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Clinical Outcomes and Total Cost of Hospitalization in Patients Treated With Ceftaroline-Fosamil in an Outpatient Parenteral Antibiotic Therapy (OPAT) Setting For Acute Bacterial Skin and Skin Structure Infections (ABSSSI): A Comparative Study

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Abstract

Outpatient parenteral antibiotic therapy (OPAT) has become a standard of therapy for treatment of various infections, of which 23% account for skin/ soft tissue infections. Ceftaroline-fosamil, a broad-spectrum β-lactam is FDA approved for management of acute bacterial skin and skin structure infections (ABSSSI); However, at present, there is no data on post approval experience with this drug administered as OPAT. The aims of this study were to assess outcomes of care with OPAT and related costs for ceftaroline versus alternative antibiotic therapies: vancomycin or daptomycin. Primary endpoints were treatment success rate at end of OPAT regimen, and related costs for each antibiotic. Among 291 patients, mean age (± SD) was 58 ± 16 years, 60% male, mean Charlson score 3.4, 48% diabetic, 41% had deep/extensive cellulitis, and patient population by antibiotic treatment was n=125 ceftaroline, n=62 daptomycin, and n=104 vancomycin. End of OPAT treatment success rate between ceftaroline, vancomycin, and daptomycin cohorts was 94% vs. 76% and 89% (p<0.001), respectively. For OPAT costs, while controlling for age, Charlson, diabetes, and OPAT duration, ceftaroline patients cost an average of $2208.97 (SE: $191.33) less than daptomycin patients, (p<0.001). Additionally, while controlling for age, Charlson, and diabetes in logistic regression model for outcome at end of OPAT, patients on vancomycin had 83% lower odds of achieving success compared to those on ceftaroline, p=0.002. In the OPAT setting, ceftaroline-related success rate for treatment of ABSSSI was high, and more cost effective compared with daptomycin. Lastly, while vancomycin had lowest OPAT costs, treatment success was signiicantly lower than ceftaroline.

Keywords: Outpatient parenteral antibiotic therapy; Methicillin-resistant *Staphylococcus aureus*; Ceftaroline fosamil; Acute Bacterial skin; Skin Structure infections (ABSSSI)

Introduction

The prevalence of acute bacterial skin and skin structure infections (ABSSSIs) are increasing at a critical rate, accounting for an estimated 3.4 million emergency department visits for the year 2011 [1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common pathogen causing approximately 35% to 72% of skin and skin structure infections [2-4]. In a study by Kaye et al, from 2001 to 2009 there was a 123% increase in hospitalizations in the United States related to SSIs, leading to an estimated burden of care of $4.5 billion [5]. Aside from increased healthcare utilization, the emergence of infections due to vancomycin-nonsusceptible *S. aureus* poses additional challenges in the management of ABSSSI [6].

To address the challenge of economical and effective use of healthcare resources, there has been a shift in the management and treatment of ABSSSI from inpatient to an outpatient setting. Outpatient parenteral antibiotic therapy (OPAT) has become a standard of therapy since its introduction in 1974, with increasing frequency for the treatment of various infections: most commonly skin and soft tissue infections: accounting for 23% of all infections treated with OPAT (data from OPAT Outcomes Registry) [7,8]. OPAT offers advantages including reduced hospital stay, patient convenience, and reduced burden on healthcare systems by avoiding inpatient treatment and admission. Guidelines for OPAT incorporate criteria for proper patient and antimicrobial selection and avoidance of hospital intervention [9,10]. The Infectious Diseases Society of America practice guidelines for the management of skin and soft tissue infections were recently updated in 2014. According to the guideline recommendations, empiric intravenous (IV) antimicrobial agents for the treatment of suspected severe MRSA ABSSSIs include vancomycin, daptomycin, linezolid, telavancin, or ceftaroline. For mild to moderate purulent infections where community-acquired MRSA should be considered, oral sulfamethoxazole/trimethoprim and doxycycline are recommended, whereas for mild to moderate non- purulent ABSSSIs, oral clindamycin is an option for treatment [9].

Notably, there is selective pressure of treating ABSSI with drug expertise in optimizing prescribing practice, selection, dosage, and outcome. Ceftaroline-fosamil (CPT-F), a broad-spectrum cephalosporin β-lactam antibiotic having rapid in vitro bactericidal activity against pathogens is approved by the FDA for management of community acquired pneumonia and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia*

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coli, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. Clinical studies have demonstrated the efficacy of ceftaroline in these indications [11], however, very little is known about the post approval experience with this drug administered as OPAT. Particularly important is to have information on comparative effectiveness of the agents, toxicity, and outcomes that may vary in the inpatient setting. With no current data on the outcomes of patients with ABSSSI who receive CPT-F OPAT, further investigation is warranted to help determine cost and clinical efficacy.

