Current Status of Outpatient Parenteral Antimicrobial Therapy (OPAT) At a University-Affiliated Acute-Care Hospital in The Republic of Korea

Eunjeong Heo
Seoul National University Bundang Hospital
https://orcid.org/0000-0002-9244-3145

Yoonhee Choi
Yeungnam University Medical Center

Hyung-sook Kim
Seoul National University Bundang Hospital

Hyung Wook Namgung
Seoul National University Bundang Hospital

Eunsook Lee
Seoul National University Bundang Hospital

Euni Lee
Seoul National University

Ju-Yeun Lee
Seoul National University

Jong Tak Jung
Seoul National University Bundang Hospital

Eu Suk Kim
Seoul National University Bundang Hospital

Hong Bin Kim
Seoul National University Bundang Hospital

Kyoung-Ho Song (✉ khsongmd@gmail.com )
Seoul National University Bundang Hospital
https://orcid.org/0000-0002-4517-3840

Research

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Abstract

Objectives

The aim of this study was to describe current status of outpatient parenteral antimicrobial therapy (OPAT) at a tertiary care hospital in the Republic of Korea.

Methods

This retrospective study was conducted on outpatients and referral patients who had a prescription of parenteral antibiotics from July to December 2019. We reviewed the prescribed antimicrobials, the indication of antimicrobial therapy, where patients administered antimicrobial injection and management of pre- and post-prescriptions.

Results

Of the 577 episodes included in this study, 399 (69.2%) were delivered by referral model, 178 (30.8%) by outpatient model. About 70% of OPATs were prescribed in the pulmonology, infectious diseases, orthopedics, gastroenterology, and hematology departments. Five antibiotics (ertapenem (26.0%), ceftriaxone (12.8%), kanamycin (11.8%), amikacin (10.1%), and cefazolin (8.5%)) accounted for 69.2% of the total OPATs. Urinary tract infections (27.3%), respiratory infections (20.8%), and intra-abdominal infections (15.9%) are the most frequent indications of OPAT. After prescription, there were 295 (73.9%) follow-up visits in referral model and 150 (84.3%) in outpatient model ($p<0.05$). Laboratory tests necessary for monitoring were totally performed in 274 (47.5%).

Conclusions

We found that significant number of OPAT was prescribed, follow-up visits were not performed in about a quarter of episodes, and laboratory monitoring was not fully conducted in more than half of the cases. Therefore, it is necessary to establish an appropriate management program for OPAT. Considering limited resources and the distribution of OPAT prescriptions, it may be effective to select frequently used antibiotics or frequently prescribed departments and start the program for them.

Background

When long-term parenteral antibiotics are required for outpatients or patients who are being discharged, patients are asked to visit outpatient injection centers or are referred to other hospitals. For such treatment, many countries have well-established outpatient parenteral antimicrobial therapy (OPAT) systems. Many studies have shown successful treatment outcome through OPAT and reported reduced costs through reduction of hospital stay. $^{(1-5)}$ According to the 2018 Infectious Diseases Society of...
America (IDSA) guideline for management of OPAT, it is important that patients are in the appropriate setting for OPAT and all patients should have infectious diseases (ID) expert review prior to initiation of OPAT. OPAT is defined as administration of intravenous antimicrobial therapy without hospital admission\(^6\) and it is recommended that an OPAT management team monitors the treatment response, test results, and side effects throughout the treatment.\(^7\)

However, systematic procedures or protocols to manage OPAT, and even information on the current status of prescription of parenteral antibiotics for outpatients and referred patients are lacking in the Republic of Korea. Therefore, the present study aims to investigate the current status of OPAT at a tertiary hospital in Korea. This study also seeks to compare pre- and post-prescription management of patients according to the administration model and to investigate the occurrence of adverse reactions.

