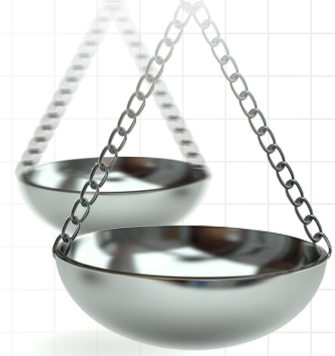
Research Article



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Ceftaroline fosamil treatment outcomes compared with standard of care among hospitalized patients with complicated skin and soft tissue infections

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Aim: Compare clinical and cost outcomes associated with ceftaroline fosamil with other commonly used antibiotics in complicated skin and soft tissue infections. **Methods:** Retrospective analysis of hospital records from 2010 to 2013 in Premier's Perspective comparative database for adults with complicated skin and soft tissue infection treated with intravenous ceftaroline fosamil, vancomycin, daptomycin, linezolid or tigecycline. Length of stay, inpatient costs and mortality were compared between propensity score-matched treatment groups. **Results & conclusion**: Compared with the other commonly used antibiotics, matched patients in the ceftaroline fosamil treatment group had an equivalent (1%) or lower (compared with linezolid, 2%) in-hospital mortality rate, and significantly lower ($p < 0.001$) average unadjusted and regression-adjusted length of stay and inpatient costs (savings of $3398.80 compared with daptomycin).

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Keywords: ceftaroline fosamil • complicated skin and soft tissue infection • economic evaluation • patient registry

Complicated skin and soft tissue infections (cSSTIs) are most commonly caused by Gram-positive bacteria including methicillin-susceptible *Staphylococcus aureus* (MSSA) but also methicillin-resistant *S. aureus* (MRSA) [1,2]. Most cases of cSSTI are mild to moderate in severity and may be treated with a variety of agents, but severe cases require hospitalization and parenteral therapy, representing a significant clinical treatment problem. An estimated 15 million cSSTIs, resulting in over 850,000 hospitalizations, occur each year in the USA [3].

Patients who are hospitalized often require coverage for resistant pathogens but with increasing antibiotic resistance the choice of empirical antibiotic treatment is becoming more difficult [1,2]. The mainstay of treatment for serious MRSA infections has until recently been the glycopeptides vancomycin and teicoplanin [4]. However, concern about the gradual development of resistance and concerns about efficacy [5] highlight the need for newer agents active against Gram-positive bacteria such as linezolid, daptomycin and tigecycline and ceftaroline fosamil, of which the latter two also include some Gram-negative coverage.

The economic impact of hospitalization associated with the increasing number of total MRSA infections is also a major concern and these resistant infections are known to prolong hospital length of stay (LOS) and increase total healthcare costs [6–8]. The mean LOS and cost of hospitalization for a patient with infections due to MRSA is 2.0- and 2.5-times more, respectively, than for patients with infections caused by MSSA [6,7] However, this is not the only burden when considering MRSA infection. Reports from some parts of the world, although not globally, of decreased

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susceptibility of *S. aureus*, including MRSA, to vancomycin and also the associated mortality and cost consequences of resistance, highlight the need for alternative antibiotics [9,10].

Ceftaroline, the active metabolite of Ceftaroline fosamil (Zinforo™, Teflaro™), is an oxyimino advanced-generation broad-spectrum cephalosporin which has *in vitro* activity against *S. aureus* and MRSA, both of which are associated with cSSTIs [11]. Ceftaroline fosamil has been found to be effective in the treatment of cSSTI in three Phase III trials – CANVAS 1 [12] (NCT00424190), CANVAS 2 [13] (NCT00423657), and COVERS [14] (NCT01499277) – which compared ceftaroline fosamil with vancomycin plus aztreonam for the treatment of cSSTI. In these studies ceftaroline fosamil was found to be noninferior to vancomycin plus aztreonam and was also effective against cSSTI caused by MRSA and other common cSSTI pathogens [15]. Ceftaroline fosamil was also well tolerated and had a safety profile concordant with other antibiotics in the cephalosporin class.

Since its approval in 2010 and commercial availability in the USA in 2011, retrospective studies describing the ceftaroline fosamil treatment of cSSTI in real world settings have reported clinical success rates between 81 and 86% when used as first- or second-line mono- or concurrent therapy [16,17]. However, real world studies comparing clinical and economic outcomes of ceftaroline fosamil with other commonly used antibiotics are not available. Here we assessed, using detailed retrospective data, differences in LOS, inpatient costs, and mortality among hospitalized patients with cSSTI who were receiving treatment with ceftaroline fosamil, compared with one of the four commonly used antibiotics – vancomycin (standard of care), linezolid, daptomycin and tigecycline.

Methods

This was a retrospective, observational, database study drawing on hospitalization records for adults aged 18 years and over with a diagnosis of cSSTI, identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-

Box 1. ICD-9-CM codes to identify patients with cSSTI (complicated skin and skin-structure infections).

