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Predictors of adverse safety events and unscheduled care among an outpatient parenteral antimicrobial therapy (OPAT) patient cohort

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Abstract

Background: Select circumstances require outpatient parenteral antimicrobial therapy (OPAT). The potency of OPAT agents presents an increased risk of adverse events and unscheduled medical care. We analyzed these outcomes among OPAT recipients as part of the implementation of a collaborative OPAT program.

Methods: Adult patients discharged home from an academic hospital with OPAT between January 2019 and June 2021 were included in this retrospective cohort; participants discharged between June 2020 and June 2021 were part of the collaborative OPAT program. Patients with cystic fibrosis were excluded. Data on patient characteristics and outcomes were collected from electronic medical records by two reviewers. Multivariable analysis was conducted to identify predictors of vascular access device (VAD) complications, adverse drug events (ADEs), and OPAT-related emergency department (ED) visits and rehospitalizations.

Results: Among 265 patients included in the cohort, 57 (21.5%) patients experienced a VAD complication; obesity [odds ratio (OR): 3.32; 95% confidence interval (CI): 1.38–8.73; $p = 0.01$) and multi-drug therapy (OR: 2.56; 95% CI: 1.21–5.39; $p = 0.01$) were associated with an increased odds of VAD complication. Eighty-two (30.9%) participants experienced an ADE; 30 (11.3%) experienced a severe/serious ADE. Lipo/glycopeptide receipt, (OR: 5.28; 95% CI: 1.89–15.43; $p < 0.01$) and Black/African American race (OR: 4.85; 95% (CI): 1.56–15.45; $p < 0.01$) were associated with an increased odds of severe/serious ADE. Inclusion in the OPAT collaborative was associated with a decreased odds of severe/serious ADE (OR: 0.26; 95% CI: 0.08–0.77; $p = 0.01$). Fifty-eight (21.9%) patients experienced an OPAT-related ED visit and 53 (20.0%) experienced an OPAT-related rehospitalization. VAD complication (OR: 2.37; 95% (CI): 1.15–4.86, $p = 0.02$) and ADEs (OR: 2.19; CI: 1.13–4.22; $p = 0.02$) were associated with OPAT-related ED visits. ADE was associated with 90-day OPAT-related rehospitalization (OR: 3.21; (CI): 1.59–6.58; $p < 0.01$).

Conclusion: Adverse safety events and OPAT-related unscheduled care occurred often in our cohort. A structured OPAT program that includes ID pharmacist antibiotic reconciliation may reduce rates of ADEs.

Keywords: OPAT, outpatient parenteral antibiotic therapy

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Introduction

Outpatient parenteral antimicrobial therapy (OPAT) allows patients to receive extended courses of antimicrobial therapy in a non-acute care setting. Now considered a standard method of treatment, OPAT can be delivered in several different settings including an infusion center, skilled nursing facility, or home.[1] In most cases,

OPAT is administered in the home by the patient or caregiver with periodic visits from home infusion nursing for management of the vascular access device (VAD) and routine monitoring.[2] OPAT offers several advantages to both the patient and the healthcare institution including shorter inpatient stays, prevention of hospital-associated conditions (e.g. infection, venous thromboembolism, pressure ulcer), and reduction in costs.[1–3]

Intravenous administration of potent antimicrobial agents is associated with risks, including adverse drug events, (ADEs) indwelling VAD complications, and, in the setting of severe infection, antimicrobial failure.[4–6] In addition, therapy with an inappropriate spectrum and/or duration can lead to selection of resistant organisms. Importantly, the transition that OPAT recipients make from inpatient to outpatient care is thought to be a vulnerable period for these events due to the potential for communication errors and absence of immediate clinical supervision, and their consequences can include unscheduled healthcare visits.[7]

Previous studies assessing the risks of ADEs among patients receiving OPAT report a broad range of results due to the diversity of ADE classifications used. The reported prevalence of ADEs in OPAT recipients range 7–39%, and the rate of ADEs ranges from 2.2 to 7.7 per 1000 days of treatment.[8–11] Similarly, published reports characterizing the rates of VAD complications ranging 3–29%.[11–15] Together, ADEs and VAD complications are considered the primary factor for around 40% of hospital readmissions during OPAT.[16] The consequences of serious ADEs and VAD complications can quickly offset the potential benefits of OPAT, especially when they threaten the successful treatment of serious infections or result in unscheduled healthcare utilization. In a retrospective review, 82/400 (21%) OPAT patients at the Cleveland Clinic were readmitted after discharge on OPAT, while a similar retrospective study found 43/216 (20%) adult patients required rehospitalization after discharge on OPAT from a hospital in the University of Illinois Hospital and Health Sciences System.[16,17] Other OPAT programs have reported rehospitalization rates as low as 6%.[2] OPAT-related ED visits vary widely among published studies, ranging 4.6–43%.[4,18,19] Unplanned healthcare utilization directly attributable to OPAT has not been well defined.

One strategy that has been employed to promote patient safety in care transitions is medication reconciliation, typically conducted by a pharmacist at the patient's discharge from the acute care setting. Published literature indicates that many ADEs could be prevented while others may be lessened in duration or severity with pharmacist involvement.[20] Some studies support reduction medication errors, and decreased readmissions in at least one study with discharge medication reconciliation.[21,22] However, in a randomized controlled trial performed at two academic medical centers in Nashville, Tennessee, and Boston, Massachusetts, approximately 50% of adult patients who received a robust pharmacist-driven intervention still experienced a clinically important medication error within one month following discharge.[20] While the results are mixed, the impact of pharmacist reconciliation of OPAT regimens at discharge is not well understood.

