



Ceftaroline fosamil for the treatment of Gram-positive endocarditis: CAPTURE study experience



Christopher J. Destache^a, David J. Guervil^b, Keith S. Kaye^{c,*}

^aSchool of Pharmacy and Health Professions, Creighton University, Omaha, NE, USA

^bMemorial Hermann-Texas Medical Center, Houston, TX, USA

^cWayne State University and Detroit Medical Center, Detroit, MI, USA

ARTICLE INFO

Article history:

Received 3 October 2018

Accepted 27 January 2019

Editor: Professor Matthew Falagas

Keywords:

Ceftaroline fosamil

Gram-positive endocarditis

Meticillin-resistant *Staphylococcus aureus*

Meticillin-susceptible *Staphylococcus aureus*

CAPTURE study

ABSTRACT

Background: The clinical experience of ceftaroline fosamil (CPT-F) therapy for Gram-positive infective endocarditis is reported from CAPTURE, a retrospective study conducted in the USA.

Methods: Data, including patient demographics, medical history, risk factors, microbiological aetiology and clinical outcomes, were collected by review of patient charts between September 2013 and February 2015.

Results: Patients ($n=55$) with Gram-positive endocarditis were treated with CPT-F. The most common risk factors were intravascular devices (43.6%), diabetes mellitus (40.0%) and injection drug use (38.2%). The most commonly isolated pathogens were meticillin-resistant *Staphylococcus aureus* (MRSA; 80%), meticillin-susceptible *S. aureus* (MSSA; 7.3%) and coagulase-negative staphylococci (7.3%). CPT-F was given as first-line therapy in 7.3% of patients and as second-line or later therapy in 92.7% of patients, and as monotherapy in 41.8% of patients and as concurrent therapy in 58.2% of patients. Clinical success was observed in 82.6% (19/23) of patients treated with CPT-F as monotherapy. In patients treated with CPT-F as first-line therapy or second-line or later therapy, 75.0% (3/4) and 70.6% (36/51) achieved success, respectively. Clinical success was observed in 77.3% (34/44) of patients with MRSA and 25% (1/4) of patients with MSSA. Two patients discontinued treatment with CPT-F due to an adverse event.

Conclusions: CPT-F treatment was associated with a high rate of clinical success in patients with Gram-positive infective endocarditis, including those with risk factors and infections caused by MRSA. A high rate of clinical success was observed in patients treated with CPT-F used as first-line therapy or second-line or later therapy, or as monotherapy or in combination with other antibiotics.

© 2019 The Authors. Published by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license.

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

1. Introduction

Infective endocarditis (IE), a disease associated with high risk of mortality and morbidity [1–3], is a growing health concern, with hospitalization rates in the USA rising from 9.3 per 100 000 to 12.7 per 100 000 between 1998 and 2009 [4]. The poor prognosis associated with IE is due to the complications and sequelae of the infection and risk of recurrence. IE causes valvular lesions (degeneration) which can result in valvular insufficiency and heart failure, and/or valvular vegetations that have high embolic potential [5]. In

addition, IE often necessitates valve replacement (native or prosthetic valve) [5].

The microbiological aetiology of IE varies depending on patient risk factors; however, the most commonly isolated pathogens are Gram-positive bacteria, including *Staphylococcus aureus*, viridans group streptococci, enterococci and coagulase-negative staphylococci (CoNS) [1,6]. In rare cases, Gram-negative bacilli may also cause IE, especially among those with a history of injection drug use (IDU) or intravascular or implanted intracardiac devices [6].

The Modified Duke Criteria for diagnosis of IE requires microbiological evidence (positive blood culture/histology results) and clinical evidence (echocardiographic evidence, fever, vascular/immunologic phenomena, history of IE or IDU) [7,8]. Type and duration of antimicrobial treatment is dependent on the pathogen isolated, the presence of prosthetic vs. native valves, whether the

* Corresponding author. Address: Division of Infectious Diseases, University of Michigan Medical School, 5510A MSRB I, SPC 5680, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-5680, USA. Tel.: +1 734 615 3604; fax: +1 734 615 5534.

E-mail address: keithka@med.umich.edu (K.S. Kaye).

patient has a history of IDU vs. non-IDU, and bacterial tolerance to antibiotic treatment [9].

