



Review of the first comprehensive outpatient parenteral antimicrobial therapy program in a tertiary care hospital in Japan



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ABSTRACT

Objectives: The infectious diseases team at Kameda Medical Center, Japan, implemented a new outpatient parenteral antimicrobial therapy (OPAT) program in July 2012 and expanded the program with the support of home care services. This study reviews the OPAT program after 5.5 years of operation.

Methods: We prospectively collected data about the age, sex, diagnoses, causative organisms, types of OPAT, modes of administration, selected antibiotics, treatment durations, bed days saved, outcomes, readmissions, and estimated cost reductions of all patients who were treated in the OPAT program from July 2012 to December 2017.

Results: Of the 66 patients treated under the OPAT program, 45 (68.2%) were treated using clinic OPAT, and 21 (31.8%) were treated using homecare OPAT. The most commonly targeted organism was methicillin-susceptible *Staphylococcus aureus*. Continuous infusion with elastomeric pumps was employed in 55 patients (83.3%). Cefazolin was the most frequently used antibiotic (39.4%), followed by penicillin G (24.2%). The median OPAT duration was 13 days (range, 3–51), and the total bed days saved was 923. The estimated medical cost reduction was approximately 87,000 US dollars.

Conclusions: Our experience shows that OPAT is a safe and feasible practice not only for efficient bed utilization and medical cost savings but also for better antimicrobial stewardship.

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Introduction

The use of outpatient parenteral antimicrobial therapy (OPAT) was initially described in 1974 for pediatric patients in the United States [Rucker et al., 1974]. Since then, the service has been widely implemented in many countries worldwide, and it plays an important role as part of the clinical management of patients with various infectious diseases (ID) [Esposito et al., 2004; Upton et al., 2004; Fisher

et al., 2006; Ravelingien et al., 2016; Gardiol et al., 2016; Howden and Grayson, 2002]. The guidelines and recommendations for OPAT are widely available and have been updated in some countries [Oliveira et al., 2017; Chapman et al., 2019; Lopez Cortes et al., 2019; Norris et al., 2019].

However, the concept of OPAT has not been widely recognized among physicians in Japan. Consequently, patients with IDs such as infective endocarditis or osteomyelitis who require long-term intravenous antimicrobial therapy need to be hospitalized for weeks until the completion of therapy. Fisher et al. reported that Australia, New Zealand, and Singapore were the only countries in the Asia Pacific region to have nationally implemented comprehensive OPAT services [Fisher et al., 2017]. On the other hand, well-organized OPAT services have not been established in Japan.

Another issue unique to Japan is that parenteral antibiotics are frequently provided outside of OPAT service. In a survey of

Abbreviations: ID, infectious diseases; OECD, Organization for Economic Co-operation and Development; OPAT, outpatient parenteral antimicrobial therapy; PICC, peripherally inserted central catheter; USD, United States dollars.

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responses from 171 institutions in 17 Asian countries, 28 of 36 institutions in Japan stated that parenteral antibiotics were provided by individual clinicians in their clinics, which is much more frequent than in other countries [Fisher et al., 2017]. Also, we previously reported that ceftriaxone was frequently prescribed by physicians for outpatients on an individual basis in a general hospital in Japan [Hase and Hosokawa, 2015]. In that study, we proved that ceftriaxone was used empirically for outpatients in most instances, and the appropriate culture test was not performed. A treatment schedule was not planned in many cases. We concluded that a systematic OPAT program is necessary to avoid inappropriate use of parenteral antibiotics and to achieve better antimicrobial stewardship.

In July 2012, we implemented an OPAT service at Kameda Medical Center, Japan, a large tertiary teaching hospital with 917 beds, after establishing a multidisciplinary team [Hase et al., 2014]. We expanded the service by collaborating with visiting nursing stations in 2013 [Hase et al., 2015]. To date, our program is the only comprehensive OPAT service in Japan. This study reviews all cases treated under our OPAT program to evaluate the efficacy, outcome, safety, and cost-effectiveness of this service.