The aim of this study was to assess the cost effectiveness of CPT-F for OPAT versus alternative antibiotic therapies- vancomycin or daptomycin alone or in conjunction with other antibiotics in *S. aureus* (either Methicillin-susceptible (MSSA) or Methicillin-resistant (MRSA)) patients with ABSSSI and having suspected *S. aureus* infection isolated from an appropriate infection site prior to treatment.

Methods

Study design

We conducted a comparative retrospective matched cohort study to evaluate the cost-effectiveness of CPT-F versus other antibiotics for the treatment of ABSSSI in an outpatient infusion setting.

Data source

Eligible patients were included from Henry Ford Hospital, a 900-bed teaching acute care tertiary care hospital in Detroit, MI. Initial identification of subjects with the infection was done through chart review. Predefined patient characteristics and outcomes, including complete demographic info, risk factors, outcomes, treatments, related cost information, and clinical and laboratory characteristics for all study subjects were abstracted from CarePlus, an electronic medical records database and entered into a study-specific catalog utilizing a standardized case report form. Hospital charges were retrieved from a financial database for each subject.

Objectives: The primary objectives were to assess the clinical effectiveness defined as bacteriologic eradication of infection at the end of OPAT regimen in the form of either a cure, improvement, or non-evaluable outcome, as well as the total charges for all services for CPT-F patients versus patients treated with other antibiotics. The secondary objective was to assess each patient's grand total charges, including both total charges for the hospitalization or acute care received in the Henry Ford system immediately prior to the OPAT, if applicable, and OPAT, duration of antibiotic therapy, total hospital length of stay (days), and the recurrence of infection in the form of a readmission. Exploratory objectives are subgroup cost analysis, by infection type, or pathogen. Other exploratory endpoints are rates of treatment complication and failure, and rate of switching antibiotic due to adverse drug reaction or resistance.

Inclusion criteria: All subjects were included in the analysis if they had a primary and final diagnosis of ABSSSI confirmed by chart review and ICD-9, defined as: a skin or skin structure infection involving deeper soft tissue or requiring significant surgical intervention, such as a wound infection (surgical or traumatic), a major abscess, an infected ulcer, or deep and extensive cellulitis, with the following ICD codes:

(1) Carbuncle and furuncle (ICD-9-CM diagnosis codes 680.XX).

(2) Cellulitis and abscess of finger and toe (681.XX).

(3) Other cellulitis and abscess (682.XX).

(4) Acute lymphadenitis (683.XX).

(5) Other local infections of skin and subcutaneous tissue (686.XX);

(6) Infection (chronic) of amputation stump (997.62).

(7) Pilonidal cyst with abscess (685).

(8) Decubitus ulcer (707.0X).

(9) Ulcers of lower limbs, except decubitus (707.1X).

(10) Chronic ulcer of other specified sites (707.8).

(11) Chronic ulcer of unspecified site (707.9).

(12) Post-traumatic wound infection, not elsewhere classified (958.3).

(13) Post-operative wound infection (998.5X).

Subjects also had to be treated for ABSSSI with vancomycin, daptomycin, or ceftaroline for at least ≥ 4 consecutive doses.

Exclusion Criteria:

• Had hospitalization <= 30 days prior to current hospital visit (for those discharged from hospital to OPAT).