- Infection due to device or graft: 996.6x
- Surgical site infection: 998.5x, 999.3x
- Nonhealing surgical wound: 998.83
- Decubitis ulcer: 707.x
- Skin and subcutaneous tissue infections: 686.x
- Erysipelas: 35
- Carbuncle and furuncle: 680.x
- Cellulitis and abscess of finger and toe: 681.x
- Other cellulitis and abscess: 682.x
- Acute lymphadenitis: 683
- Pilonidal cyst with abscess: 685
- Other local infections of skin and subcutaneous tissues: 686.x, except 686.1
- Chronic ulcer of skin: 707.x
- Abrasion or friction burn with infection: 910-917.1, 919.1
- Blister, infected: 910-917.3, 919.3
- Insect bite, nonvenomous, infected: 910-917.5, 919.5
- Superficial foreign body, infected: 910-917.7, 919.7
- Other superficial injury of specified site, infected: 910-917.9, 919.9
- Post-traumatic wound infection: 958.3
- Amputation stump infection (chronic): 997.62
- Infection due to other internal vascular device, implant, and graft (excludes central lines): 996.62
- Diabetes foot infection: 250.7x plus 681.10, 682.6, 682.7, 707.10-707.19, 785.4, 891.1, 891.2, 892.1, 892.2, 893.1, 893.2, 894.1, 894.2.
- Osteomyelitis: 730.xx
- Cellulitis and decubitus ulcers, ulcers of the skin: 680.xx, 681.xx, 682.xx, 683, 684, 685.0, 685.1, 686.1, 686.8, 686.9,709.4, 728.0, 729.3, 729.30, 729.39, 707, 707.0, 707.0x, 707.1, 707.8-707.15, 707.19
- Trauma- or surgery-related: 872.xx-875.xx, 876.0, 876.1, 877.0, 877.1, 878.xx-887.xx, 890.xx-897.xx, 910.1, 910.3, 910.7, 910.9, 911.1, 911.3, 911.7, 911.9, 912.1, 912.3, 912.7, 912.9, 913.1, 913.3, 913.7, 913.9, 914.1, 914.3, 914.7, 914.9, 915.1, 915.7, 915.9, 916.1, 916.7, 916.9, 917.1, 917.3, 917.5, 917.7, 917.9, 919.3, 919.7, 958.3, 996.6, 996.60, 996.62, 996.66, 996.69, 997.62, 998.51, 998.59
- Other serious skin infections: 040.0, 728.86, 729.4, 940.x- 949.x

9-CM) codes (Box 1). The study was conducted using the Premier Perspective comparative database (PPCD) from which data relevant to the period between 2010 and 2013 were extracted for analysis. The PPCD, believed to be the most comprehensive inpatient database in the USA consists of over 170 million patient records from approximately 500 hospitals. The PPCD database includes anonymized inpatient admission records with details on: admission and discharge dates, diagnosis and procedure codes, admission type, inpatient costs and charges (the cost was used in the analysis and extracted from the database as a single value per patient), drug use and routes of administration, and demographic and hospital characteristics.

Hospital records of patients receiving first-line (the initial treatment for cSSTI within the hospitalization episode for which the insurance claim was raised) intravenous (iv.) treatment with no more than one of the five antibiotics of interest (ceftaroline fosamil, vancomycin, daptomycin, linezolid or tigecycline) were included. Information regarding antibiotic therapy prior to cSSTI-related inpatient admission was not available. Patient records indicating more than one line of antibiotic therapy were not included in the study. Patient records of concomitant antibiotic therapy were included, but only when combined with a single antibiotic from the group of interest. Patient records with concomitant vancomycin and ertapenem use were included, but not those of vancomycin and daptomycin. Furthermore, all records indicating the use of oral vancomycin or oral linezolid therapy during the inpatient stay were excluded, as these may suggest more than one line of antibiotic therapy.

Cost per patient was extracted as a single value (the inpatient charge billed to the insurance company) as this was the only cost value uniformly reported in the database. This means that the costs assigned to a patient treated with one of the five antibiotics of interest may include a concomitant nonindex antibody therapy.

Demographic and hospital study measures extracted from the database were: age, sex, race, region, payer type, hospital bed size, teaching status and source and type of admission. Clinical characteristics were comorbidity burden (Charlson Comorbidity Index score) [18], presence of bacteremia and concomitant antibiotic use. Measures of hospital LOS (calculated using the admission and discharge date, assuming a full day on each end), inpatient costs (the total billed cost of a hospital stay after inpatient admission related to cSSTI, adjusted to US$2013 using the medical component of the Consumer Price Index) and in-hospital mortality were of primary interest.