Ceftaroline fosamil (CPT-F) is a cephalosporin that has activity against Gram-positive and -negative bacteria due to its inhibition of bacterial cell wall synthesis via binding of penicillin-binding proteins [10]. Ceftaroline has been approved for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia [10] based on successful phase 3 clinical trials for acute bacterial skin and skin structure infections (CANVAS 1, CANVAS 2) and community-acquired bacterial pneumonia (FOCUS 1 and 2) [11–14]. Recent case reports have demonstrated that ceftaroline is effective in treating patients with bloodstream infections and IE [15,16].

As randomized controlled trials are rarely performed for IE, particularly left-sided IE, data from non-randomized observational analyses can provide valuable information. CAPTURE (Clinical Assessment Program and Teflaro Utilization Registry), a multi-centre retrospective study, sought to describe the contemporary clinical use of CPT-F in the USA, including off-label use, such as for treatment of Gram-positive IE (GPIE) or bacteraemia. The clinical experience of patients with GPIE treated with CPT-F is reported, including clinical outcomes based on demographics and clinical factors.

2. Materials and methods

2.1. Study design and patients

The present analysis was performed using data from CAPTURE, a phase 4 retrospective cohort study that included adult patients treated with CPT-F for GPIE. Data were collected from participating centres by review of randomly ordered patient charts between September 2013 and February 2015; charts were randomly ordered for sequential entry on the electronic case report form and stratified by specific infectious disease, based on pharmacy listings. Chart abstraction was performed ≥ 30 days after CPT-F administration to ensure retrospective collection of data. Patients aged ≥ 18 years with a diagnosis of GPIE based on Modified Duke Criteria and who received more than four doses of CPT-F (thus allowing treatment modification based on culture results) were eligible for inclusion in the study. Patients were excluded from the study if any data regarding CPT-F dosing, hospital admission or status at the time of discharge were missing, or if their charts had been previously extracted for CAPTURE. Per protocol, no postdischarge data were collected. The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Registration of Pharmaceuticals for Human Use and met all institutional review board requirements before initiation. The list of primary investigators and names and addresses of the Investigational Research Board are found in Table A (see online supplementary material).

2.2. Data collection and analysis

Data collected for study patients included demographic information, relevant medical and surgical history, disease characteristics (including risk factors, antibiotic use, location of care, primary infection site, pathogens identified) and clinical outcomes (i.e. clinical success or failure). Clinical success was defined as any of the following: clinical cure with no further need of any antibiotic, clinical improvement with switch to treatment with antibiotic other than CPT-F, or clinical improvement while undergoing treatment with CPT-F (without evidence of failure or treatment discontinuation). For cases in which the reason for discontinuation of CPT-F was 'other', a review was undertaken to determine whether a patient was improving without evidence of treatment failure at the

time of discontinuation; such cases were considered clinical successes. Discontinuation of CPT-F due to an adverse event (including death) or a switch to another antibiotic because of insufficient therapeutic effect was categorized as clinical failure. Data were summarized using descriptive statistics and presented as mean [standard deviation (SD)], median (range) or percentages.

3. Results

3.1. Patient demographics and disease characteristics

Data were collected for patients with GPIE from 22 participating centres. Demographics and clinical characteristics of patients with GPIE are shown in Table 1. In most cases, a combination of more than one diagnostic criterion was used to identify patients with GPIE; in the majority of patients, the most common criteria for identification of GPIE were major Modified Duke Criteria of a positive blood culture and echocardiographic evidence (Table 2). The most commonly identified sources of GPIE were IDU [18/55 (32.7%)] and IVD [12/55 (21.8%)].

3.2. Pathogens

Among the 55 patients with GPIE, two independent infections were observed in one patient [1.8%; methicillin-susceptible *S. aureus* (MSSA) isolated from blood; methicillin-resistant *S. aureus* (MRSA) isolated from the respiratory tract]. MRSA was the most commonly isolated pathogen, identified in 80% (44/55) of patients. MSSA was identified in 7.3% (4/55) of patients, CoNS in 7.3% (4/55) of patients, *Enterococcus faecalis* in 1.8% (1/55) of patients and *Streptococcus mutans* in 1.8% (1/55) of patients. Of the 44 unique (one isolate per patient; first recorded isolate) MRSA isolates, 18.2% (8/44)

Table 1
Patient characteristics and location of care.