The purpose of this retrospective cohort study was to describe the ADEs, VAD complications, and OPAT-related, unscheduled healthcare use among OPAT recipients discharged to home from a large Midwest academic medical center before and after the implementation of a standardized process for OPAT plan review with medication reconciliation by ID pharmacists.

Methods

Design and setting

This was a retrospective cohort study of adult patients discharged home from M Health Fairview University of Minnesota Medical Center (UMMC) with OPAT provided by Fairview Home Infusion (FHI) services between January 2019 and June 2021. UMMC is a 743-bed, urban academic hospital. Inpatient infectious diseases (ID) consult is not mandatory at UMMC for patients discharged on OPAT. Admitted patients whose care plan includes FHI-supplied OPAT meet with a nurse liaison prior to discharge to review the logistics of home parenteral therapy. After discharge, home health agencies provide, at minimum, weekly visits for line care and blood draws for laboratory monitoring. Drug and supply delivery is coordinated by FHI. Adjustments

to OPAT elements, including laboratory monitoring or drug dosing, are made by designated OPAT providers. The designated OPAT provider is typically an ID provider that, in addition to signing parenteral antibiotic and lab monitoring orders, follows serial laboratory results and determines the length of treatment and the necessity of future clinic visits. In June 2020, a program was launched that entailed OPAT plan review by ID pharmacists after being alerted of potential OPAT discharges via electronic referral messages from care coordinators. This review occurred while prospective OPAT patients were still in the hospital and included parenteral antibiotic reconciliation and identification of a designated OPAT provider prior to discharge. Interventions made by ID pharmacists during parenteral antibiotic reconciliation included optimizing drug antimicrobial selection and dosing based on a patient's evolving clinical status and making recommendations for future laboratory monitoring, including therapeutic drug monitoring. ID pharmacists did not follow OPAT patients beyond discharge. A participant's OPAT instance was considered pre-intervention if their index discharge was prior to 14 June 2020 and post-intervention if their index discharge occurred on 14 June 2020, or later. This quality improvement project was deemed exempt from research requirements by the University of Minnesota and M Health Fairview institutional review boards.

Participants and data collection

Unique, adult patients whose orders at the time of discharge to home included more than one parenteral antimicrobial for which FHI was the recorded supplier were included. Patients receiving OPAT outside of their home, from an infusion agency other than FHI, or whose infusion agency could not be verified as FHI were excluded because EHR records for these patients are less like to reflect key OPAT events during retrospective review. Only the first course of OPAT per participant was included. Patients with cystic fibrosis were excluded. Data related to infectious indication for OPAT, VAD type, OPAT agent(s), quality of documentation for parenteral antimicrobial start date, ADEs, VAD complications, and OPAT-attributable ED visits were collected from the institution's electronic health record (EHR) system via manual chart review by two reviewers using a standardized REDCap instrument. Documentation of OPAT start date was considered adequate if there was consistent, clear, and accurate documentation of the antimicrobial start date in the discharge documentation as determined by manual review. In addition, a structured data extraction from the EHR provided data on select patient characteristics, including self-reported race, ethnicity, Charlson Comorbidity Index, (CCI) penicillin allergy documentation, and body mass index (BMI).

Outcomes

The primary outcomes assessed were frequency and severity of ADEs, frequency of VAD complications, and OPAT-related hospital readmissions and ED visits within 90 days of index hospitalization discharge. ADEs and VAD complications were identified during manual review of the EHR, and included both patient- and provider-reported events. ADEs were categorized by reaction type and stratified by severity into mild, moderate, severe, or serious events, where mild indicated a transient event requiring no special intervention, moderate indicated an event alleviated with simple therapeutic treatments, severe indicated an event requiring significant therapeutic intervention, and serious indicated an event resulting in death, life-threatening condition, hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect.[23] VAD complications were categorized by type. With the exception of central line–associated bloodstream infection (CLABSI), which were classified as both an ADE and a VAD complication, ADEs and VAD complications were distinct sets of events.

Patients may have been on an OPAT regimen or completed OPAT therapy when attributable ED visits or rehospitalizations occurred. All unscheduled healthcare events were part of the analyses, including ED visits that led to subsequent hospitalization. Events were considered OPAT-related if the reason for visit was related to an ADE, VAD complication, or recurrence of infection.

Independent risk factors for the primary outcomes were also assessed via multivariable logistic regression.

Statistical analysis

Categorical variables were summarized using counts and rates, and continuous variables were

summarized using medians and interquartile ranges. Univariate and multivariable logistic regression models were used to examine predictor variables associated with the occurrence of any ADE, severe/serious ADE, any VAD complication, OPAT-related hospital readmissions, and OPAT-related ED visits. Variables were selected for inclusion in multivariable models using forward stepwise variable selection based on Akaike's information criterion (AIC). The final models were fit using Firth's penalized method to account for quasi-complete separation. Results were reported using odds ratios with 95% confidence intervals (CIs) and *p*-values. Predictor variables included age, sex, race, ethnicity, BMI, VAD, pre- and post-implementation of ID pharmacist reconciliation of OPAT plan, CCI, length of index hospitalization, OPAT indication and antimicrobial agent, OPAT duration, single *versus* multi-drug OPAT, one *versus* multiple OPAT indications, documentation adequacy, infection with prosthesis or malignancy involvement, and presence of listed penicillin allergy. Analyses were conducted using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and OPAT regimen characteristics

Patient characteristics. Between January 2019 and June 2021, 2010 patients were discharged from UMMC with an order for parenteral antibiotics, of which 265 met the criteria for inclusion in the study cohort. The median patient age at discharge was 51.2 years, (interquartile range, IQR: 37.9, 62.0) and the median length of admission was 6 days (IQR: 4.0, 9.0). A total of 212 (80.0%) patients were White, 210 (79.2%) were not Hispanic or Latino, and 132 (52.1%) were male. Of the 215 (81.1%) patients for whom BMI was reported, 140 (65.1%) were overweight or obese. The median [IQR] CCI was 3 [1, 6].