Patients and methods

Study design

All cases treated in our OPAT program from July 2012 to December 2017 were included. We prospectively collected data about the age, sex, diagnoses, causative organisms, selected antibiotics, types of transition to OPAT (from inpatient or from outpatient), OPAT types (clinic or homecare), modes of administration (once-daily or continuous), type of infusion device (gravitational bag or elastomeric pump), departments that referred the patient to the OPAT program, OPAT durations, bed days saved, clinical outcomes, program outcomes, adverse events, readmissions, and estimated cost reductions from our OPAT database and electronic medical records when necessary. The mode of administration was categorized as either a once-daily infusion with a gravitational bag or a 24-h continuous infusion with an elastomeric pump. The number of bed days saved was defined as the days between the day of discharge, and the day of OPAT completion. The clinical outcome was classified as cured, improved, unchanged, or deteriorated. Cases in which oral antibiotics were used after OPAT completion and clinical improvement was noted were categorized as improved. Program outcomes were classified as completed, ended early, hospitalized, or died. All these outcome variables were recorded in the electronic database for each case after discussion with the attending ID doctors on the OPAT team. Adverse events included drug-related ones such as rash, hepatitis, or leukocytopenia, which required cessation of the parenteral antibiotics; pump-related events, including inappropriate residual liquid in infusion pumps; and line-related events, including catheter-related bloodstream infections, thrombosis, or inadvertent removal of the intravenous access device by the patient. Readmission was defined as any unplanned hospital admission during the OPAT period within 1 month after OPAT completion. The estimated cost reduction was calculated by subtracting the actual medical cost of OPAT and the cost of the infusion pumps from the estimated medical cost for inpatient care. The estimated medical cost for inpatient care was calculated by simulating the medical fee for inpatients according to the diagnostic procedure combination code as if the OPAT patient was treated as an inpatient instead of as an outpatient. For the medical fee over the specified period of hospital stay, the sum of the basic hospitalization fee and the fee for the intravenous drug was calculated. Any cases that were treated with parenteral antimicrobial therapy on an individual basis outside of

our OPAT service were excluded from this study. The study was approved by the Ethics Committee of Kameda Medical Center.

Description of the Kameda Medical Center OPAT program

Kameda Medical Center in Chiba, Japan, is a tertiary care teaching hospital with 917 beds. The Department of Infectious Diseases established a multidisciplinary team comprising pharmacists, nurses, and other administrative staff to implement an OPAT service in July 2012. In the OPAT program, the ID team determines whether the referred patient is suitable for OPAT. This is conducted by confirming the diagnosis, deciding whether parenteral antimicrobial therapy is necessary, and deciding the treatment duration.

Furthermore, the patient's condition must be stable enough for him or her to visit the hospital daily, failing which the homecare nurses can visit the patient's home daily; the patient must be able to manage a venous access device and must want to be treated with OPAT. A detailed explanation of OPAT is provided to both the patients and their caregivers, and written informed consent is obtained from the eligible patient if they decide to undergo OPAT. Either a peripherally inserted central catheter (PICC) or midline catheter is inserted before discharge when an elastomeric pump is planned to be used. When a gravitational bag is going to be used, a peripheral line with a venous cannula can also be selected. When using an elastomeric pump, only antibiotics that are proved to be stable for more than 24 h at room temperature can be used. The antimicrobials are compounded into elastomeric pumps in the pharmacy department at Kameda Medical Center.

Upon discharge, either the patient visits our ID clinic, or homecare nurses visit the patient's home daily. During weekends and holidays, the emergency outpatient unit is used instead of the ID clinic. Blood tests are performed at least once a week. Patients are provided with a booklet that contains the necessary contact information in case of an emergency.