**Methods**

1. **Participants**

We searched all patients who were prescribed OPAT between July 1 and December 31, 2019 at Seoul National University Bundang Hospital (SNUBH) which is a 1,300 beds tertiary-care, university-affiliated hospital. Exclusion criteria included one-day prescription of parenteral antibiotics and prescriptions through routes other than intramuscular or intravenous injections. The study was conducted under the approval of the institutional review board (IRB) of SNUBH. Informed consent was waived by the IRB. (IRB No. B-2007/625-105)

2. **Data collection and analysis**

1) **Data collection**

We reviewed the participants' 1 year of electronic medical records between January 1 and December 31, 2019 and collected the following clinical information: age, sex, department treated, diagnosis, indications, type of parenteral antibiotics, number of days, and place where the antibiotics were administered. In the referral model, the documentation of the selected facility was collected. In addition, in order to investigate the pre- and post-prescription management of OPAT, the following data were collected: outpatient visits for follow-up, lab tests, adverse reactions of OPAT, emergency room visits, and hospitalizations.

2) **Definition and analysis of study variables**

Referral model included cases where the prescribed parenteral antibiotics were administered at a nursing hospital or primary care facility. Outpatient model included cases where the parenteral antibiotics were administered at our hospital's injection center or emergency room or through our hospital's visiting injection services. Mixed model included cases where the patients received the antibiotics partially at other medical facilities and partially at our injection center or emergency room.
We compared the following variables according to the administration model: department that prescribed the parenteral antibiotics, antibiotics prescribed, indications for prescription, treatment duration, and treatment outcome. When a new parenteral antibiotic was prescribed less than 14 days from the end of the first prescription, this was counted as one case. Moreover, prescription of two or more antibiotics on the same day was also counted as one case. The department that prescribed the parenteral antibiotics and the antibiotics prescribed were counted in terms of the number of episodes, whereas the indications for prescription, treatment duration, and treatment outcome were counted in terms of the number of cases.

In terms of the possibility of conversion to oral antibiotics, discharged patients whose clinical conditions could be assessed were evaluated based on our hospital's criteria for conversion of parenteral antibiotics to oral antibiotics. The evaluation was reviewed by two pharmacists (a resident and an executive pharmacist) in the antibiotics management team. Conversion from parenteral antibiotics to oral antibiotics was considered to be possible in patients who satisfied all 5 criteria (Additional file 1).

In order to investigate whether tests necessary for monitoring following the prescription of parenteral antibiotics were ordered and performed, the list of necessary tests for each antibiotic was established based on the OPAT guideline published by the IDSA. For antibiotics that were not included in the guideline, relevant publications were reviewed. Cases were divided into those where all necessary tests were ordered, those where only some necessary tests were ordered, and those where none was ordered.

In order to investigate the presence of adverse reactions, cases of reactions documented in charts during follow-up outpatient visits after the prescription of parenteral antibiotics were collected. When patients had multiple adverse reactions to one prescription, these were counted as separate cases. The collected cases of adverse reactions were evaluated as definite and probable events using the Naranjo scale, and the results were reviewed by the two pharmacists. Moreover, cases that visited the emergency room or were readmitted within 30 days of discharge were collected. The association with cases of emergency visits or hospitalizations and adverse drug reactions were assessed based on the medical records.

3. Statistical analysis

In order to compare pre- and post-prescription management of OPAT according to the administration model, statistical analyses comparing the referral model and outpatient model were performed. Pearson's chi-square analyses were performed for follow-up visits and ordering and implementation of necessary tests. Fisher's exact test was used for prescriptions that could be switched from parenteral to oral antibiotics. Statistical analyses were conducted with IBM SPSS statistics ver. 25.0 (IBM Corp., Armonk, NY, USA). P values below 0.05 were interpreted as statistically significant.