Demographic data	Patients (n=55)
Sex, n (%)	
Male	32 (58)
Age, years	
Mean (SD)	52.3 (16.6)
Median (range)	54 (20–85)
BMI, kg/m ²	
Mean (SD)	30.3 (9.4)
BMI, kg/m ² , n (%)	
Underweight (<18.5)	1 (2)
Normal (18.5–24.9)	14 (26)
Overweight (25.0–29.9)	15 (27)
Obese (≥ 30)	23 (42)
Risk factors, n (%) ^a	
Intravascular devices	24 (43.6)
Diabetes mellitus	22 (40.0)
Intravenous drug use	21 (38.2)
Haemodialysis	8 (14.5)
Valvular heart disease	12 (21.8)
Congestive heart failure	9 (16.4)
Previous IE	8 (14.5)
Other history ^b	33 (60.0)
Type of endocarditis, n (%)	
Right-sided	26 (47.3)
Left-sided	25 (45.5)
Bilateral	4 (7.3)
Location of care during CPT-F administration, n (%)	
General hospital ward	23 (42.0)
ICU	32 (58.0)
Duration of hospital stay, days	
Mean (SD)	26 (23)
Median (range)	21 (4–145)

BMI, body mass index; CPT-F, ceftaroline fosamil; ICU, intensive care unit; IE, infective endocarditis; SD, standard deviation.

^a Patients may have more than one risk factor

^b Other history also includes prior *Staphylococcus aureus* bacteraemia.

Table 2
Diagnostic criteria among patients with Gram-positive infective endocarditis (n=55).

Diagnostic criteria ^a	Patients (n=55)
Major Modified Duke Criteria, n/N	
Positive blood culture	53/55
Echocardiographic evidence	51/55
New valvular regurgitation evidence	21/55
Pathologic evidence	10/55
Immunologic progression	4/55
Minor modified Duke Criteria, n/N	
Fever	38/55
Predisposition	27/55
Vascular phenomenon	23/55
Other positive blood culture	4/55

^a More than one diagnostic criterion was used to identify patients with Gram-positive infective endocarditis.

were tested for susceptibility to ceftaroline. Seven of eight tested MRSA isolates [87.5% (7/8)] had a CPT-F minimum inhibitory concentration (MIC) ≤ 1 $\mu\text{g}/\text{mL}$. CPT-F susceptibility was tested in 8.3% (1/12) of MSSA isolates (MIC 2 $\mu\text{g}/\text{mL}$) and in 8.3% (1/12) of CoNS isolates (MIC 0.38 $\mu\text{g}/\text{mL}$).

MRSA was isolated predominantly from blood (72/88 isolates; 87.8%); other sources were tissue from mitral valve regurgitation, intracardiac device lead tips, psoas abscess fluid and respiratory infection, pericardial fluid, pleural tissue, tricuspid valve tissue and heart valve vegetation.

In total, 108 pathogen isolates (CoNS, MRSA, MSSA and others) were identified in the 55 patients with GPIE, including 97/108 (89.8%) from blood, 4/108 (3.7%) from the respiratory tract (including one pleural effusion) and 7/108 (6.5%) from other sources.

3.3. Antibiotic therapy

The mean (SD) duration of inpatient CPT-F therapy was 13.4 (9.7) days, and the median (range) was 11 (2–45) days. Patients received a mean (SD) and median (range) of 29.1 (24.8) and 24 (4–119) doses, respectively, of CPT-F. Most [60% (33/55)] patients received 600 mg, and 35/55 (63.6%) patients received medication at 12-h intervals. Patients could have received more than one dosing or frequency regimen. CPT-F was given as first-line therapy (no prior antibiotic therapy) in 4/55 (7.3%) patients, and as second-line or later therapy (prior antibiotic therapy administered) in 51/55 (92.7%) patients. The most common (>5% of patients) antibiotic therapies given before CPT-F were vancomycin (n=42/55; 76.4%), daptomycin (n=20/55; 36.4%), piperacillin with tazobactam (n=16/55; 29.1%), ceftriaxone (n=10/55; 18.2%), cefepime (n=7/55; 12.7%) and levofloxacin (n=6/55; 10.9%).