• Transferred from another hospital

• Admitted from nursing home/long term care facility

• Had significant unrelated complications during hospital stay

• Age < 18 years

• incomplete medical records

• an unevaluable outcome- did not complete OPAT regimen

Data analysis

All continuous data are described using mean, standard deviation, median, minimum, and maximum; while categorical data are described using counts and percentages. The primary outcome of interest was clinical outcome, a 2-level categorical variable- success or failure. The univariate tests used to compare clinical outcome groups were Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables. Nonparametric tests were chosen due to the small group sizes. Cost for OPAT were calculated using micro-costing 340B pricing strategy. The univariate relationship between OPAT duration and OPAT charges with other continuous variables was examined using Spearman correlation coefficients, while the distribution of OPAT duration and OPAT charges were compared between categories using Kruskal-Wallis (>2 level variables) or Wilcoxon rank-sum (2 level variables) tests. Multivariable modeling for outcome (success/failure) was performed using multiple logistic regression, while multivariable OPAT charge modeling was performed using a general linear mixed modeling (PROC GLIMMIX) due to the non-Gaussian nature of OPAT charges. In the case of pairwise comparisons, the Benjamini-Hochberg adjustment was applied to the p-values to control the type I error rate. Multivariable modeling for outcome (success/failure) was performed using multiple logistic regression, while multivariable OPAT charge modeling was performed using a general linear mixed modeling (PROC GLIMMIX) due to the non-Gaussian nature of OPAT charges. Statistical significance was set at $p<0.05$. All analyses were performed using SAS 9.4 (SAS Inc, Cary, NC, USA). Missing data was assumed to be completely at random and is not included in the calculation of the p- value. All variables with a univariate p-value of <0.2 in Table 1A

were placed in the initial multiple logistic regression model in Table 1B. Age, Charlson score, and diabetes were forced to remain in the model regardless of significance in order to control for them. Total length of stay was not normally distributed so it was log transformed. Variables were removed in stepwise fashion to arrive at the final model.

Results

A total of 291 patients were included for analysis. Table 2 is a descriptive analysis of the entire study population; median age was 58 years, 60% males, and mean Charlson score of 3.4. Primary infection type was deep/extensive cellulitis diagnosed in 41%, infected surgical and traumatic wound infection in 24%, major abscess seen in 16%, infected burn, ulcer, and erysipelas in 19%, and 1% other infection type. The most common OPAT administration route was in-home nurse visit (44%). Overall, diabetes was present in 48%, 91% were treated both in an inpatient and OPAT setting, 20% were readmitted within 30 days from end of treatment, and 86% demonstrated clinical success. The antibiotic subsets were as follows: ceftaroline n=125 (43%), Daptomycin n=62 (21%), and vancomycin n=104 (36%).

Table 1A contains the results of the univariate tests comparing all

Variable	Response	Success (N=251)	Failure (N=40)	p-value
Age	N Mean ± Std Dev	25158.0 ± 16.0	40 54.6 ± 15.3	0.208
Gender	Male	153(61%)	22(55%)	0.475
	Female	98(39%)	18(45%)	
Race	Unknown	19(8%)	2(5%)	0.810
	White	115(46%)	20(50%)	
	Black	104 (41%)	16 (40%)	
	Asian	1 (0%)	0 (0%)	
	Hispanic	5 (2%)	0 (0%)	
	Other	7 (3%)	2 (5%)	
Charlson Score	N Mean ± Std Dev	251 3.5 ± 2.1	40 3.2 ± 2.0	0.399
ABSSSI infection type	Deep/extensive cellulitis	105(42%)	13(33%)	0.367
	Infected surgical andtraumatic wound infection	59(24%)	12(30%)	
	Major abscess	42(17%)	4 (10%)	
	Infected burn, ulcer, and erysipelas	44(18%)	11(28%)	
	Other infection type	1 (0%)	0 (0%)	
Prior hospitalization (>72h within past year)	Yes	78 (31%)	11 (28%)	0.649
Prior ICU stay within past year	Yes	21 (8%)	1 (3%)	0.192
Prior surgery within 30 days	Yes	13 (5%)	2 (5%)	0.962
Nursing home resident	Yes	0	0	N/A
Cancer	Yes	32 (13%)	7 (18%)	0.413
Total LOS (days)	N Mean ± Std Dev	234 8.9 ± 6.4	34 7.7 ± 4.5	0.197
OPAT admin route	Self administration	73 (29%)	14 (35%)	0.707
	Ambulatory care center	68 (27%)	9 (23%)	
	Nurse visit in home	110 (44%)	17 (43%)	
Alteration in OPAT therapy	Yes	7 (3%)	15 (38%)	<.001
Solid organ transplant	Yes	3 (1%)	2 (5%)	0.085
Corticosteroids >=20 mg/d for >14 days prior to infection	Yes	2 (1%)	1 (3%)	0.322
CHF	Yes	29 (12%)	9 (23%)	0.056
Diabetes	Yes	116 (46%)	23 (58%)	0.184
DM with organ damage	Yes	4 (2%)	2 (5%)	0.159
Acute renal failure	Yes	24 (10%)	4 (10%)	0.93
Chronic renal failure	Yes	41 (16%)	4 (10%)	0.303
Dialysis	Yes	11 (4%)	3 (8%)	0.392
Prior systemic abx within past 90 days	Yes	87 (35%)	16 (40%)	0.512
Case/control	Control	134 (53%)	32 (80%)	0.002
	Case	117 (47%)	8 (20%)	
OPAT or OPAT & Inpatient	OPAT	20 (8%)	6 (15%)	0.148
	OPAT & Inpatient	231 (92%)	34 (85%)	