OPAT regimen characteristics. A total of 320 antimicrobials were prescribed to the study population with cephalosporins being the most common (61.1%; see Table 1). All 43 (16.2%) patients that were prescribed a lipo/glycopeptide received either vancomycin or daptomycin. The OPAT regimen for 53 (20%) patients included more than one parenteral agent. Most patients (235, or 88.7%) received OPAT via a peripherally inserted central catheter (PICC). The most common OPAT indications were bloodstream infection ($n = 88$, 33.2%), bone or joint infection ($n = 48$, 18.1%), and skin and soft tissue infection (SSTI; $n = 43$, 16.2%). Ninety-six patients were discharged on or after the 14 June 2020 implementation date of ID pharmacist OPAT review (36.2%), of which 70 (72.9%) patients were documented to have received the intervention. Among the 26 patients that did not receive the intervention, ID pharmacists were not notified of 19 patients and missed completing the intervention for 7 patients.

Outcomes

Any ADE. One or more ADE occurred in 82 patients, (30.9%) and for 30 (11.3%) of these patients their ADE severity was severe, or serious (see Table 1). A total of 104 ADEs were documented, and of these, 37 were considered severe to serious (Table S1). The most common ADEs of any severity were diarrhea, nausea, and rash. Among ADEs stratified as severe to serious, nephrotoxicity, CLABSI, and rash were noted most often. The association of predictor variables assessed via pairwise univariate comparison with any ADE are described in Table 2. In multivariable analysis, receipt of a lipo/glycopeptide was associated with an increased odds of any ADE (OR: 5.14; CI: 2.47–10.99; $p < 0.01$). Unexpectedly, multivariable analysis demonstrated an increased risk for any ADE with adequate documentation (OR: 2.33; CI: 1.08–5.38; $p = 0.03$; see Table 2).

Severe/serious ADE. The association of predictor variables with severe or serious ADEs are described in Table 2. In multivariable assessment of predictor variables, Black or African American race (OR: 4.85; CI: 1.56–15.45; $p < 0.01$), longer planned duration of OPAT (OR: 1.27; CI: 1.01–1.54; $p = 0.04$), and receipt of a lipo/glycopeptide (OR: 5.28; CI: 1.89–15.43; $p < 0.01$) demonstrated an association with an increased odds of severe or serious ADE. An indication of bloodstream infection (OR: 0.31; CI: 0.08–0.98; $p = 0.05$) and an encounter date following the implementation of the OPAT reconciliation program (OR: 0.26; CI: 0.08–0.77; $p = 0.01$) was associated with a lower odds of severe or serious ADE.

VAD complication. Fifty-seven (21.5%) patients experienced one or more VAD complications during the course of OPAT (Table 1). A total of 66

Table 1. Clinical characteristics of UMMC patients who discharged on OPAT to FHI.

Baseline characteristic	*N* (% of 265)
Age in years, median [IQR]	51.2 [37.9, 62.0]
Male	137 (52.1)
Race	
American Indian or Alaska Native	2 (0.8)
Asian	8 (3.0)
Black or African American	41 (15.5)
Native Hawaiian or Other Pacific Islander	2 (0.8)
White	212 (80.0)
Ethnicity	
Not Hispanic or Latino	210 (79.2)
Hispanic or Latino	6 (2.3)
Missing	49 (18.5)
BMI category	
Normal	75 (28.3)
Overweight	56 (21.1)
Obese	84 (31.7)
Missing	50 (18.9)
Vascular access device type	
PICC	235 (88.7)
Peripheral IV	2 (0.8)
Midline	12 (4.5)
Tunneled catheter	2 (0.8)
Implanted catheter	13 (4.9)
Other	1 (0.4)
CCI, median [IQR]	3 [1, 6]
Length of hospitalization (days), median [IQR]	6 [4, 9]
OPAT duration (weeks), median [IQR]	2 [2, 6]
Multi-drug OPAT	53 (20.0)
⩾1 OPAT indication	51 (19.2)
Adequate OPAT plan documentation	197 (76.1)
Post-intervention OPAT	96 (36.2)
Received OPAT intervention (*N* = 96)	70 (72.9)
Indication involves infection with prosthesis involvement	53 (20.0)
Indication involves infection at site of malignancy	33 (12.8)
Penicillin allergy	25 (9.4)
OPAT indication	
Bloodstream infection, including candidemia	88 (33.2)
Bone or joint infection	48 (18.1)
SSTI	43 (16.2)
Intra-abdominal infection	38 (14.3)
Genitourinary infection	34 (12.8)
Bacterial pneumonia	17 (6.4)
Other	15 (5.7)
Endocarditis	13 (4.9)
Bacterial CNS infection	9 (3.4)
Viral infection	8 (3.0)
Fungal infection, excluding candidemia	4 (1.5)
OPAT agent class	
Cephalosporin	162 (61.1)
Carbapenem	57 (21.5)
Lipo/glycopeptide	43 (16.2)
Penicillin	18 (6.8)
Beta-lactam/beta-lactamase inhibitor	17 (6.4)
Pyrophosphate analog	6 (2.3)
Echinocandin	6 (2.3)

Table 1. (Continued)

