2019

Comparison of patient outcomes in a pharmacist-led outpatient parenteral antimicrobial therapy program

Zachary Howe
Butler University

BUTLER UNIVERSITY HONORS PROGRAM

Honors Thesis Certification

Applicant: Zachary William Howe

Thesis title: Comparison of patient outcomes in a pharmacist-led outpatient parenteral antimicrobial therapy program.

Intended date of commencement: May 11, 2019

Read, approved, and signed by:

Thesis adviser(s) [signature] 4/15/19

Reader(s) [signature] 4/15/19

Zachary Howe and Lindsay Saum, PharmD, BCPS, BCGP

A Thesis

Presented to the College of Pharmacy and Health Sciences

and

The Honors Program

of

Butler University

In Partial Fulfillment

of the Requirements for Graduation Honors

Zachary William Howe

April 13, 2019

Abstract

Purpose: Outpatient parenteral antimicrobial therapy (OPAT) is a therapeutic option meant to conserve healthcare resources when treating infections requiring the administration of IV antibiotics over a prolonged treatment course. In November 2016 at Franciscan Alliance Indianapolis, a dedicated pharmacist was hired to build a formal OPAT program for all patients discharged on IV antimicrobials under the care of the infectious disease physician group. The number of "good catch" events observed since the program's formal inception has encouraged the creation of this study designed to examine the impact of this program on patient outcomes and antimicrobial stewardship.

Methods: This was a retrospective chart review of adult patients with a discharge order for at least one IV antibiotic from Franciscan Health Indianapolis from December 1st, 2016 to May 31st, 2017. Patients receiving OPAT consults during their index hospital stay were compared to patients with similar infections who did not receive a consult. Patients residing in a nursing home or long-term care facility prior to admission were excluded from the analysis. Comparisons between patients with and without a readmission were also conducted in order to identify commonalities and differences in risk factors between groups. Demographic information collected included: the indication for parenteral antimicrobial therapy, sex, age, weight, and the type of provider prescribing the antimicrobials. The primary objective was 30-day readmission rate, with each instance being stratified based on the reason for readmission. Secondary objectives included: type of infection, antibiotic type, disposition at discharge, and duration of treatment. At least 122 patients were needed in each arm in order to detect a difference of 50 percent between treatment groups with a power of 80 percent for the primary objective.

Results: No statistically significant difference between the readmission rates of the consult group and the non-consult group was observed (14.73% versus 31.82%, $p>0.05$). The usage of antipseudomonal coverage (39.58% versus 86.36%, $p<0.0001$) and ceftriaxone (9.47% versus 45.45%, $p<0.0001$) was significantly lower in the consult group, demonstrating the potential improvements in antimicrobial stewardship an OPAT program can provide. Use of agents requiring therapeutic drug monitoring (TDM) was higher in the non-consult group, specifically vancomycin (86.36% versus 41.05%, $p<0.001$) and gentamicin (6.32% versus 22.73%, $p<0.05$). Furthermore, patients discharged to an extended care facility (ECF) or a short-term acute rehabilitation center (SAR) after receiving a consult were less likely to be readmitted (16.23% versus 54.55%, $p<0.001$). The difference in use of drugs requiring TDM for patients sent to a SAR with a consult may also have contributed to this trend (50.46% versus 100%, $p<0.0001$).

Conclusion: The OPAT service did not show a statistically significantly reduction in the 30-day readmission rate during the first 6 months of the program. However, the number of patients without a consult meeting the inclusion criteria was markedly lower than anticipated, which led to the study being underpowered. Additionally, use of the program was associated with improved antimicrobial stewardship through reduced use of antipseudomonal coverage and ceftriaxone as well as reduced readmissions in patients requiring SAR placement.