Results

1. Participants' characteristics
During the study period, a total of 321 patients were prescribed OPAT. The mean age of the patients was 71 years, and 164 (51.1%) were male. The Charlson comorbidity score had a median of 3 (inter-quartile range, IQR 2-4). There were 577 episodes of prescriptions and 383 patient cases. There were 399 (69.2%) episodes in the referral model and 178 (30.8%) episodes in the outpatient model (Table 1).

| Characteristics                              | N (%)   |
|----------------------------------------------|---------|
| Patients                                     | 321     |
| Age, Median(IQR*) (years)                    | 71 (60, 79) |
| Male                                         | 164 (51.1%) |
| Charlson-comorbidity score, Median(IQR*)     | 3 (2, 4) |
| Antibiotics administration models            |         |
| Episodes (N=577)                             |         |
| Cases (N=383)                                |         |
| Referral model                               | 399 (69.2%) | 258 (67.4%) |
| Outpatient model                             | 178 (30.8%) | 112 (29.2%) |
| Mixed model                                  | -       | 13 (3.4%) |

* Inter quartile range
† 3 episodes/3 cases administered by home-care nurse at home

2. Current status of OPAT prescription and treatment outcome

Departments that prescribed antibiotics, selected antibiotics and site of infection in OPAT prescription are included on the Table 2. Ertapenem (26.0%), ceftriaxone (12.8%), kanamycin (11.8%), amikacin (10.1%), and cefazolin (8.5%) were frequently used antibiotics for OPAT. Five departments accounted for 71.4 % of total episodes; pulmonology, infectious diseases, orthopedics, gastroenterology, hematology. 274 (74.1%) cases were treated for 14 days or less (Table 3). In terms of treatment outcome, 296 (80.0%) cases had no continued prescription of antibiotics.
Table 2
The departments that prescribed antibiotics, selected antibiotics and site of infections for outpatient parenteral antimicrobial therapy

| Department           | All, N (%) (N=577) | Referral, N (%) (N=399) | Outpatient, N (%) (N=178) |
|----------------------|--------------------|-------------------------|---------------------------|
| Pulmonology          | 143 (24.8%)        | 101 (25.3%)             | 42 (23.6%)                |
| Infectious diseases  | 85 (14.7%)         | 40 (10.0%)              | 45 (25.3%)                |
| Orthopedics          | 65 (11.3%)         | 61 (15.3%)              | 4 (2.2%)                  |
| Gastroenterology     | 60 (10.4%)         | 27 (6.8%)               | 33 (18.5%)                |
| Hematology           | 59 (10.2%)         | 57 (14.3%)              | 2 (1.1%)                  |
| Nephrology           | 49 (8.5%)          | 31 (7.8%)               | 18 (10.1%)                |
| Others               | 116 (20.1%)        | 82 (20.6%)              | 34 (19.1%)                |
| Antibiotic           |                    |                         |                           |
| Ertapenem            | 150 (26.0%)        | 77 (19.3%)              | 73 (41.0%)                |
| Ceftriaxone          | 74 (12.8%)         | 48 (12.0%)              | 26 (14.6%)                |
| Kanamycin            | 68 (11.8%)         | 45 (11.3%)              | 23 (12.9%)                |
| Amikacin             | 58 (10.1%)         | 40 (10.0%)              | 18 (10.1%)                |
| Cefazolin            | 49 (8.5%)          | 44 (11.0%)              | 5 (2.8%)                  |
| Piperacillin/tazobactam | 33 (5.7%)     | 33 (8.3%)               | 0 (0.0%)                  |
| Vancomycin           | 30 (5.2%)          | 29 (7.3%)               | 1 (0.6%)                  |
| Benzathine penicillin G | 26 (4.5%)   | 1 (0.3%)                | 25 (14.0%)                |
| Others               | 89 (15.4%)         | 82 (20.6%)              | 7 (3.9%)                  |
| Indications for prescriptions |             |                         |                           |
| Urinary tract infections | 101 (27.3%)  | 60 (23.3%)              | 41 (36.6%)                |
| Respiratory infections† | 77 (20.8%)  | 67 (26.0%)              | 10 (8.9%)                 |
| Intra-abdominal infections | 59 (15.9%)   | 34 (13.2%)              | 25 (22.3%)                |
| Bone and joint infections | 51 (13.8%)  | 49 (19.0%)              | 2 (1.8%)                  |
| Others               | 82 (22.2%)         | 48 (18.6%)              | 34 (30.4%)                |

* Based by all 370 cases; 258 cases in referral model, 112 cases in outpatient model
† Respiratory infections include TB and NTM infections (30 cases, 8.1%).

