

CEFTAROLINE AS SALVAGE THERAPY FOR METHICILLIN SUSCEPTIBLE *STAPHYLOCOCCUS AUREUS* COMPLICATED BACTEREMIA

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Abstract Infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) are still associated with significant morbidity and mortality. Treatment failures of cefazolin (CFZ) have been reported and probably related to the inoculum effect. New treatments for severe MSSA infections are needed and ceftaroline fosamil (CPT) could be an option. Our aim was to describe the clinical characteristics of five patients with complicated MSSA bacteremia failing CFZ and successfully treated with CPT. We performed a retrospective chart review in a Hospital in Buenos Aires, Argentina; in a 12-month period, five patients (24%) of 21 with MSSA bacteremia experienced CFZ failure and were salvaged with CPT. The median time of CFZ therapy was 10 days before changing to CPT; four patients had evidence of metastatic spread and 2 had endocarditis. All patients experienced microbiological and clinical cure with CPT, which was used as monotherapy in 4 and in combination with daptomycin in another. One patient discontinued CPT due to neutropenia on day 23 of treatment. In patients with MSSA BSI failing current therapy, CPT could be a good therapeutic option.

Key words: *Staphylococcus aureus*, ceftaroline, endocarditis, cefazolin, methicillin-susceptible *Staphylococcus aureus*

Resumen *Ceftarolina como tratamiento de rescate para la bacteriemia complicada por Staphylococcus aureus sensible a la metilina*

Las infecciones causadas por *Staphylococcus aureus* sensible a la metilina (SASM) todavía se asocian con una morbilidad y mortalidad significativas. Se han informado fallas en el tratamiento de cefazolina (CFZ) probablemente relacionadas con efecto inóculo. Nuevos tratamientos son necesarios para estas infecciones y ceftarolina fosamil (CPT) podría ser una opción. Nuestro objetivo fue describir las características clínicas de cinco pacientes con bacteriemia por SASM complicada con falla a CFZ y que fueron exitosamente tratados con CPT. Realizamos una revisión retrospectiva de historias clínicas en un hospital de Buenos Aires, Argentina; en un período de 12 meses, cinco pacientes (24%) de 21 con bacteriemia por SASM experimentaron falla a CFZ y fueron tratados con CPT. La mediana de tiempo de la terapia con CFZ fue de 10 días antes de cambiar a CPT; cuatro pacientes presentaban evidencia de diseminación metastásica y 2 tenían endocarditis. Todos los pacientes experimentaron curación microbiológica y clínica con CPT, que se utilizó como monoterapia en 4 y en combinación con daptomicina en otro. Un paciente interrumpió CPT debido a neutropenia el día 23 de tratamiento. En enfermos con infecciones graves por SASM que fallan en la terapia actual, CPT podría ser una buena opción terapéutica.

Palabras clave: *Staphylococcus aureus*, ceftarolina, endocarditis, cefazolina, *Staphylococcus aureus* sensible a metilina

Infections caused by *Staphylococcus aureus* are associated with considerable morbidity and mortality¹. Methicillin-susceptible *S. aureus* (MSSA) infections have increased in recent years. In many regions of the world, the burden of the *S. aureus* infection is taken now by MSSA². For example, in Europe, bloodstream infections (BSI) caused by *S. aureus* experienced a 84% increase

of MSSA between 2005 and 2018³. The same scenario appears to be happening in Argentina where, during 2019, 59.1% of the *S. aureus* bloodstream isolates were MSSA⁴.

First generation cephalosporins (1GC) such as cefazolin (CFZ) and anti-staphylococcal penicillins (ASP) are the preferred agents for invasive MSSA infections. Recent studies favored CFZ over ASPs since it was associated with less toxicity and possibly improved survival rates⁵. However, in high bacterial burden infections, failures of CFZ have been reported and related to the activity of staphylococcal β -lactamases causing inoculum effect (IE)⁶⁻⁸. Indeed, a word of caution was given for using CFZ

Received: 4-V-2022

Accepted: 12-VII-2022

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in severe MSSA cases, at least initially or until the CFZ IE could be ruled out⁹.

Novel treatment strategies are needed for severe MSSA infections. In this regard, ceftaroline fosamil (CPT) maintained its activity in vitro against β-lactamase-producing MSSA strains at high inoculum and in vivo, in an endocarditis model⁷. Nowadays, CPT is prescribed in many off label indications with good clinical responses¹⁰. Since CPT might be an option for non-responding MSSA infections, clinical data on its use are crucial.