Results

During the study period, 66 patients received intravenous antimicrobial therapy in our OPAT program (Figure 1). Table 1 summarizes the patients' demographics, OPAT type, and selected antibiotics. The median age of the patients was 67 years (range, 15–86 years). The majority of the patients started OPAT as a continuation of inpatient intravenous therapy, except for four patients (6.1%) who began OPAT from the outpatient clinic without admission. Approximately two-thirds of the patients received clinic OPAT, and the remainder received homecare OPAT in collaboration with visiting nursing stations. Elastomeric pumps were used by 55 patients (83.3%) for continuous infusion, and gravitational bags were used by 12 patients (18.2%) for once-daily infusion. The most frequently used antibiotic was cefazolin, followed by penicillin G.

The most frequent diagnosis in the patients treated with OPAT was bone and joint infection, particularly vertebral osteomyelitis, and the prevalence of bacteremia was 63.6% (Table 2). Either microbiological culture or serology was used to identify the target organisms in 59 patients (89.4%). Of them, the most commonly targeted organism was methicillin-susceptible *Staphylococcus aureus* (Table 3). The department of general internal medicine most frequently referred patients to the OPAT program (Table 4). The median OPAT duration was 13 days (range, 3–51). Either a cure or an improvement was achieved in all patients. OPAT was discontinued in three patients (4.5%); of them, two patients experienced a drug-related rash, and the other patient experienced a drug-related leukocytopenia due to cefepime administration. In these three patients, the parenteral antibiotics were changed to the

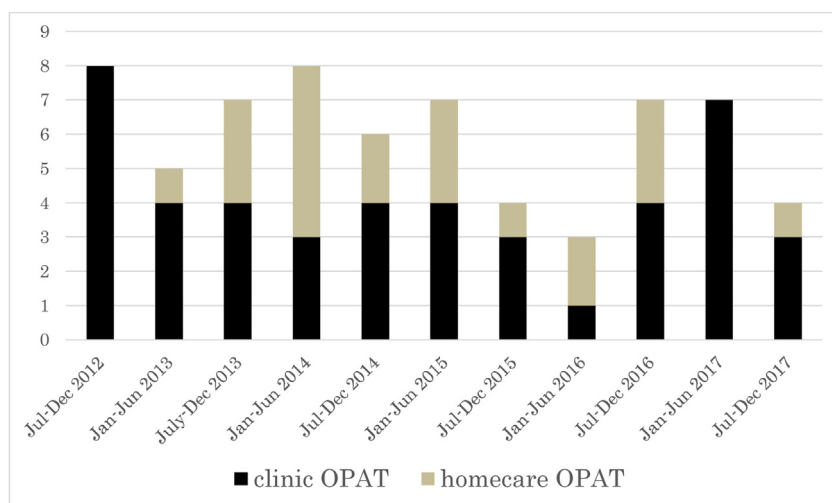


Figure 1. Trends of patients treated under the OPAT service (n = 66).
OPAT: outpatient parenteral antimicrobial therapy.

Table 1

Summary of patients' demographics, OPAT type, and selected antibiotics of the cases treated by OPAT at Kameda Medical Center, Japan, from July 2012 to December 2017 (n = 66).

Characteristic	n (%)
Median age (range), years	67 (15–86)
Sex (male/female)	46/20
Type of transition to OPAT	
From inpatient	62 (93.9)
From outpatient	4 (6.1)
OPAT type	
Clinic OPAT	45 (68.2)
Homecare OPAT	21 (31.8)
Caregiver/self	0 (0.0)
Mode of administration	
Once-daily with gravitational bag	12 (18.2) ^a
Ceftriaxone	8
Gentamicin	2
Daptomycin	2
Continuous infusion with elastomeric pump	55 (83.3)
Cefazolin	26
Penicillin G	16
Vancomycin	4
Cefepime	3
Piperacillin/tazobactam	3
Cefmetazole	2
Ceftriaxone	1

^a Both daptomycin (once-daily) and a continuous infusion of cefepime were used in one episode. OPAT: outpatient parenteral antimicrobial therapy.