Readmission within 30 days	Unknown	18 (7%)	7 (18%)	<.001
	No	195 (78%)	17 (43%)	
	Yes	38 (15%)	16 (40%)	
Antibiotics Used	ceftaroline	117 (47%)	8 (20%)	
	daptomycin	55 (22%)	7 (18%)	
	vancomycin	79 (31%)	25 (63%)	
OPAT duration (days)	N Mean ± Std Dev	251 21.6 ± 13.4	40 21.1 ± 14.8	0.809
OPAT charges	N Mean ± Std Dev	251 1331.6 ± 1897.1	40 1049.0 ± 2054.6	0.388
Hospital charges	N Mean ± Std Dev	195 49257.2 ±58306.6	26 50526.8 ± 42691.4	0.915
Abx charges	N Mean ± Std Dev	195 1850.7 ± 1700.0	26 1734.0 ± 1260.0	0.736

Table 1A: Univariate analyses of clinical outcomes.

Predictor	Level	Odds Ratio (95% CI)	P-Value
Age		0.99 (0.95, 1.05)	0.840
Charlson Score		1.22 (0.82, 1.82)	0.326
Diabetes	Yes vs No	0.41 (0.16, 1.07)	0.070
Alteration in OPAT	Yes vs No	0.08 (0.02, 0.26)	<0.001
Antibiotics	Daptomycin vs Ceftaroline	0.36 (0.09, 1.40)	0.139
	Vancomycin vs Ceftaroline	0.17 (0.06, 0.52)	0.002
Readmission at 30 days	Yes vs No	0.20 (0.08, 0.52)	0.001

Table 1B: Outcome multivariable logistic regression model - odds of success.

Variable	Response	All patients (N=291)
Age	N	291
	Mean (SD)	57.6 (15.94)
	Median	58.00
	Min, Max	21,97
Gender	Male	175 (60%)
	Female	116 (40%)
Race	White	135 (50%)
	Black	120 (44%)
	Asian	1 (0%)
	Hispanic	5 (2%)
	Other	9 (3%)
Charlson Score	N	291
	Mean (SD)	3.4 (2.08)
	Median	3
	Min, Max	0,8
ABSSSI infection type	Deep/extensive cellulitis	118 (41%)
	Infected surgical and traumatic wound infection	71 (24%)
	Major abscess	46 (16%)
	Infected burn, ulcer, and erysipelas	55 (19%)
	Other infection type	1 (0%)
Prior hospitalization (>72h within past year	Yes	89 (31%)
Prior ICU stay within past year	Yes	22(8%)
Prior surgery within 30 days	Yes	15(5%)
Nursing home resident	Yes	0
Cancer	Yes	39(13%)
Total LOS (days)	N	268
	Mean (SD)	8.7 (6.17)
	Median	7
	Min, Max	1,40

OPAT admin route	Self administration	87 (30%)
	Ambulatory care center	77(26%)
	Nurse visit in home	127(44%)
Alteration in OPAT therapy	Yes	22(8%)
Solid organ transplant	Yes	5 (2%)
Corticosteroids >=20 mg/d for	Yes	3 (1%)
>14 days prior to infection		
CHF	Yes	38(13%)
Diabetes	Yes	139 (48%)
DM with organ damage	Yes	6 (2%)
Acute renal failure	Yes	28(10%)
Chronic renal failure	Yes	45(15%)
Dialysis	Yes	14(5%)
Prior systemic antibiotic within past 90 days	Yes	103 (35%)
Case/control	Control	166 (57%)
	Case	125(43%)
OPAT or OPAT & Inpatient	OPAT	26 (9%)
	OPAT & Inpatient	265(91%)
Readmission within 30 days	yes	54 (20%)
Outcome	Success	249(86%)
	Failure	34 (12%)
	Change in plans	8 (3%)
OPAT duration (days)	N	291
	Mean (SD)	21.5 (13.54)
	Median	18.0
	Min, Max	3, 73
OPAT charges in dollars ($)	N	291
	Mean (SD)	1293 (1918)
	Median	597.4
	Min, Max	8, 16555
Hospital charges in dollars ($)	N	221
	Mean (SD)	49407 (56614)
	Median	33466
	Min, Max	6706, 520826
Antibiotic charges in dollars ($)	N	221
	Mean (SD)	1837 (1652)
	Median	1329.0
	Min, Max	154, 10879
Antibiotics Used	Ceftaroline	125(43%)
	Daptomycin	62 (21%)
	Vancomycin	104 (36%)
Outcome	Success	251 (86%)
	Failure	40 (14%)