Table 3. Durations and outcomes of outpatient parenteral antimicrobial therapy.

| Duration      | All, N (%) (N=370) | Referral, N (%) (N=258) | Outpatient, N (%) (N=112) |
|---------------|--------------------|-------------------------|---------------------------|
| 2-14 days     | 274 (74.1%)        | 198 (76.7%)             | 76 (67.9%)                |
| 15-29 days    | 60 (16.2%)         | 33 (12.8%)              | 27 (24.1%)                |
| ≥ 30 days     | 36 (9.7%)          | 27 (10.5%)              | 9 (8.0%)                  |
| Outcome       |                    |                         |                           |
| Antibiotics treatment ended | 296 (80.0%) | 212 (82.2%)            | 84 (75.0%)                |
| Change to oral antibiotics | 47 (12.7%) | 29 (11.2%)             | 18 (16.1%)                |
| ER* visit or readmission | 25 (6.8%) | 15 (5.8%)              | 10 (8.9%)                 |
| Change to other parenteral antibiotics | 2 (0.5%) | 2 (0.8%)               | -                         |

* Emergency room

3. Pre- and post-prescription management of OPAT

Of the 241 episodes of OPAT prescription for discharged patients, conversion to oral antibiotics was considered possible in 9 (3.7%), and all these 9 episodes were in the referral model (Table 4). Of the 399 episodes of OPAT prescribed for administration at another facility (referral model), the facility's name was clearly documented in the prescription only in a small subset of episodes (n = 185, 46.4%).
Table 4
Review of clinical monitoring for managing patients before/after infusion of parenteral antibiotics.

|                                | All, N (%) | Referral, N (%) (N=399) | Outpatient, N (%) (N=178) | p value |
|--------------------------------|------------|-------------------------|---------------------------|---------|
| IV to PO conversion            | 9/241 (3.7%) | 9/233 (3.9%)            | 0/8 (0.0%)                | 1.00    |
| Record of infusion center      |            | 185 (46.4%)             |                           | -       |
| Outpatient visit after administration | 445 (77.1%) | 295 (73.9%)            | 150 (84.3%)                | <0.05   |
| Order rate of laboratory test  |            |                        |                           | 0.64    |
| All                            | 318 (55.1%) | 215 (53.9%)            | 103 (57.9%)                | -       |
| Some                           | 69 (12.0%)  | 48 (12.0%)             | 21 (11.8%)                 | -       |
| None                           | 190 (32.9%) | 136 (34.1%)            | 54 (30.3%)                 | -       |
| Implementation rate of laboratory test |            |                        |                           | 0.07    |
| All                            | 274 (47.5%) | 177 (44.4%)            | 97 (54.5%)                 | -       |
| Some                           | 64 (11.1%)  | 45 (11.3%)             | 19 (10.7%)                 | -       |
| None                           | 239 (41.4%) | 177 (44.4%)            | 63 (34.8%)                 | -       |

445 (77.1%) episodes had follow-up outpatient visits after the prescription; 295 (73.9%) episodes were in the referral model, whereas 150 (84.3%) episodes were in the outpatient model (Table 4). Follow-up visits were more frequently done in the outpatient model, with a statistically significant difference between the two models (p<0.05). All necessary tests for antibiotics were ordered by attending physician in 318 episodes (55.1%) and performed in 274 episodes (47.5%).