Statistical analyses

Due to the observational, nonrandomized nature of the collected data we used the propensity score method (PSM) to match patient characteristics in the ceftaroline fosamil group with the other four antibiotic groups of interest. Here, the probability of antibiotic treatment in cSSTI patients is conditional to the baseline covariates. Prior to matching, differences in baseline covariates were compared among the comparison groups of interest using the *t*-test for continuous covariates and the χ^2 test for categorical covariates. Following the prematching comparisons, four separate logistic regression models, with a generalized logit link, were used to estimate propensity scores for the following comparison groups: ceftaroline fosamil versus vancomycin, ceftaroline fosamil versus daptomycin, ceftaroline fosamil versus linezolid and ceftaroline fosamil versus tigecycline. Caliper matching with a maximal distance of 0.001 was used to match patients without replacement in their respective treatment groups using the estimated propensity scores such that patients nearest in the ceftaroline fosamil-treatment group were matched with patients in the vancomycin, daptomycin, linezolid and tigecycline treatment groups separately [19]. Following matching, using univariate tests (*t*-test and χ^2), differences in baseline covariates were compared among the comparison groups to assess balance between the groups post matching. Outcomes with respect to mean LOS, inpatient costs and in-hospital mortality were compared between the four study groups using the unadjusted student's *t*-test and covariate-adjusted generalized linear regression for LOS and inpatient costs and the χ^2 test and Cox proportional hazard regression for in-hospital mortality.

Results

Baseline characteristics

Matched unadjusted covariate analysis

In the unmatched dataset, vancomycin (n = 418,435, used in 93.8% of patients) was the most commonly used antibiotic among patients with cSSTI followed by daptomycin (n = 13,161), tigecycline (n = 6631) and linezolid (n = 5067). Ceftaroline fosamil (n = 2834) was used in 0.6% of patients. Prior to propensity score matching, we observed some significant differences between ceftaroline fosamil and the other treatment groups in terms of demographic and hospital characteristics (Table 1). Notably, ceftaroline fosamil use was generally observed in a slightly more elderly population, with 41.3%

Table 1. Prematching characteristics of complicated skin and soft tissue infection-related hospitalizations, by index antibiotic[†].

Characteristics	Index antibiotic					p-value			
	Ceftaroline fosamil	Vancomycin	Daptomycin	Tigecycline	Linezolid	Ceftaroline fosamil vs vancomycin[‡]	Ceftaroline fosamil vs daptomycin[‡]	Ceftaroline fosamil vs tigecycline[‡]	Ceftaroline fosamil vs linezolid[‡]
Population size (n)	2834	418,435	13,161	6631	5067				
Age (years):									
– Mean (SD)	59.3 (17.9)	57.5 (17.8)	57.6 (17.2)	58.6 (17.7)	58.0 (17.9)	<0.0001	<0.0001	0.1122	0.0027
– Elderly (≥65 years); n (%)	989 (41.3)	151,022 (36.1)	4761 (36.2)	2589 (39)	1918 (37.9)	<0.0001	<0.0001	0.1267	0.0122
Sex; n (%):						0.1054	0.0011	<0.0001	0.0002
– Male	1264 (52.8)	227,244 (54.3)	6504 (49.4)	3171 (47.8)	2451 (48.4)				
Race; n (%):						<0.0001	0.5634	0.0729	0.0027
– Whites	1815 (75.8)	289,195 (69.1)	10,093 (76.7)	4936 (74.4)	3704 (73.1)				
Region; n (%):						<0.0001	<0.0001	<0.0001	<0.0001
– South	1521 (63.5)	171,328 (40.9)	6908 (52.5)	4513 (68.1)	2901 (57.3)				
Payer type; n (%):						0.0019	<0.0001	0.1766	<0.0001
– Private	561 (23.4)	102,298 (24.4)	3705 (28.2)	1594 (24)	1204 (23.8)				
– Medicare/Medicaid	1515 (63.2)	258,600 (61.8)	8303 (63.1)	4276 (64.5)	3413 (67.4)				
Bed size; n (%):						<0.0001	<0.0001	<0.0001	<0.0001
– 0–199	398 (16.6)	76,892 (18.4)	1752 (13.3)	1716 (25.9)	1056 (20.8)				
– 200–399	1404 (58.6)	160,656 (38.4)	4963 (37.7)	3059 (46.1)	2277 (44.9)				
– 400+	594 (24.8)	180,887 (43.2)	6446 (49)	1856 (28)	1734 (34.2)				
Source of admission; n (%):						<0.0001	<0.0001	<0.0001	<0.0001
– Outpatient	2185 (91.2)	328,906 (78.6)	10,668 (81.1)	5229 (78.9)	3987 (78.7)				
Type of admission; n (%):						<0.0001	<0.0001	<0.0001	<0.0001
– Emergency	1536 (64.1)	294,274 (70.3)	7265 (55.2)	3961 (59.7)	3162 (62.4)				
Discharge status; n (%):						<0.0001	<0.0001	<0.0001	<0.0001
– Died	15 (0.6)	4123 (1)	118 (0.9)	83 (1.3)	112 (2.2)				
– Transferred to home care	1944 (81.1)	315,546 (75.4)	9909 (75.3)	4985 (75.2)	3549 (70)				
– Transferred to other hospital	380 (15.9)	88,946 (21.3)	2934 (22.3)	1445 (21.8)	1311 (25.9)				
– Not yet discharged	0 (0)	56 (0)	1 (0)	0 (0)	1 (0)				
– Other	44 (1.8)	8773 (2.1)	186 (1.4)	112 (1.7)	86 (1.7)				

[†]Antibiotic received after inpatient admission related to complicated skin and soft tissue infection.
[‡]p-values based on student's *t*-test for continuous measures and χ^2 test for categorical measures.
[§]Selected CCI comorbidities are presented in this table.
CCI: Charlson Comorbidity Index; SD: Standard deviation.