CPT-F was used as monotherapy in 23 (41.8%) patients and concurrently with another antibiotic in 32 (58.2%) patients. The most common (>5% of patients) antibiotics given concurrently with CPT-F were daptomycin (n=19/55; 34.5%), vancomycin (n=9/55; 16.4%) and rifampin (n=7/55; 12.7%). Thirty-one of 55 (56.4%) patients were given antibiotics after CPT-F treatment. The most common (>5% of patients) antibiotics used after CPT-F were daptomycin (n=10/55; 18.2%), retreatment with CPT-F (n=8/55; 14.5%) and vancomycin (n=6/55; 10.9%).

3.4. Clinical outcome

A summary of clinical success with CPT-F treatment is provided in Table 3. Details regarding individual patients, type of endocarditis, dosing regimen, and isolated pathogen and outcomes on either monotherapy or concurrent therapy (Table 4) are provided.

Overall, clinical success was observed in 70.9% (39/55) of patients treated with CPT-F. Of those treated with CPT-F as

Table 3
Clinical success rates for ceftaroline fosamil treatment among patients with Gram-positive infective endocarditis.

Clinical success, n/N (%)	Patients (n=55)
Overall clinical success	39/55 (70.9)
Line of therapy	
First-line	3/4 (75.0)
Second-line or later	36/51 (70.6)
Treatment setting	
General hospital ward	19/23 (82.6)
ICU	20/32 (62.5)
Type of endocarditis	
Right-sided	21/26 (80.8)
Left-sided	17/25 (68.0)
Bilateral	1/4 (25.0)
BMI (kg/m ²)	
Underweight (<18.5)	1/1 (100)
Normal (18.5–24.9)	11/14 (78.6)
Overweight (25.0–29.9)	8/15 (53.3)
Obese (≥ 30)	17/23 (73.9)
Type of bacterial infection	
MRSA	34/44 (77.3)
MSSA	1/4 (25.0)
CoNS	3/6 (50.0)
Type of therapy	
Monotherapy	19/23 (82.6)
Concurrent therapy	20/32 (62.5)
Risk factor	
IDU	17/21 (81.0)
IVD	16/24 (66.7)
Dosing regimen	
q8h	16/23 (69.6)
q12h	24/35 (68.6)
q24h	2/3 (66.7)
Treatment duration (days)	
<11	14/26 (53.8)
≥ 11	25/29 (86.2)

BMI, body mass index; CoNS, coagulase-negative staphylococci; ICU, intensive care unit; IDU, injection drug use; IVD, intravascular device; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h.

first-line therapy, clinical success was observed in 75.0% (3/4) of patients; clinical success was observed in 70.6% (36/51) of patients treated with CPT-F as second-line or later therapy. Most patients with right-sided GPIE achieved clinical success [80.8% (21/26)], as did most patients with left-sided GPIE [68.0% (17/25)]. Of the patients with bilateral GPIE, 25.0% (1/4) achieved clinical success. The majority of patients in all body mass index (BMI) groups achieved clinical success, including the patient who was underweight and 78.6% (11/14) and 73.9% (17/23) of normal and obese (BMI ≥ 30 kg/m²) patients, respectively. Slightly more than half of the overweight patients [BMI 25–29.9 kg/m²; 53.3% (8/15)] achieved clinical success.

Clinical success was observed in 77.3% (34/44) of patients with MRSA, 25% (1/4) of patients with MSSA, 50% (3/6) of patients with CoNS, 100% (1/1) of patients with *E. faecalis* when CPT-F was given in combination with ampicillin, and 100% (1/1) of patients with *S. mutans*. Clinical success was observed in 82.6% (19/23) of patients treated with CPT-F as monotherapy. Among all patients treated with concurrent antibiotics, clinical success was observed in 62.5% (20/32), including 63.2% (12/19) of patients treated with daptomycin, 57.1% (4/7) treated with rifampin and 55.6% (5/9) treated with vancomycin. Clinical success was observed in 66.7% (16/24) of patients not given subsequent treatment with antibiotics after CPT-F treatment. Clinical success of patients given either monotherapy or combination therapy, stratified by type of endocarditis, was calculated (Table 4).