4. Adverse drug reactions

The adverse reaction was developed were documented in 57 (12.8%) episodes. Of these episodes, 16 episodes had Naranjo scale scores corresponding to definite or probable (3.6%); of these, 13 were in the referral model (4.4%), and 3 were in the outpatient model (2.0%) (Table 5). A total of 70 episodes involved emergency room visits or hospitalizations within 30 days of prescription of OPAT (12.1%); of these, 3 (0.5%) were considered to be associated with the parenteral antibiotics prescribed (ertapenem and kanamycin).
Table 5
Adverse drug reaction related with prescribed parenteral antibiotics.

|                                | All, N (%) | Referral, N (%) | Outpatient, N (%) |
|--------------------------------|------------|-----------------|-------------------|
| Adverse events associated episodes* | 57/445 (12.8%) | 44/295 (14.9%) | 13/150 (8.7%) |
| ADR† associated episodes        | 16/445 (3.6%) | 13/295 (4.4%) | 3/150 (2.0%) |
| ER‡ visit or admission          | 70/577 (12.1%) | 43/399 (10.8%) | 27/178 (15.2%) |
| Related with parenteral antibiotics | 3/577 (0.5%) | 2/399 (0.5%) | 1/178 (0.6%) |

* Adverse events instigated only for episodes that had outpatient visit after administration; All (445 episodes)
† Adverse drug reaction
‡ Emergency room

Discussion

The present study assessed the current status and management of OPAT at a single hospital in the Republic of Korea, for the first time. In Korea, post-acute care patients refer to long term care facility to maintain parenteral antibiotics. But there are no fees or reimbursement for OPAT management and few institutions implement OPAT management team. This study may show the current status of OPAT in Korea. During the 6-month study period, significant number (577 episodes) of OPAT prescriptions were made through outpatient or referral models, and we investigated the administration model, follow-up outpatient visit rates after prescription, and monitoring test rates.

We found that prescriptions from the top 5 departments that prescribe OPAT often accounted for approximately 70% of all prescriptions. This suggests that pre- and post-prescription management can be introduced preferentially to departments with high rates of prescription. Ertapenem, ceftriaxone, and kanamycin were often prescribed at our hospital, but studies of OPAT at other hospitals reported that ceftriaxone and teicoplanin were frequently prescribed. The use of teicoplanin was low at our hospital as we use vancomycin as first line treatment for antibiotic-resistant gram-positive bacterial infection, such as methicillin-resistant Staphylococcus aureus. This difference is thought to be caused by each hospitals' had different patient groups and antibiotic prescribing behaviors. Thus, it is important that each hospital should develop its own strategy for antimicrobial stewardship based on the analysis of antibiotic use of the institution.

Common indications for parenteral antibiotics in this study included urinary tract infection, respiratory infection, intra-abdominal infection, and bone and joint infection, consistent with other OPAT studies.
reporting that bone and joint infections are major indications for OPAT.\(^{(13–17)}\) This finding might be due to the clinical characteristics of bone and joint infections requiring relatively long uses of parenteral antibiotics. In contrast, other studies have also reported that skin and soft tissue infections are major indications for OPAT.\(^{(12,14,16,17)}\)

In the referral model, 46.6% of episodes had clear documentation of the facility selected to administer the antibiotics, and this indirectly suggests that management of administration of OPAT is inadequate. In the referral model in which the administration of OPAT is handed over to another facility, the transition can be made through hospitalization or outpatient visits to general hospitals, nursing hospital, clinics, and other various types of facilities. In Korea, there is no fee claims available for these referrals, and sharing of treatment information is also not systematic. As different facilities may be capable of different levels of tests and monitoring, it is important to confirm the facility to which the patient is being referred in advance to confirm whether the facility is capable of maintaining and managing OPAT. Moreover, systematic changes should be made to support continued treatment and management through exchange of information between facilities.

More patients in the outpatient model had follow-up outpatient visits after the administration of OPAT than those in the referral model. This may be because patients who continued their care at another facility may have been followed up at that facility, thus not presenting to our hospital for follow-up. In addition, patients who received acute treatment at our hospital may have continued their treatment at a medical facility close to their home. In terms of the implementation of tests necessary for monitoring of parenteral antibiotics, the rate was higher in the outpatient model than in the referral model with a non-significant difference between the two models. Based on these findings, when follow-up at the same hospital is not carried out, the list of necessary tests for management of parenteral antibiotics and possible side effects should be offered at the time of referral. Subsequently, continued management should be offered through phone calls with patients.

