to that of a previous study conducted by Quintens et al.[9]. However, in other studies skin and soft tissue infections or bone and joint infections were the most common diagnoses[8]. The patient population, hospital structure, OPAT model, and the antimicrobial drug used differs based on the location of the OPAT unit. It varies depending on the location of the OPAT unit, patient population, hospital structure, OPAT model, and antimicrobial drug used based on the causative agent.

In this study, the most frequently isolated agent was *E. coli* (n=139). Unlike in previous studies, an analysis of the resistance rates in Gram-negative bacteria in this study revealed that the ESBL positivity was very high (88.8%)[10]. Most of the patients treated in our OPAT unit had a urinary tract infection caused by ESBL-positive organisms. According to the Central Asian and Eastern European Antimicrobial Resistance Surveillance Network 2020, 53% of the *E.coli* and 73% of the *K. pneumoniae* isolated from the blood and cerebrospinal fluid samples in Turkey were resistant to third generation cephalosporins[11]. Because patients requiring broad-spectrum antibiotics for infections caused by antimicrobial-resistant microorganisms were treated in our OPAT units, higher resistance rates were encountered than in the local data.

The complication risk during OPAT is reportedly approximately 25%[12]. Furthermore, in a 10-year follow-up study conducted between 2001 and 2010, the rate of adverse drug reactions was 9.8%[13]. However, according to recent studies the side effects and complications during OPAT are gradually decreasing[14]. Similar to the findings in these studies, only 5.2% of our study participants developed drug-related side effects. Furthermore, only two patients had drug-related side effects that required discontinuation of the drug. Due to the prospective nature of this study, follow-up of the patients and side effects were performed accurately and systemically.

In the present study, 77.2% of the patients had at least one comorbidity. In the study conducted by Bastug et al.[6] from

2013 to 2017, this rate was 63.3%. In a 10-year follow-up conducted by Barr et al.[13] of patients treated in the OPAT unit, the percentage of comorbidities in the patients increased from 69.8% to 82.3%. Patients with multiple comorbidities are referred to OPAT units more often as the units become more experienced in treating patients. Additionally, the treatment of more complicated infections (such as infective endocarditis, fungal infections, and aortic graft infections) with OPAT indicates that the clinicians' confidence in OPATs have gradually increased.

In the present study, the success rate at the end of the treatment was high (92.2%), which is comparable with the finding of a previous study[13]. In our cohort, nine patients were hospitalized during treatment due to clinical worsening; two of these patients died. This low rate was similar to that of a previous study[8].

The treatment plan should to be discussed in detail with the patients and their relatives before initiating the treatment to ensure their compliance. The OPAT unit location and lack of ease of access may contribute to treatment discontinuation. Eleven patients did not complete treatment due to the OPAT unit location, and they were included in the treatment failure group. During the study, 32 patients were readmitted within 28 days of treatment completion for the same reason for which they were first admitted. In the study conducted by Bastug et al.[6] at an OPAT unit which was more easily accessible to patients, this rate was 7.2%. Li et al.[15] reported that the readmission rate increased from 2.69% in 2004 to 8.21% in 2013. In another study conducted in 2019, the rate of readmission within 28 days for the same presenting condition was 12%, which is similar to our study finding[16]. In our study, the presence of comorbidities and immunosuppressant administration in the preceding year were significant risk factors for readmission. Erba et al.[8] reported that the high Charlson Comorbidity Index score and presence of immunosuppression are significant risk factors for readmission. Lymphoma is also a significant risk factor for readmission[17]. These findings indicate that the readmission rates have increased over the years and that the presence of comorbidities and immunosuppression in patients referred to OPAT units may play an important role.

The use of OPAT units have saved the use of 3040 beds, with an average of 4.05 beds per day for patients who are critically ill and require hospitalization. Considering the six months lost during hospital relocation and the first wave of the COVID-19 pandemic, the number of bed days saved per day was 5.33. With the adaptation of patients and healthcare professionals to the pandemic conditions, OPAT units are preferred. Other important advantages of OPAT are that hospital beds, which were very important during the pandemic, can be effectively used, and it prevents secondary hospital-acquired infections. The increase in the use of empirical antibiotics during the pandemic may be attributed to the fact that more patients who were admitted to the emergency department were referred to the OPAT unit.

A wide range of cost analysis studies conducted in various countries have determined that OPAT is cost-saving[18,19]. In a study in which only direct costs were analyzed, OPAT was 25% less costly than inpatient parenteral antibiotic therapy. In another study, this rate was 40%. It is difficult to compare the cost analysis rates between countries because the health system and reimbursement conditions of each country differ. Most of the cost analysis studies in the literature have been conducted from a hospital perspective[6,20]. However, in our study it was conducted from both the hospital's and primary caregiver's perspectives. Transportation costs and daily caregiver costs were also included. The cost of using the OPAT unit was approximately 50% cheaper than hospitalizing the patient. Although hospitalization costs are cheaper in Turkey due to the relatively lower wages of healthcare professionals and lower reimbursement rates, OPAT units are still safe and cost-effective.

Study Limitations

The study had some limitations. This was a single-center study with a relatively short duration of patient follow-up. In future studies, hospitals in more than one different region can be evaluated together.

Conclusion

The OPAT unit is effective, safe, and cost-effective in the context of the Turkish national health system. Additionally, local guidelines should be prepared to standardize the inclusion and follow-up criteria and to determine the working principles of the unit.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Ankara Training and Research Hospital (no: E-18-2137; date: 19.07.2018).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.O.Ö., Concept: B.O.Ö., H.B., Design: A.B., H.B., Data Collection or Processing: B.O.Ö., E.Ö., Analysis or Interpretation: A.B., E.Ö., Literature Search: B.O.Ö., A.B., Writing: B.O.Ö., A.B., E.Ö.

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