Baseline characteristic	*N* (% of 265)
Aminoglycoside	3 (1.1)
Azole	2 (0.8)
Lincosamide	2 (0.8)
Nucleoside analog	2 (0.8)
Monobactam	1 (0.4)
Nitroimidazole	1 (0.4)
Experienced any ADE	82 (30.9)
Moderate/severe/serious ADE	46 (17.4)
Severe/serious ADE	30 (11.3)
Experienced a VAD complication	57 (21.5)
ED visit related to OPAT	58 (21.9)
Rehospitalization related to OPAT	53 (20.0)

ADE, adverse drug events; BMI, body mass index; CCI, Charlson comorbidity index; CNS, central nervous system; ED, emergency department; FHI, Fairview home infusion; IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy; PICC, peripherally inserted central catheter; SSTI, skin and soft tissue infection; UMMC, University of Minnesota Medical Center; VAD, vascular access device.

complications occurred in the study population with the most common complication being access device occlusion, occurring in 32 OPAT courses; other VAD complications were observed at a much lower frequency (see Table S2). The association of predictor variables with VAD complication are described in Table 2. In multivariable analysis, obese BMI (OR: 3.32; CI, 1.38–8.73; $p \leqslant 0.01$) and multidrug therapy (OR: 2.56; CI: 1.21–5.39; $p = 0.01$) were associated with an increased odds of VAD. There was no association between VAD complications and overweight or missing BMI. Adequate documentation of OPAT plan prior to discharge was associated with a decreased odds of VAD complication (OR: 0.31; CI: 0.14–0.65; $p < 0.01$).

OPAT-related ED visits. OPAT-related ED visits occurred often in the study cohort. Fifty-eight (21.9%) patients experienced an OPAT-related ED visit (see Table 1). Record of any ADE was found to increase the risk of an OPAT-related ED visit in both the univariate and multivariable models (univariate OR: 2.40; CI: 1.32–4.36; $p < 0.01$; multivariable OR: 2.19; CI: 1.13–4.22; $p = 0.02$; see Table 3). VAD complications also increased the risk of an OPAT-related ED visit in each model (univariate OR: 2.50; CI: 1.30–4.75; $p < 0.01$; multivariable OR: 2.37; CI: 1.15–4.86; $p = 0.02$). In the multivariable analysis, SSTIs (OR: 0.26; CI: 0.08–0.72; $p < 0.01$) and endocarditis (OR: 0.18; CI: 0.02–0.99; $p < 0.05$) had lower odds of unscheduled OPAT-related ED visits.

OPAT-related hospital readmissions. Fifty-three (20.0%) patients required rehospitalization related to OPAT within 90 days of index discharge (see Table 1). OPAT-related hospital readmissions yielded similar results as those seen with OPAT-related ED visits, though not identical. Any ADE was associated with an increased odds of OPAT-related readmissions (univariate OR: 2.94; CI: 1.59–5.47; $p < 0.01$, multivariable OR: 3.21; CI: 1.59–6.58; $p < 0.01$; see Table 3). While VAD complications were significantly associated with ED visits, the association with OPAT-related hospitalizations trended toward but did not reach significance (multivariable OR: 1.85; CI: 0.82–4.07; $p = 0.14$). Similar to what was observed for ED visits, an indication of SSTI demonstrated a protective effect against OPAT-related readmission in multivariable analysis (OR: 0.30; CI: 0.07–0.87; $p = 0.03$).

Discussion

In this retrospective cohort study of 265 patients discharged on home OPAT from UMMC, safety events and unscheduled healthcare were frequent. ADEs occurred in 30.9% of patients and VAD complications in 21.5%. OPAT-related ED visits and rehospitalization were observed for 21.9% and 20% of the study population, respectively. The data we present identify potentially modifiable risk factors for unfavorable OPAT and will be helpful in structuring our institution's OPAT program to optimize care. Longer OPAT duration, use of multiple parenteral antimicrobial agents, and prescription of lipo/glycopeptides during OPAT increased the risk of both ADEs and VAD complications. Unsurprisingly, the rate

Table 2. Risk factors for any ADE, severe/serious ADE, and VAD complication.