Table 2: Descriptive statistics of all variables collected for entire study population.

variables of interest between the two clinical outcome groups- success or failure. Importantly, age, Charlson score, race, infection type, and OPAT administration route were similar in both groups. Success rates by type of antibiotic was as follows: ceftaroline 47%, daptomycin 22%, vancomycin 31%, p<0.001. All variables with a univariate p-value of <0.2 in Table 1A were placed in the initial multiple logistic regression model shown in Table 1B. Age, Charlson score, and diabetes were forced to remain in the model regardless of significance in order to control for them. Total length of stay was not normally distributed so it was log transformed. Variables were removed in stepwise fashion to arrive at the final model. Thus, Table 1B shows an odds ratio of success for vancomycin versus ceftaroline as 0.17, signifying 83% lower odds of success with vancomycin treatment in comparison to ceftaroline (p=0.002). Additionally, while controlling for the other variables in the model, patients with alterations in OPAT therapy had significantly lower odds of success as compared to patients without alterations. And patients with readmission had significantly lower odds of success as compared to those without readmission.

Table 3A gives the results of univariate relationships between all variables and OPAT charges. The distribution of OPAT charges was examined and found to be left skewed. Table 3B contains the results of the multiple linear regression model for OPAT charges. It shows that while controlling for the other variables in the model, CPT-F-treated patients cost $1007.33 (SE $165.55) more than vancomycin patients, and daptomycin patients cost $3216.29 (SE $197.59) more than vancomycin patients. Additionally, every one-day increase in OPAT duration is associated with an increased cost of $57.24.

Table 4A contains the pairwise comparisons that were significant from results of a univariate comparison of all variables of interest

Variable	Response	Correlation or mean (SD), median (min, max) OPAT charges ($)	P-Value
Age	N	291	0.472
	Correlation coefficient	0.042	
Gender	Male	1424.5(2184.7) 583.7(7.9,16555.0)	0.179
	Female	1094 (1411.3) 636.7(10.5, 8324.8)	
Race	White	1502.4 (2237.7) 742.8(10.5, 16555.0)	0.068
	Black	999.9 (1581.) 475.3(7.9, 8324.8)	
	Asian	1751(.) 1751 (1751, 1751)	
	Hispanic	1455.8-1524.5 1324.4(78.6, 3873.4)	
	Other	970 (680.8) 1167.3(26.2, 1910.2)	
Charlson Score	N	291	0.385
	Correlation coefficient	-0.051	
ABSSSI infection type	Deep/extensive cellulitis	939.9-1735.7 477.5(7.9, 16555.0)	0.046
	Infected surgical and traumatic wound infection	1576.2-1824.3 1114.3 (10.5, 8324.8)	
	Major abscess	1082.8 (1436.2) 477.5 (23.6, 7946.4)	
	Infected burn, ulcer, and erysipelas	1877.3 -2534 742.8 (21.0, 11068.2)	
	Other infection type	318.4 (.) 318.4 (318.4, 318.4)	
Prior hospitalization (>72h within past year	Yes	1631.9 (2005.0) 756.8 (15.7, 8324.8)	0.027
Prior ICU stay within past year	Yes	1573.9 (1830.6) 849.0 (18.3, 7000.4)	0.196
Prior surgery within 30 days	Yes	2187.6 (1878.4) 1644.9 (47.2, 5676.0)	0.012
Nursing home resident	No	1292.8 (1918.3) 597.4 (7.9, 16555.0)	
	Yes	.	N/A
Cancer	Yes	997.3 (1094.8) 424.5 (10.5, 3973.2)	0.547
Total LOS (days)	N	268	
	Correlation coefficient	0.062	0.311
	Self administration	1423.2 (1914.6) 636.7 (10.5, 8324.8)	
OPAT admin route	Ambulatory care center	1208.5 (2316.8) 318.4 (7.9, 16555.0)	0.077
	Nurse visit in home	1254.4 (1646.9) 689.8 (31.4, 11068.2)	
Alteration in OPAT therapy	Yes	791.8 -1173.8 201.7 (10.5, 3873.4)	0.048
Solid organ transplant	Yes	426.3 (696.5) 62.9 (15.7, 1644.9)	0.070
Corticosteroids >=20 mg/d for >14 days prior to infection	Yes	913.1 (1002) 371.4 (298.7, 2069.3)	0.942
Congestive Heart Failure	Yes	998.2 (1435.2) 601.3 (15.7, 8324.0)	0.343
Diabetes	Yes	1220.1 (1577.7) 636.7 (10.5, 11068.2)	0.787
DM with organ damage	Yes	1107.0 (717.1) 829.4 (473.0, 2387.7)	0.333
Acute renal failure	Yes	747.9 (981.7) 398 (10.5, 4162.4)	0.060
Chronic renal failure	Yes	1034.0 (1874.8) 477.5 (7.9, 11068.2)	0.030