Table 1. Prematching characteristics of complicated skin and soft tissue infection related hospitalizations, by index antibiotic[†] (cont.).

Characteristics	Index antibiotic					p-value			
	Ceftaroline fosamil	Vancomycin	Daptomycin	Tigecycline	Linezolid	Ceftaroline fosamil vs vancomycin[‡]	Ceftaroline fosamil vs daptomycin[‡]	Ceftaroline fosamil vs tigecycline[‡]	Ceftaroline fosamil vs linezolid[‡]
– Unknown	13 (0.5)	991 (0.2)	13 (0.1)	6 (0.1)	8 (0.2)				
CCI score:									
– Mean (SD)	4.57 (2.23)	4.27 (2.33)	4.35 (2.42)	4.53 (2.41)	4.59 (2.37)	<0.0001	<0.0001	0.399	0.72
CCI comorbidities[§]; n (%):									
– Congestive heart failure	429 (15.1)	56,510 (13.4)	1940 (14.7)	954 (14.4)	829 (16.3)	0.0087	0.5412	0.3399	0.1696
– Chronic pulmonary disease	660 (23.3)	86,369 (20.6)	2854 (21.6)	1491 (22.5)	1141 (22.4)	0.0003	0.0498	0.3877	0.3966
– Mild liver disease	163 (5.7)	18,736 (4.5)	598 (4.5)	251 (3.8)	203 (4)	0.0009	0.0054	<0.0001	0.0004
– Hypertension	1276 (45)	172,032 (40.9)	5353 (40.5)	2870 (43.2)	2004 (39.4)	<0.0001	<0.0001	0.1202	<0.0001
– Any tumor	28 (1)	7164 (1.7)	208 (1.6)	95 (1.4)	90 (1.8)	0.0032	0.0185	0.0805	0.0058
– Skin ulcers/cellulitis	2632 (92.8)	323,113 (76.9)	9279 (70.2)	5401 (81.4)	3900 (76.7)	<0.0001	<0.0001	<0.0001	<0.0001
– Moderate or severe liver disease	29 (1)	3494 (0.8)	108 (0.8)	63 (0.9)	64 (1.3)	0.2632	0.2806	0.7382	0.3497
Duration of index antibiotic therapy; mean (SD)	4.1 (2.75)	3.95 (3.17)	4.52 (4.25)	4.62 (3.69)	4.46 (3.79)	0.0124	<0.0001	<0.0001	<0.0001
Other concomitant antibiotics; n (%)	1986 (70.1)	352,113 (84.2)	10,398 (79.0)	4482 (67.6)	4173 (82.4)	<0.0001	<0.0001	0.0172	<0.0001

[†]Antibiotic received after inpatient admission related to complicated skin and soft tissue infection.
[‡]p-values based on student's *t*-test for continuous measures and χ^2 test for categorical measures.
[§]Selected CCI comorbidities are presented in this table.
CCI: Charlson Comorbidity Index; SD: Standard deviation.

Table 2. Characteristics of complicated skin and soft tissue infection-related hospitalization post-propensity score matching†.

Characteristic	Propensity score matched cohorts											
	Antibiotic groups											
	Ceftaroline fosamil	Vancomycin	p-value‡	Ceftaroline fosamil	Daptomycin	p-value‡	Ceftaroline fosamil	Tigecycline	p-value‡	Ceftaroline fosamil	Linezolid	p-value‡
Population size (n)	2834	2834		2651	2651		2606	2606		2554	2554	
Age (years):			0.7175			0.786			Missing			0.8818
– Mean (SD)	59.3 (17.9)	59.1 (17.9)		59.4 (17.9)	59.5 (17.6)		59.5 (18.0)	59.4 (17.8)		59.0 (17.7)	59.1 (17.8)	
Sex; n (%):			0.8523			0.26			0.9779			0.3135
– Male	1338 (47.2)	1345 (47.5)		1275 (48.1)	1316 (49.6)		1290 (48.7)	1291 (48.7)		1221 (46.1)	1257 (47.4)	
Race; n (%):			0.8026			0.0077			0.083			0.2615
– Whites	2159 (76.2)	2167 (76.5)		2036 (76.8)	2116 (79.8)		2002 (75.5)	2054 (77.5)		1938 (73.1)	1972 (74.4)	
Region; n (%):			0.6603			0.0556			0.1346			0.1116
– South	1769 (62.4)	1785 (63.0)		1656 (62.5)	1723 (65.0)		1706 (64.4)	1757 (66.3)		1573 (59.3)	1628 (61.4)	
Payer type; n (%):			0.9646			0.0114			0.3455			0.0022
– Private	639 (22.5)	637 (22.5)		615 (23.2)	619 (23.3)		600 (22.6)	583 (22.0)		605 (22.8)	569 (21.5)	
– Medicare/ Medicaid	1843 (65.0)	1851 (65.3)		1715 (64.7)	1778 (67.1)		1688 (63.7)	1733 (65.4)		1646 (62.1)	1748 (65.9)	
Bed size; n (%):			0.9492			<0.0001			0.0012			<0.0001
– 0–199	461 (16.3)	470 (16.6)		415 (15.7)	555 (20.9)		448 (16.9)	491 (18.5)		419 (15.8)	524 (19.8)	
– 200–399	1650 (58.2)	1644 (58)		1531 (57.8)	1293 (48.8)		1508 (56.9)	1377 (51.9)		1485 (56)	1283 (48.4)	
– 400+	723 (25.5)	720 (25.4)		705 (26.6)	803 (30.3)		650 (24.5)	738 (27.8)		650 (24.5)	747 (28.2)	
Source of admission; n (%):			0.8863			0.284			0.3981			0.924
– Outpatient	2592 (91.5)	2595 (91.6)		2409 (90.9)	2431 (91.7)		2364 (89.2)	2346 (88.5)		2312 (87.2)	2310 (87.1)	
Type of admission; n (%):			0.9261			0.2332			0.1127			0.0003
– Emergency	1826 (64.4)	1840 (64.9)		1683 (63.5)	1697 (64)		1676 (63.2)	1728 (65.2)		1613 (60.8)	1658 (62.5)	
Duration of index antibiotic therapy, mean (SD)	4.10 (2.75)	3.85 (3.04)	0.0011	4.12 (2.77)	4.35 (3.88)	0.0145	4.12 (2.74)	4.59 (3.57)	<0.0001	4.13 (2.81)	4.34 (3.35)	0.0158
Other concomitant antibiotics; n (%)	1986 (70.1)	1993 (70.3)	0.8389	1895 (71.5)	1865 (70.4)	0.3643	1815 (69.6)	1837 (70.5)	0.5058	1935 (75.8)	1947 (76.2)	0.6942