In patients treated with additional antibiotics after treatment with CPT-F based on the clinical judgement of the treating

Table 4
Details related to type of endocarditis, dosing regimen, pathogen and clinical outcome in patients treated with ceftaroline fosamil (CPT-F) therapy.

Patient	Type of endocarditis	Dosing regimen	Pathogen	Outcome ^a	Details related to outcome	
Monotherapy						
1	Right-sided	600 mg, q12h	<i>Staphylococcus epidermidis</i>	Failure	Insufficient therapeutic effect and switch to another antibiotic	
2	Left-sided	400 mg, q12h	MRSA	Success	Patient discharged on ceftaroline, IV for 35 days	
3	Right-sided	400 mg, q8h; 400 mg, q12h; 600 mg, q8h	MRSA	Success	Continue therapy as outpatient	
4	Right-sided	200 mg, q8h; 300 mg, q8h; 400 mg, q8h; 600 mg, q8h	CoNS	Success	Clinical cure with no further need for antibiotic	
5	Left-sided	600 mg, q8h	MSSA	Failure	Adverse event	
6	Left-sided	300 mg q12h; 400 mg, q12h	MRSA	Success	Discharged on ceftaroline	
7	Right-sided	600 mg, q12h	MRSA	Success	Patient refused IV therapy, discharged on oral antibiotics	
8	Right-sided	400 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic	
9 ^b	Left-sided	200 mg, q12h	MRSA	Success	Clinical cure with no further need of antibiotic	
10	Left-sided	200 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic/ clinical improvement with discharge on IV ceftaroline	
11	Bilateral	600 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic/ clinical improvement with discharge on IV ceftaroline	
12	Right-sided	200 mg q12h; 300 mg q12h	MRSA	Success	Clinical improvement with switch to another antibiotic	
13	Left-sided	600 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic	
14	Right-sided	600 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic/ patient discharged on ceftaroline	
15	Right-sided	600 mg, q12h	MRSA	Success	Clinical improvement with switch to another antibiotic/ patient discharged on ceftaroline	
16	Left-sided	400 mg, q12h	MRSA	Success	Developed bacteraemia and <i>Escherichia coli</i> bacteraemia, changed to ertapenem and linezolid	
17	Right-sided	600 mg, q8h	MRSA	Success	Clinical improvement with switch to another antibiotic	
18	Left-sided	600 mg q24h, 300 mg q12h	MRSA	Success	Clinical improvement with switch to another antibiotic	
19	Left-sided	600 mg, q8h	<i>Streptococcus mutans</i>	Success	Clinical improvement with switch to another antibiotic	
20	Right-sided	300 mg, q12h	MRSA	Success	Clinical cure (no need for further antibiotic)/discharged with ceftaroline for 14 more days	
21 ^b	Left-sided	300 mg, q12h	MRSA	Failure	Death	
22	Left-sided	600 mg, q8h	MSSA	Failure	Cultures grew MSSA with switch to nafcillin	
23 ^b	Left-sided	300 mg, q8h	MRSA	Success	Ceftaroline continued for 6–8 weeks at rehabilitation	
Concurrent therapy						
24	Bilateral	600 mg, q12h	MSSA	Failure	Daptomycin, gentamicin, piperacillin with tazobactam	Death
25	Bilateral	600 mg, q12h	MRSA	Failure	Tobramycin	Death
26	Right-sided	600 mg, q12h	MRSA	Success	Daptomycin	Clinical improvement with continuation of concurrent antibiotic
27	Right-sided	600 mg, q8h	MRSA	Success	Daptomycin	Clinical cure with no further need of antibiotic
28	Right-sided	300 mg, q8h	MRSA	Success	Doripenem, linezolid	Clinical improvement with switch to another antibiotic
29	Right-sided	600 mg, q12h	CoNS	Success	Vancomycin	Clinical improvement with switch to another antibiotic
30 ^b	Left-sided	400 mg, q12h	CoNS	Success	Daptomycin, vancomycin	Clinical improvement with switch to another antibiotic
31	Right-sided	600 mg, q12h	MRSA	Success	Daptomycin, rifampicin, vancomycin	Clinical improvement with switch to another antibiotic
32	Left-sided	600 mg, q12h	CoNS	Failure	Daptomycin, gentamicin, vancomycin	Concern regarding possibility of <i>Clostridium difficile</i> colitis (no positive stool)
33	Left-sided	200 mg, q12h; 300 mg, q8h; 200 mg q8h; 600 mg q8h	MRSA	Failure	Vancomycin	Sterilized blood; however, had massive left middle cerebral artery/posterior cerebral artery stroke, likely septic emboli, acute renal failure, sepsis, cardiomyopathy
34	Right-sided	400 mg, q8h	MRSA	Success	Daptomycin	Clinical improvement with switch to another antibiotic; discharged with ceftaroline to complete 14-day treatment
35	Left-sided	600 mg, q8h	MRSA	Success	Doxycycline, gentamycin, imipenem, metronidazole, rifampicin	Cleared blood culture but had valvular vegetations, became septic, cardiomyopathy
36	Right-sided	600 mg, q8h	MRSA	Success	Daptomycin	Clinical cure with no further need of antibiotic
37	Right-sided	600 mg, q8h	MRSA	Success	Daptomycin	Clinical cure with no further need of antibiotic
38	Right-sided	400 mg, q12h, 300 mg, q12h	MRSA	Failure	Daptomycin, rifampicin, vancomycin	Death
39	Right-sided	600 mg, q12h	MRSA	Success	Daptomycin	Clinical improvement with switch to another antibiotic