appropriate oral antibiotics. A line-related adverse event was only observed in one patient, whose PICC was dislocated and reinserted. Neither catheter-related bloodstream infection nor thrombosis was documented. In three of the patients receiving penicillin G by continuous infusion, antibiotic liquid remained in the elastomeric pumps. This issue was resolved by adjusting the amount of diluted solution in two of the patients and by changing penicillin G to once-daily ceftriaxone in one patient. Unplanned readmission occurred in three patients (4.5%). Two were readmitted for conditions unrelated to the previous OPAT (hemoptysis and pseudogout, respectively); the other patient was readmitted because of the recurrence of bacteremia after the completion of OPAT for pyelonephritis and was later diagnosed with infective

Table 2

Diagnosis and proportion of proved bacteremia in the patients treated with OPAT (n = 66) at Kameda Medical Center from July 2012 to December 2017.

Diagnosis category	n (%)
Bone and joint infections	24 (36.4)
Vertebral osteomyelitis	12
Other osteomyelitis	8
Septic arthritis	4
Skin and soft tissue infections	9 (13.6)
Pyomyositis	5
Cellulitis	2
Surgical site infection	1
Retroperitoneal abscess	1
Urinary tract infections	8 (12.1)
Pyelonephritis	3
Prostatitis	2
Cystitis	1
Epididymitis	1
Renal abscess	1
Central nervous system infections	6 (9.1)
Neurosyphilis	4
Bacterial meningitis	1
Brain abscess	1
Infective endocarditis	6 (9.1)
Intra-abdominal infections	2 (3.0)
Cholangitis	1
Surgical site infection	1
Ear, nose, and throat infection	2 (3.0)
Pelvic inflammatory disease	2 (3.0)
Pneumonia, empyema	2 (3.0)
Catheter-related bloodstream infection, septic thrombophlebitis	1 (1.5)
Vascular graft infections	1 (1.5)
Bacteremia ^a	42 (63.6)

^a Bacteremia was complicated with other diagnoses, except for three cases with primary bacteremia. OPAT: outpatient parenteral antimicrobial therapy.

endocarditis. The total bed days saved was 923, and the estimated medical cost reduction was 9,264,384 yen (approximately 87,000 US dollars [USD]) (Table 5).

Discussion

We reviewed 5.5 years of operation of a comprehensive OPAT program at a large tertiary care hospital in Japan. To the best of our knowledge, this is the first study written in English from Japan that evaluates an OPAT program. Our research shows that a

Table 3

Causative organisms in the patients treated with OPAT at Kameda Medical Center from July 2012 to December 2017.

Organisms	n
Methicillin-susceptible <i>Staphylococcus aureus</i>	23
Enterobacteriaceae	8
<i>Streptococcus pneumoniae</i>	6
β -Streptococci	5
α -Streptococci	5
Coagulase-negative staphylococci	5
<i>Treponema pallidum</i>	4
Anaerobes	3
Methicillin-resistant <i>Staphylococcus aureus</i>	2
<i>Corynebacterium</i> spp.	2
<i>Enterococcus</i> spp.	2
<i>Helicobacter cinaedi</i>	2
<i>Gemella morbillorum</i>	1
<i>Propionibacterium avidum</i>	1
<i>Pseudomonas aeruginosa</i>	1
Unknown	7

OPAT: outpatient parenteral antimicrobial therapy.

Table 4

Breakdown of the departments that referred patients (n = 66) to the OPAT services at Kameda Medical Center, Japan, from July 2012 to December 2017.

Department	n
General internal medicine	30
Urology	7
Infectious diseases	5
Cardiology	4
Obstetrics/gynecology	4
Orthopedics	3
Oncology	2
Cardiovascular	2
Plastic surgery	1
Neurosurgery	1
Spine surgery	1
Otorhinolaryngology	1
Gastroenterology	1
Dentistry	1
Palliative care	1
Thoracic surgery	1
General surgery	1

OPAT: outpatient parenteral antimicrobial therapy.

comprehensive OPAT program run by ID specialists with a multidisciplinary team can provide a safe and cost-effective treatment option for patients who require parenteral antimicrobial treatment under the Japanese healthcare system.