†Propensity scores were estimated using four separate logistic regression models with a generalized logit link. The caliper (0.001) matching method was used to match patients in the ceftaroline fosamil group with patients in vancomycin, linezolid, tigecycline and daptomycin cohorts.

‡p-values based on student's *t*-test for continuous measures and χ^2 for categorical measures.

SD: Standard deviation.

of ceftaroline fosamil-treated patients aged 65 years or over compared with 36.1, 36.2, 39 and 37.9% of patients treated on admission with vancomycin, daptomycin, tigecycline and linezolid, respectively. Ceftaroline fosamil was more commonly prescribed to patients admitted from outpatient clinics (91.2%) compared with the alternative antibiotics considered (78.6–81.1%). A higher proportion of patients using ceftaroline fosamil had a discharge disposition of 'transfer to homecare' (81.1 vs 75.4, 75.3, 75.2 and 70% for the alternative antibiotics) compared with patients in the other antibiotic groups, potentially indicating a lower use of resources by the ceftaroline fosamil group.

Compared with patients treated with alternative antibiotics, those treated with ceftaroline fosamil demonstrated statistically significant ($p < 0.001$) higher rates of comorbidity in cases of obesity; skin ulcers; liver disease (with the exception of patients treated with daptomycin); and hypertension (with the exception of patients treated with tigecycline), and statistically significant ($p < 0.001$) lower rates of comorbidity in cases of diabetes (with the exception of patients treated with vancomycin and daptomycin) and hemiplegia (data not shown). Additionally, in the unmatched data ceftaroline fosamil-treated patients had statistically significant ($p < 0.001$) fewer coprescribed antibiotic medications (with the exception of patients treated with tigecycline) and duration of therapy was shorter ($p < 0.001$) than for the alternative antibiotics (with the exception of patients treated with vancomycin).

Logistic regression analysis

Matching of cohorts yielded balanced populations across the antibiotics selected on all demographic measures including age, sex, race, gender and treatment- and admission-characteristics. Most hospital characteristics were also balanced, with the exception of the ceftaroline fosamil and linezolid comparison group, which differed ($p < 0.001$) with respect to payer type, bed size and type of admission, as illustrated in Table 2.

The matching of cohorts also reduced differences in comorbidity rates across the comparison groups. A number of overall differences remained, notably ceftaroline fosamil treated patients had increased rates ($p < 0.001$) of skin ulcers, and significantly ($p < 0.001$) lower rates of diabetes (with the exception of patients treated with vancomycin [$p = 0.045$] and daptomycin [$p = 0.077$]) and hemiplegia compared with all other antibiotic comparison groups. Post matching, rates of congestive heart failure and hypertension were balanced across all treatment comparison groups with the exception of the ceftaroline fosamil–linezolid comparison group, which revealed ceftaroline fosamil patients having significantly ($p < 0.001$) lower rates of congestive heart failure and higher rates of hypertension (Table 3).

A shorter duration of antibiotic treatment was observed for ceftaroline fosamil-treated patients compared with patients treated with the alternative antibiotics, except in the case of vancomycin in which duration of ceftaroline fosamil therapy was longer than that of vancomycin (4.10 vs 3.85 days; $p < 0.001$).