(continued on next page)

Table 4 (continued)

Patient	Type of endocarditis	Dosing regimen	Pathogen	Outcome ^a	Details related to outcome	
40	Right-sided	600 mg, q12h; 300 mg q12h	MRSA	Failure	Daptomycin, piperacillin with tazobactam, rifampicin	Death (organ failure)
41	Left-sided	600 mg, q24h	MRSA	Success	Ciprofloxacin, daptomycin	Clinical improvement with switch to another antibiotic
42	Right-sided	600 mg, q8h	MRSA	Failure	Daptomycin	Transferred to another hospital
43	Bilateral	400 mg, q8h, 300 mg, q8h, 200 mg q8h	<i>Staphylococcus epidermis</i>	Failure	Azithromycin, daptomycin, meropenem, piperacillin with tazobactam	Death (disease progression)
44	Right-sided	600 mg, q8h; 600 mg q12h; 400 mg, q12h	MRSA	Success	Daptomycin, vancomycin	Clinical improvement with switch to another antibiotic
45	Left-sided	400 mg q8h; 600 mg q8h	MRSA	Success	Rifampicin	Clinical improvement with switch to another antibiotic
46	Right-sided	300 mg, q12h	MRSA	Failure	Vancomycin	Adverse event
47 ^b	Left-sided	200 mg, q8h	MRSA	Failure	Daptomycin, gentamicin, rifampicin	Persistent MRSA bacteraemia because source control needed and patient was not a surgical candidate
48	Left-sided	400 mg, q8h	MRSA	Success	Vancomycin	Combination therapy with vancomycin and ceftaroline was changed to vancomycin alone
49	Left-sided	300 mg, q12h; 300 mg, q24h; 400 mg, q24h	MRSA	Failure	Meropenem, metronidazole	Comfort care; all treatment withdrawn
50	Right-sided	600 mg, q8h	MRSA	Success	Daptomycin	Clinical improvement with switch to another antibiotic
51	Left-sided	400 mg, q12h	MRSA	Success	Daptomycin	Clinical improvement with switch to another antibiotic
52	Left-sided	400 mg, q12h	<i>Enterococcus faecalis</i>	Success	Ampicillin	Excellent response with continuation of ceftaroline and ampicillin
53	Left-sided	600 mg, q12h; 600 mg, q8h;	MRSA	Failure	Clindamycin, levofloxacin	Comfort care
54 ^b	Left-sided	200 mg, q8h	MRSA	Success	Cefazolin, ciprofloxacin, linezolid, meropenem, rifampicin	Clinical improvement with switch to another antibiotic
55	Right-sided	600 mg, q12h	MSSA MRSA	Success	Cefazolin, cefepime, penicillin G	MSSA switched to cefazolin

CoNS, coagulase-negative staphylococci; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours.