	Any ADE						Severe/serious ADE						Any VAD complication					
	Univariate			Multivariable			Univariable			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (per 10 years)	0.99	0.84–1.17	0.94				0.95	0.75–1.21	0.69				1.02	0.84–1.22	0.87			
Sex (male *versus* female)	1.06	0.63–1.79	0.83				1.05	0.50–2.26	0.89				1.08	0.60–1.94	0.81			
Race (reference: White)																		
American Indian or Alaska Native	046	0.00–576	0.59				1.78	0.01–22.85	0.73	8.00	0.05–141	0.30	0.70	0.01–8.76	0.84			
Asian	0.89	0.74–2.94	0.87				1.78	0.18–8.75	0.56	0.20	0.00–2.52	0.24	1.34	0.24–5.45	0.71			
Native Hawaiian or other Pacific Islander	0.46	0.00–5.76	0.59				1.78	0.01–22.85	0.73	3.46	0.02–88.27	0.51	0.70	0.01–8.76	0.81			
Black or African American	1.49	0.74–2.94	0.26				2.26	0.90–5.28	0.08	**4.85**	**1.56–15.45**	**< 0.01**	0.8B	0.37–1.93	0.77			
Hispanic or ethnicity	0.62	0.06–3.19	0.59				1.82	0.18–9.61	0.55				2.20	0.37–40.30	0.35			
BMI (reference: normal)																		
Overweight	1.64	0.78–3.45	0.19				1.18	0.37–3.60	0.78				1.43	0.59–3.44	0.43	2.02	0.72–5.80	0.18
Obese	1.10	0.55–2.20	0.79				1.15	0.42–3.26	0.79				2.06	0.97–4.54	0.06	**3.32**	**1.38–8.73**	**0.01**
VAD type (reference: PICC)																		
Peripheral	0.46	0.00–5.75	0.59	0.71	0.01–9.17	0.82	1.58	0.01–20.13	0.78				0.72	0.01–8.99	0.82			
Midline	1.22	0.34–3.81	0.75	1.94	0.52–6.35	0.30	1.88	0.35–6.97	0.42				1.32	0.32–4.34	0.67			
Tunneled	0.46	0.00–5.75	0.59	0.18	0.00–3.03	0.25	1.58	0.01–20.13	0.78				0.72	0.01–8.99	0.82			
Implanted	2.65	0.89–8.15	0.08	5.18	1.24–2458	0.02	1.72	0.32–6.26	0.48				0.78	0.15–2.75	0.72			
Other	0.77	0.01–14.55	0.87	0.96	0.01–18.63	0.98	2.64	0.02–50.71	0.59				1.19	0.01–22.73	0.92			
OPAT intervention, post *versus* pre	0.82	0.47–1.40	0.46	0.63	0.32–1.23	0.18	0.52	0.21–1.19	0.13	**0.26**	**0.08–0.77**	0.01	0.70	0.37–1.30	0.27			
CCI	1.01	0.94–1.08	0.73				0.99	0.89–1.09	0.82				1.00	0.92–1.08	0.95			
LOS (days)	0.99	0.96–1.02	0.59				1.01	0.98–1.04	0.36				1.00	0.97–1.03	0.95			
Duration of OPAT (weeks)	**1.14**	**1.01–1.31**	**0.04**				**1.27**	**1.09–1.53**	**< 0.01**	**1.27**	**1.01–1.54**	**0.04**	**1.18**	**1.03–1.36**	**0.02**			
No. of agents, 2+ *versus* 1	**2.94**	**1.59–5.47**	**< 0.01**				**3.72**	**1.67–8.17**	**< 0.01**				**2.04**	**1.04–3.94**	**0.04**	**2.56**	**1.21–5.39**	**0.01**

(Continued)

Table 2. (Continued)

	Any ADE						Severe/serious ADE						Any VAD complication					
	Univariate			Multivariable			Univariable			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
No. of indications, 2+ *versus* 1	1.04	0.53–1.97	0.91				0.67	0.21–1.77	0.44				0.77	0.34–1.60	0.49			
Adequate documentation	1.73	0.92–3.43	0.09	**2.33**	**1.08–5.38**	**0.03**	1.17	0. 49–3.17	0.73	2.18	0.75–7.47	0.16	**0.39**	**0.21–0.75**	**< 0.01**	**0.34**	**0.16–0.70**	**< 0.01**
Infection with prosthesis involvement	1.45	0.77–2.69	0.25				1.53	0.62–3.49	0.34				1.42	0.02–2.79	0.33			
Infection at site of malignancy	1.31	0.60–2.74	0.49				1.94	0.70–4.82	0.19				0.67	0.23–1.65	040			
Penicillin allergy	0.89	0.34–2.09	0.79				1.69	0.50–4.70	0.37	3.53	0.76–14.24	0.10	1.53	0.59–3.65	0.37			
OPAT indication																		
Bloodstream infection	**0.55**	**0.30–0.98**	**0.04**				**0.22**	**0.06–0.62**	**< 0.01**	**0.31**	**0.08–0.98**	**0.05**	**0.48**	**0.23–0.92**	**0.03**			
Endocarditis	0.73	0.18–2.31	0.61				1.71	0.32–6.21	0.48				1.21	0.30–3.89	0.76			
Skin or soft tissue infection	0.75	0.35–1.52	0.43				0.84	0.26–2.23	0.75	0.44	0.11–1.51	0.20	1.16	0.52–2.42	0.71			
Bone or joint infection	1.61	0.84–3.04	0.15				2.20	0.92–4.97	0.08				1.91	0.94–3.77	0.07			
Intraabdominal infection	1.05	0.49–2.15	0.89				0.27	0.03–1.08	0.07				0.84	0.33–1.88	0.68			
Genitourinary infection	0.94	0.42–2.00	0.88				0.83	0.21–2.39	0.75				0.64	0.22–1.56	0.34			
Bacterial pneumonia	0.51	0.31–1.54	0.25				1.25	0.24–4.33	0.76				1.65	0.53–4.51	0.37			
Bacterial CNS	**4.38**	**1.21–18.81**	**0.03**	**5.07**	**1.14–25.44**	**0.03**	**4.49**	**1.02–16.85**	**0.05**				1.21	0.22–4.69	0.80			
Viral infection	**12.09**	**2.58–116.0**	**< 0.01**				**8.74**	**2.14–35.79**	**< 0.01**	**29.07**	**3.63–414**	**< 0.01**	1.40	0.25–5.67	0.66			
Fungal infection, excluding candidemia	5.36	0.86–55.91	0.07				**8.19**	**1.22–54.98**	**0.03**				1.56	0.15–9.70	0.66			
Other	1.17	0.37–3.30	0.77				0.78	0.08–3.34	0.77				1.44	0.42–4.23	0.53			
OPAT agent class																		
Aminoglycoside	0.31	0.00–3.28	0.38				1.09	0.01–11.63	0.96				2.19	0.20–16.82	0.47			
Azole	2.24	0.18–27.88	0.49				1.53	0.01–19.40	0.80				0.72	0.01–8.99	0.83			

(Continued)

Table 2. (Continued)