OPAT was completed as planned in 95.5% of patients, a cure or improvement was achieved in 100% of patients, and the unplanned readmission rate was 4.5% in our OPAT service. The completion rate, cure/improvement, and unplanned readmission were 84–86%, 87–92.4%, and 3.6–12.6%, respectively, in a previous review of adult OPAT programs [MacKenzie et al., 2014]. The relatively favorable outcomes in our cohort may reflect the careful selection of candidates; in part, they may also be because the infusion is not self-administered nor is administered by a caregiver.

Our program achieved a saving of 923 bed days in total by providing OPAT to 66 patients with various diagnoses. According to the data from the Organization for Economic Co-operation and Development (OECD), the average length of hospital stay in acute care hospitals in Japan is 16.2 days, which is more than twice the average in other OECD countries [OECD iLibrary, 2017]. Thus, a comprehensive OPAT service would be useful to shorten the length of hospital stays and be especially beneficial in hospitals with a high rate of bed occupancy. Although we did not validate this in our program, patient satisfaction with OPAT was high in previous studies [Saillen et al., 2017; Durojaiye et al., 2019].

The total estimated medical cost reduction achieved with the use of our OPAT program was 9,264,384 yen (approximately 87,000 USD). A meta-analysis of 35 studies that performed an economic evaluation of OPAT reported an average OPAT financial saving of 57.19% (from –13.03% to 95.47%) [Psaltikidis et al., 2017]. The Japanese government has been attempting to reduce dramatically increasing medical costs due to an increase in the proportion of the aging population. Under these circumstances, comprehensive OPAT services would be useful tools to increase the efficiency of hospital bed utilization and reduce healthcare costs.

The use of elastomeric pumps provides an option to use narrow-spectrum parenteral antimicrobials for OPAT. In our study, elastomeric pumps were used in 83.3% of cases, with cefazolin or penicillin G being used in more than half of the cases. Elastomeric pumps are particularly useful in Japan because neither self-infusion nor caregiver infusion is generally acceptable, and the device enables the use of various antibiotics with a daily dose. However, two issues need to be addressed regarding the use of elastomeric pumps for antibiotic administration in Japan. First, the cost of the elastomeric pumps is not reimbursed by the public health insurance system in Japan. Concerned authorities have suggested that the indication for continuous infusion should be included in the package insert of each antibiotic to expand the use of elastomeric pumps for antibiotic administration, but this is yet to be achieved and requires support from the academic

Table 5

Treatment duration, outcomes, adverse events and economic evaluation of 66 cases of OPAT treatment at Kameda Medical Center, Japan, from July 2012 to December 2017.

Factor	Number (%) of patients
Median treatment duration, days (range)	13 (3–51)
Clinical outcomes	
Cure	46 (69.7)
Improved	20 (30.3)
Unchanged/failed	0 (0.0)
Program outcomes	
Completed	63 (95.5)
Ended early	3 (4.5)
Hospitalized	0 (0.0)
Adverse events	
Adverse drug reactions	3 (4.5)
Pump-related events	3 (4.5)
Line-related events	1 (1.5)
Readmission	
Unplanned readmission within 30 days after OPAT completion	3 (4.5)
Total bed days saved	923
Estimated cost reduction (Yen/US dollars)	9,264,384/87,000

OPAT: outpatient parenteral antimicrobial therapy.

community. Second, some domestic antibiotics lack stability data for use in elastomeric pumps. According to the original Infectious Diseases Society of America guideline, the drug used for OPAT with a continuous infusion device should be stable for ≥ 24 h at room temperature [Tice et al., 2004].

Furthermore, domestic penicillin G is not as stable as that available abroad; however, it has been reported that domestic penicillin G dissolved in acetate Ringer's solution remained sufficiently stable to be used with elastomeric pumps [Nakamura et al., 2018]. Thus, we used acetate Ringer's solution instead of normal saline when using penicillin G with elastomeric pumps in our OPAT program. Although the cause has not been determined, the pump-related adverse event that we experienced may be partly related to the viscosity of diluted penicillin G.