In-hospital mortality, LOS & inpatient costs

Matched unadjusted covariate analysis

The average unadjusted LOS and inpatient costs were significantly ($p < 0.001$) lower among patients in the ceftaroline fosamil treatment group than among those in the vancomycin (mean LOS: 5.1 vs 5.6 days; costs: $8051 vs $10,089), daptomycin (LOS: 5.0 vs 6.3 days; costs: $7824 vs $10,227), tigecycline (LOS: 5.2 vs 6.1 days; costs: $8264 vs $11,353) and linezolid (LOS: 5.1 vs 6.4 days; costs: $8081 vs $12,020) treatment groups (data not shown).

Logistic regression analysis

The in-hospital mortality rate was approximately 1% for ceftaroline fosamil, vancomycin, tigecycline and daptomycin groups. In the case of the linezolid-treatment group mortality was 2% representing a significant difference between ceftaroline fosamil and linezolid-associated mortality rates (0.8 vs 2%; $p = 0.0004$) (Table 4).

The predicted inpatient costs as determined by covariate-adjusted generalized linear regression are illustrated in Figure 1. Savings per patient treated with ceftaroline fosamil versus vancomycin were $2037.70 and versus daptomycin were $3398.80 (Table 4 & Figure 1).

Discussion

cSSTIs reportedly account for up to 10% of admissions to infection units in the USA [20] and in the UK [21]. The treatment costs for the management of SSTIs caused by *S. aureus* can be substantial but vary by factors such as populations studied, cost perspective and antibiotic therapy chosen [22,23]. A large study of Nationwide Inpatient Sample and Census Bureau data in 2009 reported the average associated cost of a *S. aureus*–SSTI hospitalization at $11,622 [24]. The difference in hospitalization costs associated with different study antibiotics varies according to the metrics being compared. For example daptomycin has been found to be a significant

Table 3. Comorbidity burden post-propensity score matching[†].

Antibiotic group	Ceftaroline fosamil (n = 2834)	Vancomycin	p-value[‡]	Ceftaroline fosamil	Daptomycin	p-value[‡]
Population size (n)	2834	2834		2651	2651	
CCI score: mean (SD)	4.57 (2.23)	4.57 (2.31)	0.9488 (NS)	4.55 (2.23)	4.56 (2.47)	0.8562 (NS)
CCI comorbidities, n (%) (significantly different)						
Mild liver disease						
Diabetes						
Depression	344 (12.1)	440 (15.5)	0.0002			
Hypertension						
Hemiplegia	54 (1.9)	95 (3.4)	0.0007	51 (1.9)	105 (4)	<0.0001
Skin ulcers/cellulitis	2631 (92.8)	2268 (80)	<0.0001	2456 (92.6)	2001 (75.5)	<0.0001
Obesity	798 (28.2)	604 (21.3)	<0.0001	740 (27.9)	601 (22.7)	<0.0001
Bacteremia	24 (0.8)	84 (3)	<0.0001	24 (0.9)	144 (5.4)	<0.0001
CCI comorbidities, n (%) (not significantly different)						
Congestive heart failure						
Peripheral vascular disease						
Ulcer disease	8 (0.3)	23 (0.8)	0.0069			
Mild liver disease				145 (5.5)	105 (4)	0.0096
Diabetes				996 (37.6)	1097 (41.4)	0.0045
Use of warfarin				309 (11.7)	376 (14.2)	0.0061
Diabetes with end-organ damage						
Any tumor	28 (1)	57 (2)	0.0015	26 (1)	48 (1.8)	0.01

[†]Propensity scores were estimated using four separate logistic regression models with a generalized logit link. The caliper (0.001) matching method was used to match patients in the ceftaroline fosamil group with patients in vancomycin, linezolid, tigecycline and daptomycin cohorts.
[‡]p-values based on student's *t*-test for continuous measures and χ^2 test for categorical measures.
CCI: Charlson Comorbidity Index; SD: Standard deviation

positive predictor of overall costs [23], likely due to lower costs of monitoring and hospitalization compared with vancomycin [25].

The very low number of patients in this large observational sample selected for ceftaroline fosamil therapy may reflect a reservation to use a new drug without empirical data (ceftaroline fosamil was approved in 2010 and became commercially available in the US in 2011). Of those treated, significantly lower inpatient costs and LOS were observed among patients prescribed ceftaroline fosamil as opposed to vancomycin or one of the other three commonly prescribed antibiotics. Additionally, mortality rates were comparable to or lower than (in the case of linezolid) the alternative antibiotics.

Historical metrics for LOS associated with cSSTIs in the USA are consistent with those observed in the current study: For example, a cohort of 900 patients showed median LOS of 5 days for hospital acquired infection and 4 days for community acquired infection [26]. Real world data on the management of cSSTIs in ten European countries, demonstrated longer average LOS (18.5 days ± 19.9) and higher but comparable mortality (3.4%) than observed in this cohort and may indicate differences in the patients studied or in healthcare service provision in Europe versus the USA [27]. Differences in comorbidities across treatment groups suggests that any further consideration of the current data would benefit from factoring in their effect on LOS, costs and mortality for the treatment of cSSTIs.

While a retrospective observational study using this very large PPCD database provides an opportunity for gaining insight into the usefulness of a newly licensed drug, the limitations inherent to this type of analysis may have led to a confounding of the relationship between the antibiotics of interest and the outcomes tested. Thus it is possible that many

Table 3. Comorbidity burden post-propensity score matching† (cont.).