Background

Outpatient parenteral antimicrobial therapy (OPAT) is defined as the administration of parenteral antimicrobials for at least 2 doses given on different days and without a hospitalization between.[1] Rather than requiring a patient to remain in a hospital solely to receive antimicrobial therapy after being medically cleared to go home, he or she can be discharged for a portion of the therapy. The ability to send a patient on intravenous antimicrobial therapy has been shown to potentially reduce the high costs associated with chronic administration of antibiotics,[2] increase the patient's quality of life by granting improved flexibility and convenience, and reduce the likelihood that the patient will acquire a nosocomial infection. As a result, OPAT has grown at a breakneck pace since its inception in the 1970s, and projections of its market share predict that it will soon reach the multibillion-dollar-a-year threshold.[1]

Furthermore, input from pharmacists to assist in the appropriate selection of antimicrobials and durations of therapies has the potential to attempt to stem the rising tide of resistant microorganisms. The interventions related to spectrum and duration can lead to vastly reduced rates of adverse effects due to unnecessary antimicrobial use and can also reduce the likelihood that the patient may encounter an infection caused by a resistant organism later in life.[3] Additionally, it may reduce the rate of multidrug resistant organisms, which is especially critical for patients who must be admitted but are also most at risk. Through appropriate recommendations related to the spectrum and duration of therapy, selection of resistant microorganisms can be minimized, which partially mitigates these risks.

In addition to pharmacist involvement, interprofessional collaboration and careful selection of patients designated to receive OPAT are critical to ensuring successful therapy. Beyond the clinical expertise offered by the ID physicians, coordination of social support and third-party authorizations between case management and pharmacy contribute significantly to a patient's ability to receive appropriate therapy. Additionally, in patients for whom adequate monitoring and follow up cannot be guaranteed, complications related to vascular access devices and drug adverse reactions can lead to significant harm.[4] Therefore, both social and medical evaluations should be integral steps in the process utilized to identify patients appropriate to receive OPAT.

In November 2016 at a community hospital, a dedicated pharmacist was hired to continue to build a formal OPAT program for all patients discharged on IV antimicrobials under the care of the infectious disease physician group. Through a collaborative practice agreement, the pharmacist's responsibilities upon consultation were to evaluate and make recommendations related to antimicrobial selection, therapy duration, and monitoring parameters, as well as the provision of patient education and assistance to case managers involved with disposition planning. Upon discharge from the hospital, the pharmacist continued weekly monitoring throughout the duration of therapy of all patients that received such consultative services during their inpatient stay. Due to the relatively new nature of this OPAT program and the number of "good catch" events observed since its formal inception, this study sought to examine the impact of an OPAT program for those patients receiving OPAT at hospital discharge.

Methods

This was a retrospective observational cohort study examining adult patients with an order for an IV antibiotic following discharge from a community hospital within the time period of December 1, 2016 to May 31, 2017. Patients who received OPAT consults during their index hospital stay were compared to those patients who did not in the same time period. Patients

residing in a nursing home or long-term care facility prior to admission and those also receiving oral antimicrobials were excluded from the analysis. The primary objective was thirty-day readmission rate, which was stratified by the reason for readmission (ID process, drug adverse event, or unrelated reason). Type of infection, antimicrobial selection (including agents with antipseudomonal activity or requiring therapeutic drug monitoring), duration of treatment, and disposition at hospital discharge were also collected from the electronic medical record.

Statistical Analysis

The Fisher's Exact Test and Chi Square Analyses were utilized, as appropriate, for nominal endpoints including: the 30-day readmission rate, use of each antimicrobial class, and the use of agents with a high risk of a *C. difficile* infection, such as ceftriaxone, or requiring therapeutic drug monitoring. The Wilcoxon Ranked Sum Test was utilized to determine the significance of differences in length of stay and duration of therapy. Statistical Package for the Social Sciences software available through Butler University was utilized for these analyses. All other variables and baseline demographic information were described utilizing descriptive statistics.

Results

No statistically significant differences between groups were seen in terms of demographic information (**Table 1**).