The overuse of OPAT should be avoided, and an OPAT service may paradoxically unnecessarily prolong treatment duration with intravenous antibiotics. In our OPAT service, our ID team carefully assessed the indication for the candidate OPAT patients and decided to switch from intravenous to oral administration when parenteral antimicrobial therapy was no longer necessary. Additionally, our team selected the best parenteral antibiotics with the narrowest spectrum. Thus, our ID physician-driven OPAT program avoided both unnecessary parenteral antimicrobial therapy and the use of broad-spectrum antibiotics. Previous studies have also demonstrated that the commitment of ID specialists helped prevent inappropriate OPAT [Sharma et al., 2005; Shrestha et al., 2012; Conant et al., 2014]. We believe that discussing the indication of OPAT for patients with IDs created an intrinsic opportunity for antimicrobial stewardship.

Collaboration with visiting nursing stations would be beneficial to expand OPAT programs. When we first implemented OPAT, many patients were candidates for OPAT but were unable to visit the clinic daily due to the inconvenient accessibility of our clinic. However, the use of visiting nursing stations near the patients' homes made this possible. In our program, approximately one-third of OPAT patients were treated using homecare OPAT. According to a survey of the number of home-visiting nursing stations in 2019, there are about 10,000 home-visiting nurse stations throughout Japan [The National Association for Visiting Nurse Service, 2019]. Thus, effective collaboration with visiting nursing stations could help in the provision of OPAT to more patients.

The unavailability of self-administration or caregiver administration in Japan acts as a barrier to more eligible patients using OPAT. Self or caregiver administration is regarded as a safe way to deliver OPAT [Matthews et al., 2007; Barr et al., 2012a,b; Seetoh et al., 2013], and IDSA guidelines recommend that patients or their caregivers should be allowed to self-administer OPAT [Norris et al., 2019]. In fact, this model has been widely available and is a common model of OPAT delivery in many countries [Kieran et al., 2009; Barr et al., 2012a,b; Seetoh et al., 2013; Subedi et al., 2015; Saillen et al., 2017]. However, self or caregiver administration of intravenous antibiotics is not applicable under the public health insurance system in Japan because parenteral antimicrobials are not regarded as drugs for self-administration at home. Therefore, a revision of the healthcare insurance system is needed to solve this issue.

The improvement of patients' incentives is also vital to expand OPAT services in Japan. In our service, we only provided OPAT to 66 patients during the study term, although there were many more eligible patients. The reason for the failure to recruit patients for OPAT included poor accessibility to the clinic, patient anxiety toward having a venous access device as part of their daily life, and the reluctance of other family members. Additionally, patients do not have sufficient financial incentives to move from inpatient to outpatient care because the cost of hospitalization is not that expensive within the public insurance system in Japan. Moreover, the financial burden of patients using OPAT could be more costly

than that of inpatient care because typical private health insurance often only covers inpatient and not outpatient costs. Promotional support from the academic community would help expand OPAT services in Japan.

Our study has some limitations. First, this study does not include cases that were treated with parenteral antimicrobial therapy outside of our OPAT service. Therefore, the result does not reflect the actual situation of how parenteral antimicrobial therapy was used for outpatient cases in our hospital. Second, the medical cost saving was estimated using our own simple method of calculation, which did not focus on productivity costs, such as those associated with morbidity. However, a direct comparison between the estimated inpatient cost and the OPAT cost in the Japanese healthcare system is sufficiently valuable to consider its financial impact.

In conclusion, our study demonstrated that a comprehensive OPAT program run by ID specialists with a multidisciplinary team is a safe and feasible practice not only for efficient bed utilization and medical cost savings but also for better antimicrobial stewardship. Several unique barriers that negatively impact the expansion of OPAT service in Japan exist, such as financial disincentives, unavailability of self/caregiver administration, or non-indication of elastomeric pumps for antimicrobial administration. We hope that the comprehensive OPAT program would become available in more institutions in Japan with the support of the academic community and government.

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Declarations of interest

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