	Any ADE						Severe/serious ADE						Any VAD complication					
	Univariate			Multivariable			Univariable			Multivariate			Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Beta-lactam/beta-lactamase inhibitor	0.72	0.21–2.04	0.56				0.20	0.00–1.58	0.16	0.32	0.00–3.24	0.40	2.17	0.75–5.82	0.15			
Carbapenem	0.85	0.44–1.59	0.62				0.95	0.35–2.26	0.91				0.47	0.19–1.02	0.06			
Cephalosporin	0.74	0.44–1.25	0.26				0.94	0.44–2.05	0.87				1.22	0.67–2.26	0.52			
Echinocandin	4.16	0.90–24.28	0.07	4.85	0.89–30.53	0.07	4.51	0.76–21.38	0.09				2.05	0.35–9.50	0.39			
Lincosamide	2.24	0.18–27.88	0.49				7.95	0.63–100	0.10				0.72	0.01–8.99	0.83			
Lipo/glycopeptide	**3.53**	**1.82–6.94**	**< 0.01**	**5.14**	**2.47–10.99**	**< 0.01**	**4.39**	**1.92–9.82**	**< 0.01**	**5.28**	**1.89–15.43**	**< 0.01**	2.03	0.98–4.08	0.06			
Monobactam	0.74	0.01–13.97	0.85				2.56	0.02–49.15	0.60				1.20	0.01–22.86	0.91			
Nitroimidazole	0.74	0.01–13.97	0.85				2.56	0.02–49.15	0.60				1.20	0.01–22.86	0.91			
Nucleoside analog	2.24	0.18–27.88	0.49				7.95	0.63–100	0.10				0.72	0.01–8.99	0.83			
Penicillin	1.49	0.55–3.84	0.42				0.63	0.07–2.67	0.58				1.52	0.49–4.09	0.44			
Pyrophosphates	31.18	3.61–4085	< 0.01	33.15	3.34–4461	< 0.01	**8.45**	**1.72–41.75**	**0.01**				2.05	0.35–9.50	0.39	10.10	1.32–80.03	0.03

ADE, adverse drug events; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CNS, central nervous system; LOS, length of stay; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio; PICC, peripherally inserted central catheter; VAD, vascular access device.

Table 3. Risk factors for OPAT-related hospitalizations and OPAT-related ED visits.

	OPAT-related hospitalizations						OPAT-related ED visits					
	Univariate			Multivariable			Univariable			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (per 10 years)	0.94	0.77–1.13	0.49	0.85	0.68–1.07	0.17	0.94	0.78–1.13	0.48	0.83	0.67–1.03	0.09
Sex (male *versus* female)	1.37	0.75–2.54	0.30				0.98	0.55–1.76	0.95			
Race (reference: White)												
American Indian or Alaska Native	0.85	0.01–10.73	0.92				0.74	0.01–9.26	0.84			
Asian	1.64	0.29–6.69	0.53				0.74	0.08–3.50	0.73			
Native Hawaiian or other Pacific Islander	4.26	0.34–53.48	0.23				3.68	0.29–46.14	0.28			
Black or African American	1.42	0.63–3.02	0.39				1.39	0.63–2.89	0.40			
Hispanic or Latino ethnicity	0.53	0.20–1.21	0.14				0.89	0.09–4.60	0.90			
BMI (reference: normal)												
Overweight	0.47	0.19–1.12	0.09				0.51	0.20–1.21	0.13			
Obese	0.56	0.26–1.18	0.13				0.81	0.39–1.67	0.56			
VAD type (reference: PICC)												
Peripheral	0.75	0.01–9.46	0.85				0.65	0.00–8.15	0.77			
Midline	0.90	0.17–3.23	0.88				0.77	0.15–2.78	0.72			
Tunneled	0.75	0.01–9.46	0.85				0.65	0.00–8.15	0.77			
Implanted	0.82	0.16–2.90	0.78				0.39	0.04–1.67	0.23			
Other	1.26	0.01–23.91	0.89				1.08	0.01–20.62	0.96			
OPAT intervention, post *versus* pre	1.09	0.58–2.01	0.78				1.10	0.60–2.00	0.74			
CCI	1.01	0.93–1.09	0.87				0.97	0.89–1.05	0.44			
LOS (days)	1.00	0.96–1.02	0.87				0.98	0.94–1.01	0.35			
Duration of OPAT (weeks)	0.97	0.82–1.12	0.66				1.03	0.89–1.17	0.71			
No. of agents, 2+ *versus* 1	1.42	0.68–2.82	0.34				1.23	0.59–2.42	0.57			
No. of indications, 2+ *versus* 1	0.86	0.37–1.80	0.69				0.75	0.33–1.56	0.45			

(Continued)

Table 3. (Continued)