Table 1: Demographics

	OPAT Consult (N=95)	**No OPAT Consult (N=22)**	**p Value**
Median Age (IQR)	61 (21)	63 (26)	0.503
Sex (%) M F	 42 (44) 53 (56)	 6 (27) 16 (73)	0.146
Median Weight (IQR)	91 kg (35 kg)	79 kg (41 kg)	0.085
Median Index LOS (IQR)	6 (5)	7 (8)	0.313

No statistically significant difference between the readmission rates of the OPAT consult group and the non-consult group was observed (14.73% vs 31.82%, p=0.07). Additionally, the proportion of patients requiring a change in disposition did not vary significantly between groups, with 39 (41%) patients with a consult and 12 (55%) patients without a consult being discharged to a short-term acute rehabilitation center (SAR) or extended care facility (ECF) (P=0.252). Bacteremias with various sources of infection were the most common type of infection requiring therapy in both groups, constituting 35% of patients in the OPAT consult group and 59% of the patients without a consult. Differences in provider type and indication for

therapy between groups were statistically significant (p=<<0.0001; 3×10^{-12}). The median total days of therapy for patients with a consult was 24 days in comparison to 25 days in the non-consult group (p=0.095).

The most significantly differing trends between groups were evident in prescribing practices. The usage of antipseudomonal coverage was significantly lower in the OPAT consult group (39.58% vs 86.36%, p=0.00006). Additionally, utilization of ceftriaxone, known for its potential to predispose patients to *C. difficile* infections, was also significantly lower in the OPAT consult group (9.47% vs 45.45%, p=0.00004). Differences in other key antibiotics that serve as stewardship targets were also seen with piperacillin-tazobactam, cefepime, and vancomycin (**Table 2**). Also of interest, patients without an OPAT consult discharged to a SAR or ECF were significantly more likely to have been prescribed agents requiring therapeutic drug monitoring (100% vs 59.56%, p=0.038) and to have later required readmission (54.55% vs 16.22%, p=0.001).

Table 2: All Patients

	OPAT Consult (N=95)	**No OPAT Consult (N=22)**	**p Value**
Disposition Change	39 (41%)	12 (55%)	0.252
Indication for Therapy			3×10^{-12}
Empyema	7	2	
Osteomyelitis	11	2	
Bacteremia	33	13	
Intra-Abdominal	10	3	
Skin and Soft Tissue (SSTI)	25	0	
Other	9	2	
Primary Provider Type			0.000095
Pulmonary	5	7	
Cardiology	10	1	
Surgery	25	4	
Internal Medicine	52	8	
Oncology	3	2	
Median Days of Therapy (IQR)	24 (19)	25 (17)	0.095

Table 3: Drug Choice

Drug Choice	OPAT Consult (N=95)	No OPAT Consult (N=22)	P Value
Ampicillin	5	2	0.495
Ampicillin-Sulbactam	12	2	0.645
Piperacillin-Tazobactam	13	11	0.0001
Cefazolin	15	3	0.801
Ceftazidime	1	0	0.203
Ceftriaxone	9	10	0.00004
Cefuroxime	1	1	0.255
Cefepime	10	7	0.011
Meropenem	8	5	0.054
Ertapenem	4	1	0.944
Gentamicin	6	5	0.017
Tobramycin	0	4	0.0002
Vancomycin	39	19	0.0001
Linezolid	0	2	0.023
Daptomycin	1	0	0.213
Metronidazole	2	5	0.0002
Clindamycin	2	2	0.104
Fluconazole	2	2	0.104
Antipseudomonal Agents	37	19	0.00006

Readmitted Subgroup

When examining readmitted patients as a subgroup, several differences between those receiving a consult and those without were seen (**Table 4)**. Significant differences in the indications for therapy in this population were seen (p=0.009), with bacteremias and SSTIs as the most common in the OPAT consult (71%) and non-consult (43%) groups, respectively. Additionally, a trend was seen showing that patients in this subgroup without a consult were more likely to have experienced a change in disposition (85.71% vs 42.86%, p=0.061).