For management of OPAT, not only OPAT team but antimicrobial stewardship intervention can be helpful. When we evaluated the possibility of changes in the route of administration prior to antibiotics administration, conversion to oral antibiotics was considered to have been possible in 3.7% of prescriptions. Our hospital manages restricted antibiotics by regular ID consultations, and there is an electronic alert with automated consultations for positive blood culture test, so it seems to be well managed\(^{(18)}\). And Pharmacists in the antimicrobial stewardship team continue to offer the intervention (parenteral-to-oral conversion) to inpatients at our hospital.\(^{(19,20)}\) And antimicrobial stewardship team can suggest appropriate duration of antimicrobial therapy. In the future, prescription of parenteral antibiotics for patients planned for discharge should be reviewed in advance to reduce inappropriate antibiotic use.

In the present study, adverse drug reactions were confirmed in 3.6% of prescriptions of parenteral antibiotics in outpatient and referral models, and less than 1% of prescriptions led to emergency room visits or hospitalizations associated with adverse drug reactions. However, a previous study reported that
adverse reactions were seen in 18% of cases within 2 weeks of discharge,\(^{(12)}\) and another study reported that re-hospitalization was seen in up to 27% of patients.\(^{(21)}\) Referring to the other studies, since only medical records were analyzed retrospectively, mild side effects might not be recorded by physicians and it cannot be recognized in our study. Moreover, although we did not confirm any catheter-associated bloodstream infections in this study, these infections were frequently reported in studies conducted in other countries.\(^{(13,22)}\) In Korea, self-administration of intravenous agents by patients is not allowed, and patients are often discharged without central venous catheters. These differences in practice may have led to the differences seen in the results.

A few limitations should be considered when interpreting the results of this study. First, because of retrospective nature of this study, we could not assess the treatment outcome, adverse reaction of antibiotics, whether antibiotics had changed or added etc. in patients without follow-up visit. Second, when no follow-up visits were done, more adverse reactions than those documented could have happened. However, as these were not documented, the number of adverse reactions could have been underestimated given the retrospective design of the present study. Last, since this study was conducted at a single hospital, the results may be different from other hospitals in South Korea.

This study investigated the departments that frequently prescribe parenteral antibiotics for outpatients and referred patients, as well as frequently prescribed antibiotics and the indications for them. The study also found that appropriate candidates for monitoring should be selected prior to administration of parenteral antibiotics and that monitoring should be implemented. This study is significant in that it was able to confirm the participants who require monitoring of parenteral antibiotics, the scope of monitoring, and the necessity of a monitoring system through its findings.

**Conclusion**

According to the present study findings, approximately 70% of OPAT were prescribed in 5 departments, and 5 antibiotics accounted for 70% of all prescriptions. We also confirmed that follow-up after prescription is lacking. Therefore, a comprehensive monitoring system and antimicrobial stewardship for safe and effective OPAT is necessary, and the findings of this study will serve as useful basic data for the system.

**Declarations**

**Ethics approval and consent to participate**

This retrospective study was approved by the institutional review board (IRB) of Seoul National University Bundang Hospital (B-2007/625-105), and a waiver for written consent was obtained from the IRB.

**Consent for publication**

All authors agree publication of this paper.
Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

All authors declare that there are no conflicts of interest.

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Authors’ contributions

YC, EH, JYL, KHS designed study and drafted paper. YC, EH collected and analyzed the patient data. JYL, HWN, EL1, EL2 analyzed and interpreted the patient data regarding antibiotic therapy and antibiotic adverse reaction. EH, JTJ, ESK, HBK, KHS analyzed and interpreted the patient data regarding infectious disease and outpatient parenteral antibiotic therapy (OPAT). All authors read and approved the final manuscript.

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