Dialysis	Yes	421.6 (688.6) 49.7 (7.9, 1986.6)	0.001
Prior systemic antibiotic within past 90 days	Yes	1523.6 (1882.6) 902 (13.1, 8324.8)	0.030
	Control	1454.3 (2499.0) 227.2 (7.9, 16555.0)	
Case/control	Case	1078.3 (737.5) 849.0 (159.2, 3873.4)	<0.001
	OPAT	2866.1 (3577.2) 2010.7 (49.8, 16555.0)	
OPAT or OPAT & Inpatient	OPAT & Inpatient	1138.4 (1600.9) 530.6 (7.9, 11068.2)	<0.001
Readmission within 30 days	Yes	1179.7 (2333.5) 548.3 (10.5, 16555.0)	0.537
OPAT duration	N	291	<0.001
	Correlation coefficient	0.541	
Hospital charges	N	221	0.347
	Correlation coefficient	0.064	
Antibiotic charges in dollars ($)	N	221	0.354
	Correlation coefficient	0.063	
Outcome(binary)	Success	1331.6 (1897.1) 689.8 (7.9, 16555.0)	
	Failure	1049 (2054.6) 196.5 (10.5, 8324.8)	0.002
Antibiotics	Ceftaroline	1078.3 (737.5) 849 (159.2, 3873.4)	
	Daptomycin	3619.2 (2923.3) 2648.8 (378.4, 16555.0)	<0.001
	Vancomycin	163.6 (209.0) 104.8 (7.9, 1644.9)	

Table 3A: Univariate tests for OPAT charges.

Variable	Level	Estimate	Standard Error	P-Value
Age		-2.28	7.94	0.774
Charlson Score		-34.72	62.94	0.582
Diabetes	Yes versus No	-9.31	154.48	0.952
Antibiotics	Ceftaroline vs Vancomycin	$1007.33	165.55	<0.001
	Daptomycin vs Vancomycin	$3216.29	197.59	<0.001
	Ceftaroline vs Daptomycin	$2208.97	191.33	<0.001
OPAT duration (days)		57.24	5.35	<0.001

Table 3B: Multivariable linear regression for OPAT charges.

Variable	Ceftaroline vs Daptomycin	Vancomycin vs Ceftaroline	Daptomycin vs Vancomycin
Age	0.309	0.002	0.135
Surgery within 30 days	0.049	0.474	0.265
Alteration in OPAT therapy	>0.999	0.065	0.065
Dialysis	0.538	0.076	0.538
Prior systemic antibiotic within past 90 days	0.101	0.571	0.060
OPAT or OPAT & Inpatient	0.012	0.275	0.001
OPAT duration (days)	0.014	0.653	0.044
OPAT charges in dollars ($)	<0.001	<0.001	<0.001
Outcome	0.263	<0.001	0.088

Table 4A: Adjusted p-values for pairwise comparisons between antibiotic groups.

between the three antibiotic groups from Table 4B. Average age was significantly different between the vancomycin versus ceftaroline group, indicating that even though the vancomycin treated cohort was younger: mean (SD) age 53.4 (15.85) versus CPT-F treated cohort: mean (SD) age 60.8 (15.17), overall success was observed in 94% of CPT-F subjects, versus 76% in the vancomycin subset. Moreover, OPAT duration was significantly shorter in the CPT-F group with a median of 16 days versus daptomycin with a median OPAT duration of 27 days (p=0.014).