^a Overall clinical success rates were: 90.0% (9/10), 75.0% (9/12) and 100% (1/1) for right-sided, left-sided and bilateral endocarditis, respectively, with monotherapy, and 75.0% (12/16), 61.5% (8/13) and 0% (1/1), respectively, with concurrent therapy.

^b Patients who had a previous history of haemodialysis; doses of CPT-F were adjusted as a result of this status.

physician, clinical success was observed in 74.2% (23/31) of patients, including 100% (6/6) of patients treated with vancomycin and 70% (7/10) of patients treated with daptomycin. Overall, 3/55 patients (5.5%) were switched from CPT-F treatment to another antibiotic due to insufficient therapeutic effect with CPT-F.

Keeping in mind that patients could have received more than one treatment regimen, clinical success was observed in 69.6% (16/23) of patients treated with CPT-F every 8 h, and in 68.6% (24/35) and 66.7% (2/3) of patients treated every 12 and 24 h, respectively.

Two (3.6%) patients discontinued treatment with CPT-F because of an adverse event (acute kidney injury, rash): one patient was given CPT-F as monotherapy, and one patient was given CPT-F in combination with vancomycin.

4. Discussion

Overall, the clinical success rate with CPT-F therapy was high among patients with GPIE regardless of location of care (ICU vs. general hospital ward), location of infection (left- vs. right-sided) or presence of risk factors, including IDU and IVD. Of note, clinical success rates were high in patients with GPIE caused by MRSA; this finding was significant because MRSA was the most commonly isolated pathogen in the study population, and because IE caused by MRSA carries a greater risk of mortality and morbidity compared with other pathogens [17]. Patients treated with CPT-F as monotherapy experienced a higher rate of clinical success compared with patients who received CPT-F with concurrent therapy.

The high rate of success observed with second-line or later CPT-F treatment is also an important finding because this is likely a better representation of contemporary clinical practice, in which CPT-F is selected as second-line or later therapy for GPIE. The fact that CPT-F was mainly used as second-line or later therapy in this study may also explain the relatively short duration of treatment. Similar to previous reports [11,12], the low number of discontinuations due to adverse events demonstrates that CPT-F was well tolerated, albeit for a relatively short treatment duration.

Three case reports showed that CPT-F treatment produced clinical success in 88.9% (8/9), 60.0% (3/5) and 100% (3/3) of patients with GPIE caused by MRSA infection after prior antibiotic therapy, primarily daptomycin and vancomycin [15,18,19]. Although the number of patients in these case reports is low, the expanded data set provided by CAPTURE suggests that CPT-F holds the potential to provide clinical benefit in patients with GPIE, particularly in cases caused by MRSA infection in which prior antibiotic therapy failed to provide clinical cure.

The limitations of this study are inherent to a retrospective study, and the study design did not include a comparator arm. Data, including microbiological and clinical, were limited to those entered in patient charts, and the total population of GPIE patients was small. Ceftaroline susceptibility data for study isolates were limited. However, CPT-F activity vs. Gram-positive pathogens is well established; for example, 97.6% of 12 514 MRSA strains tested over a 5-year period (2009–2013) were susceptible to CPT-F [20]. Additionally, data regarding duration of antibiotic therapy before CPT-F initiation were not collected. Outcome data were only

collected during hospitalization, despite many patients completing long-term antibiotic therapy after discharge. Due to the method of data collection, interpretation of the findings is also limited by the ability to pinpoint exactly which antibiotic was given in a specific time frame, as well as a lack of information regarding the duration of overlapping, concurrent therapy. Additional limitations include the fact that this was a secondary, subgroup analysis and not the primary analysis of CAPTURE; and that ceftaroline was analysed mostly as second-line or salvage therapy. Finally, the study represented a mixture of right-, left- and bilateral endocarditis patients.

CPT-F treatment was associated with clinical success in patients with GPIE during their hospitalization, including patients with known risk factors for poor outcome. Patients with GPIE caused by MRSA experienced a high rate of clinical success, as did those who received CPT-F as second-line or later therapy. Additional, appropriately designed, clinical studies will be required to determine the role of CPT-F as monotherapy as well as part of combination therapy regimens in patients with GPIE.