Ceftaroline fosamil	Tigecycline	p-value‡	Ceftaroline fosamil	Linezolid	p-value‡
2606	2606		2504	2504	
4.57 (2.22)	4.60 (2.40)	0.6062(NS)	4.55 (2.23)	4.62 (2.39)	<0.0001
CCI Comorbidities, n (%) (significantly different)					
147 (5.8)	85 (3.3)	<0.0001			
992 (38.1)	1121 (43)	0.0003	954 (37.4)	1082 (42.4)	0.0003
			1140 (44.6)	1005 (39.4	0.0001
51 (2)	108 (4.1)	<0.0001	51 (2)	132 (5.2)	<0.0001
2413 (92.6)	2154 (82.7)	<0.0001	2362 (92.5)	2034 (79.6)	<0.0001
731 (28.1)	630 (24.2)	0.0014	720 (28.2)	598 (23.4)	<0.0001
			22 (0.9)	63 (2.5)	<0.0001
CCI Comorbidities, n (%) (not significantly different)					
			376 (14.7)	447 (17.5)	0.0069
323 (12.4)	389 (14.9)	0.0078			
			7 (0.3)	24 (0.9)	0.0022
250 (9.6)	315 (12.1)	0.0038			
25 (1)	37 (1.4)	0.1252	22 (0.9)	44 (1.7)	0.0064

†Propensity scores were estimated using four separate logistic regression models with a generalized logit link. The caliper (0.001) matching method was used to match patients in the ceftaroline fosamil group with patients in vancomycin, linezolid, tigecycline and daptomycin cohorts.
‡p-values based on Student's *t*-test for continuous measures and χ^2 test for categorical measures.

of the subjects who were treated with ceftaroline fosamil may have been systematically different from subjects given any of the other comparator agents in ways not measured by the variables included in the multivariable analysis. Specific circumstances that would strongly favour the use of ceftaroline fosamil include previous antimicrobial resistance to alternative agents, adverse reactions or risk of these reactions to alternative agents in a specific patient, failure of previously used therapies, need for simultaneous coverage of a second pathogen with a single intravenous drug and ease of use because of the lack of need for monitoring therapeutic levels (as needed for vancomycin). Furthermore, a precise comparison between the outcomes of the study is limited by possible unmeasured confounding variables, such as the possibility that ceftaroline fosamil-treated subjects may have been more likely to have successful therapy, because the drug would otherwise not be chosen to treat an cSSTI. A further limitation is that because the available data did not include admission time to discharge time in hours, LOS was calculated using the admission date to discharge date assuming a full day on each end. As a result, LOS is greater than duration of SSTI therapy, suggesting that patients waited a day before initiation of therapy, which is unlikely. It should also be noted that increased LOS reduces the overall impact of drug cost, thereby creating a bias toward more expensive drugs. An additional limitation was the lack of information available for complications of SSTIs, such as endocarditis, foreign body infection or osteomyelitis, as these may be confounders in the association of drug choice and measured outcomes.

Viewing this research as a pilot study, and bearing in mind its shortcomings, the wide differences between the number of patient records selected for ceftaroline fosamil-treated patients, which was only

Table 4. In-hospital mortality and inpatient utilization and costs associated with complicated skin and soft tissue infection-related inpatient admission, by index antibiotic†.

Propensity score matched cohorts						
	Antibiotic groups					
Characteristic	Ceftaroline fosamil	Vancomycin	p-value	Ceftaroline fosamil	Daptomycin	p-value
In-hospital mortality; n (%):			0.3248			0.1779
– Died	22 (0.8)	29 (1)		18 (0.7)	27 (1)	
– Alive	2812 (99.2)	2805 (99)		2633 (99.3)	2624 (99)	
Length of stay (days); mean (SD)	5.08 (4.48)	5.6 (5.18)	<0.0001	5.12 (4.56)	6.43 (7.22)	<0.0001
Inpatient costs ($); mean (SD):						
– Overall inpatient admissions costs	8051.40 (8585.00)	10,089.10 (12719.40)	<0.0001	8081.00 (8773.90)	12,019.80 (18,855.00)	<0.0001
– Per day inpatient costs	1630.10 (861.70)	1807.40 (1180.20)	<0.0001	1615.60 (854.60)	1959.90 (1864.10)	<0.0001
– Costs associated with index antibiotic treatment ($); mean (SD)	434.40 (579.00)	142.10 (216.40)	<0.0001	432.80 (585.60)	1688.50 (8404.50)	<0.0001

†Antibiotic-received post complicated skin and soft tissue infection related inpatient admission.
SD: Standard deviation.

0.6%, as opposed to those treated with alternative antibiotics, the current findings capture initial antibiotic prescribing practices of ceftaroline fosamil in the USA and provide a point of departure for further exploring its real-world effectiveness in comparison with other commonly used antibiotics for the treatment of cSSTIs.