	OPAT-related hospitalizations						OPAT-related ED visits					
	Univariate			Multivariable			Univariable			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Adequate documentation	0.89	0.45–1.83	0.73				0.58	0.31–1.12	0.11			
Infection with prosthesis involvement	0.93	0.42–1.93	0.86				1.75	0.88–3.40	0.11	1.89	0.89–3.97	0.10
Infection at site of malignancy	1.12	0.44–2.58	0.80				0.80	0.30–1.89	0.63			
Penicillin allergy	1.70	0.65–4.07	0.27				1.83	0.73–4.30	0.19	2.08	0.77–5.40	0.14
OPAT indication												
Bloodstream infection	0.76	0.39–1.45	0.42				0.58	0.29–1.10	0.10	0.50	0.23–1.01	0.05
Endocarditis	0.85	0.16–3.00	0.82				0.76	0.14–2.66	0.69	**0.18**	**0.02–0.99**	**0.05**
Skin or soft tissue infection	**0.30**	**0.08–0.81**	**0.02**	**0.30**	**0.07–0.87**	**0.03**	**0.35**	**0.11–0.89**	**0.03**	**0.26**	**0.08–0.72**	**<0.01**
Bone or joint infection	1.27	0.58–2.60	0.54				1.86	0.92–3.65	0.09			
Intraabdominal infection	1.83	0.82–3.85	0.13				1.59	0.72–3.33	0.24			
Genitourinary infection	1.57	0.67–3.45	0.29				1.62	0.71–3.50	0.24			
Bacterial pneumonia	1.82	0.59–5.00	0.28				1.19	0.35–3.38	0.76			
Bacterial CNS	1.33	0.24–5.16	0.71				1.18	0.22–4.58	0.82			
Viral infection	1.54	0.28–6.24	0.58				1.37	0.25–5.54	0.68			
Fungal infection, excluding candidemia	1.71	0.16–10.66	0.60	0.03	0.00–1.19	0.06	0.39	0.00–3.70	0.47			
Other	0.72	0.14–2.47	0.63	0.13	0.00–1.10	0.07	0.99	0.25–3.06	0.98			
OPAT agent class												
Aminoglycoside	0.56	0.00–5.90	0.68				0.50	0.00–5.26	0.62			
Azole	4.03	0.32–50.36	0.25				3.59	0.29–44.85	0.29			
Beta-lactam/beta-lactamase inhibitor	1.34	0.39–3.83	0.61				1.61	0.52–4.40	0.39			
Carbapenem	1.26	0.61–2.49	0.52				1.23	0.61–2.39	0.55			
Cephalosporin	0.65	0.36–1.20	0.17	0.56	0.28–1.13	0.11	0.80	0.44–1.44	0.45			
Echinocandin	4.15	0.86–20.11	0.08	6.65	0.67–86.38	0.10	2.00	0.34–9.28	0.41			

(Continued)

Table 3. (Continued)

	OPAT-related hospitalizations						OPAT-related ED visits					
	Univariate			Multivariable			Univariable			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Lincosamide	**20.63**	**1.65–2862**	**0.02**	**58.97**	**1.36–22102**	**0.03**	**18.36**	**1.47–2547**	**0.02**			
Lipo/glycopeptide	1.50	0.69–3.12	0.30				1.51	0.71–3.07	0.28			
Monobactam	12.14	0.64–1782	0.09				1.18	0.01–22.36	0.92			
Nitroimidazole	1.32	0.01–25.06	0.87				1.18	0.01–22.36	0.92			
Nucleoside analog	0.79	0.01–9.86	0.87				0.70	0.01–8.79	0.81			
Penicillin	0.58	0.11–1.93	0.40	**0.19**	**0.02–0.88**	**0.03**	0.28	0.03–1.17	0.09			
Pyrophosphates	2.25	0.38–10.45	0.34				2.00	0.34–9.28	0.41			
VAD complication	1.87	0.94–3.64	0.07	1.85	0.82–4.07	0.14	**2.50**	**1.30–4.75**	**0.01**	**2.37**	**1.15–4.86**	**0.02**
Any ADE	**2.94**	**1.59–5.47**	**<0.01**	**3.21**	**1.59–6.58**	**<0.01**	**2.40**	**1.32–4.36**	**<0.01**	**2.19**	**1.13–4.22**	**0.02**

ADE, adverse drug events; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CNS, central nervous system; ED, emergency department; LOS, length of stay; OPAT, outpatient parenteral antimicrobial therapy; OR, odds ratio; PICC, peripherally inserted central catheter; VAD, vascular access device.
Odds ratios for which the p value is ≤ 0.05 appear in bold text.

of unscheduled healthcare use was increased in patients that experienced any ADE and patients that had a VAD complication. This finding underscores the notion that optimizing antimicrobial regimens through the principles of antimicrobial stewardship is critical to the development of OPAT plans that are poised to maximize the likelihood of clinical success and minimize the likelihood of adverse outcomes.

During the study period, a program for ID pharmacist-led OPAT plan reconciliation, which included designated provider identification and antibiotic optimization, was implemented. Receipt of OPAT during the post-intervention period was associated with decreased risk for non-mild ADEs, but interestingly was not associated with reduction of VAD complications or OPAT-attributable unscheduled care. Having identified risk factors for OPAT-attributable adverse outcomes, this investigation will inform future adjustments to this collaborative program to create a more efficient, safe, and reproducible model for OPAT delivery in the home.

This investigation demonstrated an association between an OPAT indication of bloodstream and a reduced odds of severe/serious ADE. Furthermore, bloodstream infection and SSTI were associated with a reduced odds of OPAT-attributable unscheduled care. While this association may be explained by a lower severity of illness in patients with SSTI, bloodstream infections are historically considered a severe infection. Interestingly, a prior investigation also identified a reduced odds of ADEs in patients whose OPAT indication was uncomplicated bacteremia.[8] It is possible that clinicians exhibit a lower threshold to diagnose and treat bloodstream infections, and as a consequence the severity of illness among OPAT patients with a diagnosis of bloodstream infection are less ill than other OPAT recipients.

Our finding that patients who identify as Black or African-Americans experienced an increased odds of severe/serious ADE is consistent with published literature on racial disparities in health status.[24,25] Only a subset of published reports have assessed for association between race and outcomes, and results are somewhat mixed. In a large US cohort of OPAT patients, racial disparities in safety outcomes were measured but not observed.[26] In a separate, smaller cohort of US-based patients receiving treatment for

prosthetic joint infection, non-White race was associated with PICC-related ED visits.[27] Prior investigations evaluating care transitions beyond those specific to OPAT have demonstrated racial disparities in scheduled and unscheduled care following discharge from acute care.[28–32] Racial disparities in healthcare training and resources may underlie the outcomes of Black patients in our analysis. A national cross-sectional survey of US residents also reveals disparities in the comfort level of caregivers who assist adults following a discharge from acute care.[33] Caregivers who were Black or who experienced financial difficulty were half as likely to report receiving adequate training to meet the care needs of complex patients. Additional research is necessary to elucidate the mechanism(s) responsible for racial disparities in the outcomes of OPAT patients.