5. Conclusions

The clinical success rate with CPT-F therapy was high among patients with GPIE regardless of location of care (ICU vs. general hospital ward), location of infection (left- vs. right-sided) and the presence of risk factors, including IDU and IVD. Furthermore, clinical success rates were high in patients with GPIE caused by MRSA. Patients treated with CPT-F as monotherapy experienced a higher rate of clinical success compared with patients who received CPT-F with concurrent therapy. The high rate of success observed with second-line or later treatment is also an important finding because this is likely a better representation of contemporary clinical practice, in which CPT-F is selected as second-line or later therapy for GPIE. Similar to previous reports, the low number of discontinuations due to adverse events demonstrates that CPT-F was well tolerated, albeit for a relatively short treatment duration.

Acknowledgements

Writing and editorial assistance was provided to the authors by Todd J. Waldron, PhD, Jennifer L. Venzie, PhD, and John E. Fincke, PhD, of Complete Healthcare Communications, LLC (North Wales, PA, USA) and funded by Allergan plc (Dublin, Ireland). All authors met the International Committee of Medical Journal Editors authorship criteria. Neither honoraria nor payments were made for authorship.

Funding

This work was supported by Allergan plc (Dublin, Ireland). Other than supporting the work and providing funding for writing and editorial assistance, Allergan played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Competing interests

CJD and DJG have received clinical research support from Durata Therapeutics, Inc. (now Allergan plc). KSK has served as a consultant for Allergan plc, for which he received consulting fees.

Ethical approval

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Registration of Phar-

maceuticals for Human Use and met all institutional review board requirements before initiation. Patient consent was collected before data extraction as appropriate based on the institutional review board requirements of individual sites.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2019.01.014](https://doi.org/10.1016/j.ijantimicag.2019.01.014).

References

- [1] Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis Prospective Cohort Study. *Arch Intern Med* 2009;169:463–73.
- [2] Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation* 2005;112:69–75.
- [3] Netzer ROM, Altwegg SC, Zollinger E, Täuber M, Carrel T, Seiler C. Infective endocarditis: determinants of long term outcome. *Heart* 2002;88:61–6.
- [4] Bor DH, Woolhandler S, Nardin R, Brusck J, Himmelstein DU. Infective endocarditis in the U.S., 1998–2009: a nationwide study. *PLoS One* 2013;8:e60033.
- [5] Castillo JC, Anguita MP, Ramirez A, Siles JR, Torres F, Mesa D, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. *Heart* 2000;83:525–30.
- [6] Chopra T, Kaatz GW. Treatment strategies for infective endocarditis. *Exp Opin Pharmacother* 2010;11:345–60.
- [7] Thanavaro KL, Nixon JV. Endocarditis 2014: an update. *Heart Lung* 2014;43:334–7.
- [8] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–8.
- [9] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075–128.
- [10] Teflaro® (ceftaroline fosamil). Full prescribing information. Dublin: Allergan plc; 2016.
- [11] File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 1: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother* 2011;66:19–32 iii.
- [12] Low DE, File TM Jr, Eckburg PB, Talbot GH, David Friedland H, Lee J, et al. FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother* 2011;66:33–44 iii.
- [13] Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T, et al. CANVAS 1: the first phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010;65:41–51 iv.
- [14] Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T, et al. CANVAS 2: the second phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother* 2010;65:53–65 iv.
- [15] Ho TT, Cadena J, Childs LM, Gonzalez-Velez M, Lewis JS 2nd. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. *J Antimicrob Chemother* 2012;67:1267–70.
- [16] Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. *Antimicrob Agents Chemother* 2014;58:2541–6.
- [17] Chang FY, MacDonald BB, Peacock JE Jr, Musher DM, Triplett P, Mlytle JM, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. *Medicine (Baltimore)* 2003;82:322–32.
- [18] Polenakovic HM, Pleiman CM. Ceftaroline for methicillin-resistant *Staphylococcus aureus* bacteraemia: case series and review of the literature. *Int J Antimicrob Agents* 2013;42:450–5.
- [19] Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. *J Infect Chemother* 2013;19:42–9.
- [20] Sader HS, Flamm RK, Streit JM, Farrell DJ, Jones RN. Ceftaroline activity against bacterial pathogens frequently isolated in U.S. medical centers: results from five years of the AWARE surveillance program. *Antimicrob Agents Chemother* 2015;59:2458–61.