Table 4: Readmitted Patients

	OPAT Consult (N=14)	No OPAT Consult (N=7)	P Value
Median Age (IQR)	61 (16)	64 (26)	0.711
Sex			
Male	8	5	0.525
Female	6	2	
Indication for Therapy			0.009
Osteomyelitis	2	1	
Bacteremia	3	5	
Intra-Abdominal	2	1	
Skin and Soft Tissue	6	0	
Other	1	0	
Median Index Length of Stay (IQR)	6 (2)	7 (3)	0.352
Median Days to Readmission (IQR)	12 (14)	9 (6)	0.368
Disposition at Discharge			0.061
Home	8	1	
ECF or SAR	6	6	
Disposition Change	6 (43%)	6 (86%)	0.061
Median Total Days of Therapy (IQR)	28 (24)	28 (27)	0.190
Reason for Readmission			0.216
ID Process	2	3	
Drug Adverse Event	3	1	
Unrelated Process	9	3	

Discussion

No statistical significance in terms of the primary objective, thirty-day readmission rates, was seen in the study. However, the more than two-fold difference in readmission rate can certainly be seen as clinically significant. The readmission rate of 14.74% was also similar to the 21.5% readmission rate reported by another study, which somewhat adds to the confidence with which the results from this study can be interpreted.[5]

Considerable improvements in antimicrobial stewardship were seen when comparing the group of patients receiving a consult to those that did not. This enhancement in stewardship was primarily via reduced utilization of antipseudomonal coverage, vancomycin, and ceftriaxone, which demonstrated the key role that such programs can have on selecting therapy with an appropriately narrow spectrum. One way by which OPAT can reduce costs and improve patient outcomes comes via the involvement of infectious disease specialists to improve the selection of appropriately narrow spectrum antimicrobials. By avoiding the use of overly broad coverage, the risk of off target eradication of the gut microbiome and subsequent development of a *Clostridium difficile* infection can be significantly reduced. Beyond the clinical impact of this variety of infectious diarrhea, this microbe leads to 4.8 billion dollars in additional costs to hospitals in the United States annually.[6] For example, unnecessary use of ceftriaxone, a cephalosporin utilized for a variety of infections, has become a potential target for antimicrobial stewardship programs due to its common use and propensity for causing this type of infection.[6,7] It is imperative that therapies are selected appropriately to only cover the types of microorganisms likely to be causing the patient's infection, and narrowed when culture and susceptibility data are available, which is a major point of impact for pharmacist-led OPAT services.

The difference in readmissions seen for patients without a consult sent to a SAR or ECF highlights the value of including a dedicated infectious disease clinical pharmacy specialist to coordinate careful monitoring during the course of OPAT. Especially when utilizing agents requiring therapeutic drug monitoring, such as vancomycin or aminoglycosides, the potential for significant adverse effects is considerable, and lack of lab value availability during the course of OPAT has been noted to be a significant risk factor for readmission, which may partially explain the difference seen here.[8] The potentially increased debility or acuity of patients more likely to be sent to a SAR or ECF in comparison to a patient able to be sent home could have contributed to this observation, but such a difference was not seen amongst patients sent to these facilities after receiving a consult.

The need for appropriate monitoring and communication between healthcare systems should be given careful consideration prior to the implementation of OPAT. One report noted that 26% of sites surveyed had a team specifically designated to handle OPAT cases.[5] A survey of practitioners involved in an OPAT service indicated that up to 70% had seen such therapy implemented without a consult from an ID specialist, and another study showed the addition of a pharmacist or ID physician or pharmacist to an OPAT team raised adherence to monitoring by 32% and 64%, respectively.[9, 10] One study showed that cases reviewed by an ID physician led to changes in therapy from parenteral to oral agents in 27-40% of cases.[9] This shows the value of a dedicated OPAT team's ability to improve patient care via appropriate selection of antimicrobial therapy from a therapeutic perspective, which often reduces costs.