Variable	Response	Ceftaroline (N=125)	Daptomycin (N=62)	Vancomycin (N=104)	P-Value
Age	N	125	62	104	0.003
	Mean (SD)	60.8 (15.17)	58.1 (16.23)	53.4 (15.85)	
	Median	61.00	58.00	55.00	
	Min, Max	21, 97	21, 89	21, 92	
Gender	Male	76 (61%)	39 (63%)	60 (58%)	0.787
	Female	49 (39%)	23 (37%)	44 (42%)	
Race	White	57 (49%)	37 (66%)	41 (42%)	0.161
	Black	51 (44%)	17 (30%)	52 (54%)	
	Asian	1 (1%)	0 (0%)	0 (0%)	
	Hispanic	2 (2%)	1 (2%)	2 (2%)	
	Other	6 (5%)	1 (2%)	2 (2%)	
Charlson Score	N	125	62	104	0.068
	Mean (SD)	3.8 (2.06)	3.3 (2.09)	3.1 (2.06)	
	Median	3.00	3.00	3.00	
	Min, Max	0, 8	0, 8	0, 8	
ABSSSI infection type	Deep/extensive cellulitis	58 (46%)	18 (29%)	42 (40%)	0.256
	Infected surgical and traumatic wound infection	22 (18%)	20 (32%)	29 (28%)	
	Major abscess	19 (15%)	10 (16%)	17 (16%)	
	Infected burn, ulcer, and erysipelas	25 (20%)	14 (23%)	16 (15%)	
	Other infection type	1 (1%)	0 (0%)	0 (0%)	
Prior hospitalization (>72h within past	Yes	39 (31%)	24 (39%)	26 (25%)	0.176
Prior ICU stay within past year	Yes	10 (8%)	6 (10%)	6 (6%)	0.635
Prior surgery within 30 days	Yes	3 (2%)	7(11%)	5 (5%)	0.034
Cancer	Yes	13 (10%)	10 (16%)	16 (15%)	0.423
Total LOS (days)	N	117	51	100	
	Mean (SD)	9.0 (6.07)	8.6 (6.72)	8.5 (6.03)	0.552
	Median	8.00	7.00	7.00	
	Min, Max	2, 36	1, 39	2, 40	
OPAT admin route	Self administration	38 (30%)	20 (32%)	29 (28%)	
	Ambulatory care center	28 (22%)	17 (27%)	32 (31%)	0.655
	Nurse visit in home	59 (47%)	25 (40%)	43 (41%)	
Alteration in OPAT therapy	Yes	6 (5%)	2 (3%)	14 (13%)	0.017
Solid organ transplant	Yes	2 (2%)	0 (0%)	3 (3%)	0.381
Corticosteroids (>=20 mg/d) for >14 days prior to infection	Yes	2 (2%)	0 (0%)	1 (1%)	0.592
CHF	Yes	20 (16%)	4 (6%)	14 (13%)	0.187
Diabetes	Yes	69 (55%)	26 (42%)	44 (42%)	0.088
DM with organ damage	Yes	4 (3%)	2 (3%)	0 (0%)	0.182
Acute renal failure	Yes	13 (10%)	4 (6%)	11 (11%)	0.364
Chronic renal failure	Yes	21 (17%)	7 (11%)	17 (16%)	0.589
Dialysis	Yes	2 (2%)	3 (5%)	9 (9%)	0.046
Prior systemic abx within past 90 days	Yes	42 (34%)	30 (48%)	31 (30%)	0.046
OPAT or OPAT & Inpatient	OPAT	9 (7%)	13 (21%)	4 (4%)	
	OPAT & Inpatient	116 (93%)	49 (79%)	100 (96%)	<0.001
Readmission within 30 days	Yes	23 (20%)	11 (22%)	20 (20%)	0.969
OPAT duration (days)	N	125	62	104	
	Mean (SD)	20.1 (13.46)	25.5 (13.11)	21.0 (13.57)	0.016
	Median	16	27	16.5	
	Min, Max	3, 73	4, 49	3, 57	

OPAT charges	N	125	62	104	
	Mean (SD)	1078 (737.5)	3619 (2923)	164 (209.0)	<0.001
	Median	848.96	2648.8	104.8	
	Min, Max	159, 3873	378, 16555	8, 1645	
Hospital charges	N	96	40	85	
	Mean (SD)	45690 (40501)	55787 (84242)	50601 (56637)	0.932
	Median	31498	37174	31986	
	Min, Max	6706, 197886	7922, 520826	7474, 359883	
Antibiotic charges	N	96	40	85	
	Mean (SD)	1869 (1314)	2216 (2744)	1622 (1259)	0.150
	Median	1544.5	1177.5	1219	
Outcome	Min, Max	154, 7230	213, 10879	162, 5754	
	Success	117 (94%)	55 (89%)	79 (76%)	
	Failure	8 (6%)	7 (11%)	25 (24%)	<0.001

Table 4B: Univariate tests by antibiotic treatment group.