Conclusion

This research serves as an initial step toward assessing outcomes associated with ceftaroline fosamil in treating cSSTIs in the real-world setting. In general, mortality associated with ceftaroline fosamil monotherapy treatment (1%) was similar to that in patients

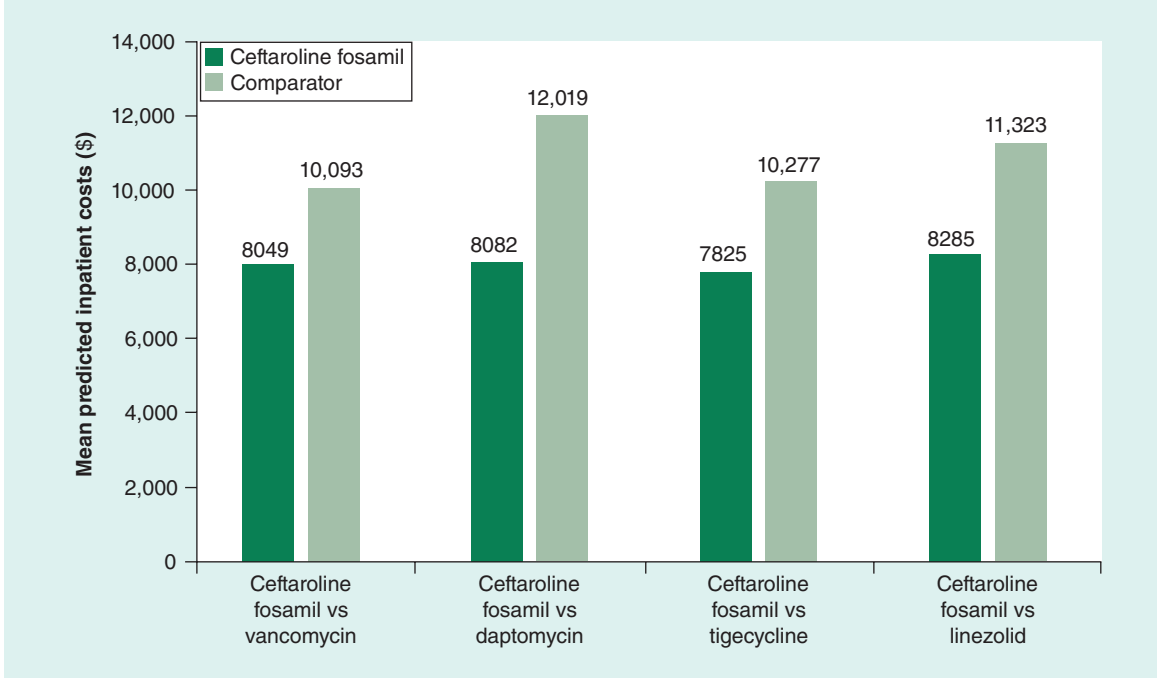

Figure 1. Generalized linear regression predicted mean inpatient costs.

Table 4. In-hospital mortality and inpatient utilization and costs associated with complicated skin and soft tissue infection-related inpatient admission, by index antibiotic† (cont.).

Propensity score matched cohorts					
Antibiotic groups					
Ceftaroline fosamil	Tigecycline	p-value	Ceftaroline fosamil	Linezolid	p-value
		0.3742			0.0004
20 (0.8)	26 (1)		21 (0.8)	51 (2)	
2586 (99.2)	2580 (99)		2533 (99.2)	2503 (98)	
5.02 (4.35)	6.27 (6.3)	<0.0001	5.21 (4.63)	6.08 (5.96)	<0.0001
7824.10 (8331.40)	10,277.50 (15,190.60)	<0.0001	8263.90 (8868.10)	11,352.70 (14,814.10)	<0.0001
1605.70 (863.70)	1693.70 (1620.60)	<0.0001	1630.00 (870.80)	1868.90 (1264.90)	<0.0001
423.80 (575.20)	720.30 (737.00)	<0.0001	435.40 (595.50)	843.50 (972.10)	<0.0001

†Antibiotic-received post complicated skin and soft tissue infection related inpatient admission.

treated with vancomycin, daptomycin, and tigecycline but lower than that associated with linezolid (2%). However, significant reductions in LOS and inpatient costs were observed with ceftaroline fosamil treatment compared with other commonly used antibiotics in the management of cSSTI. Further, more detailed, research is required to examine the full clinical and economic impacts of alternative antibiotics for cSSTIs.

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Executive summary

- Ceftaroline fosamil was approved in the USA in 2010 for the treatment of complicated skin and skin structure infections (cSSTIs) and became commercially available in the USA in 2011.
- Real world studies demonstrate clinical success rates between 81 and 86% when used as first- or second-line mono- or concurrent therapy for cSSTIs but real-world clinical and health economic outcomes compared with other frequently used antibiotics are unknown
- This retrospective study of hospital records from 2010 to 2013 compared clinical and cost outcomes associated with ceftaroline fosamil with other commonly used antibiotics in cSSTIs.
- Compared with the other commonly used antibiotics, propensity score matched patients in the ceftaroline fosamil treatment group had lower ($p < 0.001$) average unadjusted length of stay and inpatient costs and a similar in-hospital mortality rate (~1%).
- Limitations of administrative claims data such as potential misclassification due to coding errors, missing data, limited clinical information and attrition bias should be considered in interpreting the study findings.

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