While poor communication can be a barrier to the success of OPAT, adverse effects have been cited as the primary reason for OPAT discontinuation or therapy modification in 3-5% of cases.[9] A survey of infectious disease physicians conducted in 2012 showed that only 22% of the OPAT programs in which they worked had a way to track medication errors, "near misses", or adverse events.[5] Additionally, it is of utmost importance that patients who are to receive OPAT be carefully selected to ensure that they have to appropriate social and financial support to receive therapy at home, an infusion center, or another location. The potential ramifications for patients inappropriately selected for outpatient therapy include both clinical decompensation as well as the potential for enhanced resistance by the responsible pathogen due to incomplete eradication.

Several limitations should be considered when interpreting the results of the study. The small sample size and timing of the study period at the advent of the program could have impacted the results. Additionally, the significantly lower number of eligible non-consult patients noted previously was a phenomenon that should also be considered. This trend could possibly have been due to the novelty of the new program or increased provider confidence in the utilization of a formalized OPAT program able to more consistently offer improved monitoring and follow up after discharge. The lack of assessments related to comorbidities, severity of infection, or causative pathogen limit the generalizability of these findings. Finally, due to the method by which cost data for the non-consult was requested, namely via use of ICD-10 coding, a certain level of uncertainty was introduced. It was hypothesized that this may have been due to inconsistent coding practices and likely did not skew the results in favor of either group, but it should be noted nonetheless.

As OPAT services continue to expand in the United States, further investigations utilizing larger sample sizes and examining shifting trends in patient outcomes should be conducted in order to further assess the value of the program and monitor for potential quality improvement opportunities. Furthermore, patient and provider satisfaction data could be included to better assess the improvements in quality of life and perception of value associated with the program, respectively. This study serves as a promising indication for the potential patient care improvements related to antimicrobial stewardship and improved patient outcomes that OPAT services can offer to their patients.

References

1. Tice AD, Rehm SJ, Dalovisio, JR. Practice guidelines for outpatient parenteral antimicrobial therapy. *Clin Infect Dis.* 2004;38:1661-1672. doi.10.1086/420939.
2. Ruh CA, Parameswaran GI, Wojciechowski AL, Mergenhagen KA. Outcomes and pharmacoeconomic analysis of a home intravenous antibiotic infusion program in veterans. *Clin Ther.* 2015;37(11):2527-2535. doi.10.1016/j.clinthera.2015.09.009.
3. Diaz Granados CA. Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. *Am J Infect Control.* 2012;40(6):526-529. doi.10.101/j.ajic.2011.07.011.
4. Chung EK, Beller CB, Muloma EW, et al. Development and implementation of a pharmacist-managed outpatient parenteral antimicrobial therapy program. *Am J Health Syst Pharm*. 2016;73(1):e24-e33. doi.10.2146/ajhp150201.
5. Lane MA, Marschall J, Beekmann SE, et al. Outpatient parenteral antimicrobial therapy practices among adult infectious disease physicians. *Infect Control Hosp Epidemiol.* 2014;35(7):839-844. doi.10.1086/676859.
6. Scott II RD. The direct medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention 2009. Division of Healthcare Quality Promotion National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention.
7. Ceftriaxone [package insert]. Indianapolis, IN. Hoffmann La Roche; 1984.
8. Huck D, Ginsberg JP, Gordon SM, et al. Association of laboratory test result availability and rehospitalizations in an outpatient parenteral antimicrobial therapy programme. *J Antimicrob Chemother*. 2014;69(1):228-233. doi.10.1093/jac/dkt303.

9. Muldoon EG, Snydman Dr, Penland EC, Allison GM. Are we ready for an outpatient parenteral antimicrobial therapy bundle? A critical appraisal of the evidence. *Clin Infect Dis*. 2013;57(3):419-424. doi.10.1093/cid/cit955.
10. Shah PJ, Bergman SJ, Graham DR. Monitoring of outpatient parenteral antimicrobial therapy and implementation of clinical pharmacy services at a community hospital infusion unit. *J Pharm Pract*. 2014;28(5):462-468. doi.10.1177/0897190014544786.