Discussion

The primary goal of outpatient parenteral antibiotic therapy is to optimize clinical outcomes in an outpatient setting while minimizing hospitalizations and related burden of costs on the healthcare system [12,13]. This was a large observational study which demonstrated a positive impact of OPAT for the treatment of acute bacterial skin and skin structure infections with an overall success rate of 86%. Ceftaroline-related success rate was high at 94%, versus 89% for daptomycin, and 76% for vancomycin. Patients treated with vancomycin had 83% significantly lower odds of success as compared to those on ceftaroline (OR 0.17, p=0.002) In the controlled model, ceftaroline patients cost $1007.33 (SE $165.55) more than vancomycin patients, daptomycin patients cost $3216.29 (SE $197.59) more than vancomycin patients, and ceftaroline patients cost an average of $2208.97 (191.33) less than daptomycin patients (p<0.001). Even more, 93% of the CPT-F subset was treated both in an inpatient and OPAT setting, versus 79% of daptomycin-treated patients (P=0.012). Thus, the ceftaroline subset of patients was more cost-effective compared with daptomycin accompanied with a shorter OPAT duration, and while vancomycin had the lowest OPAT costs, treatment success was significantly lower than CPT-F (p<0.001), thus necessitating careful consideration of optimal management strategy for ABSSSI in OPAT. Limitations included a single-center, retrospective study design. However, we obtained a large, consecutive sample size, and unique in providing strong, comparative matching criteria for each ceftaroline fosamil-treated patient, controlling for confounding factors in the multivariable logistic regression model for predicting odds of success. Age, diabetes, and Charlson comorbidity score were all variables that may contribute to failure and were thus, controlled for in the analysis and comparable showing no statistical significance in predicting odds of success.

At present, the clinical and/or economic data on ceftaroline use for treatment of ABSSSI in an OPAT setting is absent. In a 2013 cohort study by Stephens et. al., observational data suggested that OPAT is safe, effective, and acceptable for treating a wide variety of infections. Observed trends over a 10-year period suggest that this model of infection management is adaptable and sustainable. [14] Athans et. al. studied ceftaroline versus vancomycin in an OPAT setting, but exclusively for the treatment of osteoarticular infection; noting no significant difference between the two treatments in effectiveness or tolerability and no evaluation of related costs [15]. Moreover, overall success of OPAT with standard of care antibiotics ceftriaxone and teicoplanin in patients with skin soft tissue infections has been reported to be as high as 87% versus 94% from the present study [16]. Single-center studies have suggested positive outcomes with daptomycin in OPAT for complicated skin and soft-tissue infections, osteomyelitis, foreign body/prosthetic infections, and endocarditis, demonstrating 89% success, which is similar to the success rate of Daptomycin in our study [17].

Conclusion

To date, no study has examined ceftaroline in the OPAT setting. This is the first comparative study of its kind assessing both clinical outcomes and related economic analysis between ceftaroline and commonly prescribed daptomycin and vancomycin. From this study, the use of ceftaroline as a successful agent in an OPAT setting for the treatment of ABSSSI is warranted given the clinical success rate when compared to vancomycin and daptomycin and its use likely offsets any cost difference.

OPAT offers flexibility in treating ABSSSI with the option of preventing inpatient admission for IV antimicrobial therapy, thus reducing the overall financial burden of health care costs, as treatment can be given on an outpatient basis in an ambulatory care center, via self-administration, or commonly by a nurse visit in home. With healthcare costs on the rise, further studies are warranted for analysing novel once-weekly dosing options, such as dalbavancin and/or oritavancin on an outpatient basis in comparison to standard of care antibiotic regimens, such as the ones in this study. These additional options need to be evaluated for both treatment success rates and costs, as they may shorten duration of overall treatment, eliminate the need for inpatient admission and placement of long-term central venous catheter placement, which has significant implications on the cost, quality of life, and prevention of central line-associated bloodstream infections and complications.

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