In our cohort, 82 out of 265 (30.9%) patients experienced an ADE, with 30 (11.3%) experiencing a severe/serious ADE. The prevalence of all ADEs in the current investigation is higher than other published reports, though direct comparison is somewhat difficult due to heterogeneous patient populations and ADE definitions. Investigators in a similar investigation examined 339 OPAT patients and determined that 49 (14.5%) experienced a clinically significant ADE, the definition of which was parallel to the severe/serious ADE definition in this study. The high rate of ADEs observed in our cohort may thus reflect increased detection of mild/moderate events. This increased detection may be a consequence of selecting only patients receiving OPAT through our institution's home infusion agency, as clinical events for these patients was more likely to be documented in the EHR. Another study reported an even lower incidence of ADEs with a rate of 6.6%, although, in this study, agents eligible for OPAT were restricted to beta-lactam/beta-lactamase inhibitors and vancomycin.[13] In contrast, our OPAT program had no limitations on antimicrobial selection and included agents with a more significant adverse event profile than beta-lactam/beta-lactamase inhibitors.[34]

The incidence of VAD complications in our study is also higher than other published reports whose methodology involves varied definitions of VAD complications.[9,13,15] Line occlusions, which encompassed >50% of VAD complications in our study population, were included in our definition of VAD complication since they require an additional nursing visit, thus increasing healthcare utilization. In a report from 2013, a VAD complication rate of 9% was observed with approximately half of complications being characterized as occlusion.[15] This study, however, included patients receiving OPAT through an outside agency, and found this subgroup to have a significantly lower risk of VAD complication. This prompted the authors to identify this as a source of reporting bias. Since we evaluated only patients monitored through FHI, we minimized reporting bias of this kind but also increased sensitivity for the reporting of VAD complications. Unexpectedly, we found that adequate documentation of OPAT plan details by inpatient providers was directly correlated with the odds of ADEs, but inversely correlated with VAD complications. This finding suggests that documentation quality may be a surrogate marker for unmeasured confounders in our analysis.

We also assessed OPAT-related ED visits and rehospitalizations, where events were considered OPAT-related if the chief complaint was related to an ADE, VAD complication, or recurrence of infection. Both types of healthcare utilization were observed at a similar rate to that described in the available literature.[4,16–19] One published report cited an overall rehospitalization rate of 20% and an OPAT-related rehospitalization rate of 14.4%. In another published cohort, 33.7% of OPAT patients required an unplanned healthcare encounter.

This study has several limitations. Patient data were limited to a single center and only reflective of those whose infusion agency of record was FHI; patients whose agencies of record were 'home' or 'other infusion company' or who had no agency recorded for infusion company of record were excluded. Data capturing patients' infusion company of record are entered as free-text by clinicians and is not a mandatory EHR field, so we suspect that our methods may have failed to capture eligible patients and we acknowledge that this may be a source of bias in our sample. ADEs and VAD complications were only captured if they were documented in the EHR. Thus, we may have underestimated the rates of these events; however, including only patients receiving OPAT through FHI increased our ability to obtain documentation during therapy. We regarded CLABSI as both an ADE and a VAD complication and acknowledge that the impact of

CLABSI on our measured outcomes may have been inflated. However, CLABSI accounted for only 5 of 105 (4.8%) ADEs and 5 of 65 (7.7%) of VAD complications, and thus we do not strongly suspect our findings were significantly impacted by this methodology. Actual length of therapy was unobtainable during this study, so the rate of events per therapy days was not calculated. The finding that documentation quality was inversely proportional to the rate of VAD complications while being directly proportional to the rate of any ADEs suggests potential confounding. There were patients seen in the ED that were subsequently admitted for OPAT-related reasons, resulting in some overlap in patients reported to require OPAT-related ED visits and hospitalizations. Implementation of the ID-pharmacist OPAT program midway through the study period represents a major change in the workflow for discharging patients to home on OPAT and could have biased prescriber habits in the post-intervention period. There were also significant changes to the healthcare landscape in response to the COVID-19 pandemic during our study period that likely introduced heterogeneity in patient characteristics and health care operations.

In conclusion, safety events and unscheduled care occurred often in patients treated with OPAT in the home. Several modifiable risk factors identified in this study can be targeted in future efforts to improve programs, including ID pharmacist reconciliation processes, for OPAT in the home: duration of therapy as well as number and type of agents to be administered via OPAT. Future research opportunities include evaluation of the entire cohort ($n = 2010$), analysis of social deprivation index among OPAT recipients and its impact on ADEs, development of standardized documentation and definitions for OPAT safety outcomes, and identification of additional opportunities to reconcile OPAT after discharge.

Declarations

Ethics approval and consent to participate

This quality improvement project was deemed exempt from research requirements, including the requirement for informed consent, by the University of Minnesota and M Health Fairview Institutional Review Boards.

Consent for publication

Not applicable.

Author contributions

Kaylyn N. Billmeyer: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Jennifer K. Ross: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Michael D. Evans: Data curation; Formal analysis; Methodology; Writing – review & editing.

Susan E. Kline: Conceptualization; Methodology; Writing – review & editing.

Alison L. Galdys: Conceptualization; Funding acquisition; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

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Supplemental material

Supplemental material for this article is available online.

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