Our primary objective was to report a series of cases with complicated MSSA BSI experiencing treatment failure of intravenous 1GC treated with CPT as salvage therapy. We performed a retrospective chart review of patients with MSSA BSI failing 1GC treatment, between June 2018 and June 2019, that were hospitalized in a 200-beds hospital in La Plata, Buenos Aires, Argentina. It should be noted that in Argentina ASPs are not commercially available and the existing 1GCs are CFZ and cephalothin. We defined treatment failure as persistent positive blood cultures for more than 4 days despite appropriate treatment and source control. Clearance of bacteremia together with resolution of all signs and symptoms of infection with no further need for antibiotic during hospitalization were required for clinical success. Clinical and microbiological features were retrospectively recorded. Clinical strains were not available for analysis.

Information collected for the study had been recorded in institutional charts as standard of care. Personal identifiable information was anonymized before disclosure by data protection policies. The project was approved by the local Ethical Committee and the need for a signed consent form was waived.

Report of cases

During the 12-month study period, 32 *S. aureus* bacteremia episodes were identified, 21 (67%) of which were caused by MSSA. Five of these cases (24%) experienced clinical failure to 1GC. All the isolates were susceptible to CPT by disk diffusion, and only one showed erythromycin and clindamycin resistance. Clinical data of these patients are shown in Table 1.

Clinical case 1

A 71-year-old diabetic man was admitted with fever and left knee pain. He had history of joint knee replacement surgery 5 years prior and a cardiac pacemaker placement 3 years. At admission, blood cultures were positive for MSSA. He was treated with vancomycin for 48 hours, replaced by CFZ (2 g every 8 hours) when susceptibilities were available. Knee prosthetic-joint infection (PJI) was diagnosed and debridement with prosthetic removal was required on day 3. Intraoperative samples also yielded MSSA. On day 5 the patient still had positive blood cultures and fever; CFZ was changed for CPT and a second source control surgery was performed. Blood cultures cleared within 2 days after antimicrobial switch. Trans-esophageal echocardiogram (TEE) ruled out endocarditis.

TABLE 1.— Series of patients treated with ceftaroline as salvage therapy in methicillin susceptible *S. aureus* complicated bacteremia

Case	Age	Origin*	Source of bacteremia	Infective endocarditis	Metastatic foci	Anti-staphylococcal agents	Days failing prior to CPT	CPT dose and duration	Time to negative blood cultures after CPT initiation	Clinical cure	Adverse events
1	71	CA	Primary bacteremia	No	Late PJI (knee)	Vancomycin, cefazolin	5	600 mg q12h for 17 ds	2 ds	Yes	No
2	53	HA	SSI, early PJI (hip)	No	No	Cefazolin	7	600 mg q8h for 23 ds	7 ds	Yes	No
3	58	CA	Primary bacteremia	Yes, aortic valve	Epidural abscess	Cefazolin	11	600 mg q12h for 28 ds	2 ds	Yes	No
4	51	CA	Primary bacteremia	Yes, aortic valve	Epidural abscess, septic arthritis	Vancomycin, cefazolin	10	600 mg q12h for 23 ds	2 ds	Yes	Yes, leukopenia
5	49	CA	Primary bacteremia	No	Gluteal pyomyositis	Cefazolin	10	600 mg q8h for 3 ds followed by 600 mg q12h for 18 ds	3 ds	Yes	No

SSI: surgical site infection; PJI: prosthetic joint infection; CA: community-acquired; HA: hospital-acquired; CPT: ceftaroline; q8h: every 8 hours; q12h: every 12 hours; ds: days

Patient improved and was discharged home on hospital day 21 to complete a 12-week course of oral minocycline.

Clinical case 2

A 53-year-old woman with hip PJI was admitted for definitive prosthesis implantation. One week after arthroplasty, she developed signs of surgical site infection and MSSA bacteremia. She underwent surgical debridement (MSSA grew from intraoperative samples) and CFZ (2 g every 8 hours) was started. One week later, the patient had persistent fever, local signs of infection, and positive blood cultures. Antibiotic treatment was changed to CPT; 2 more surgical debridement were required but tissue cultures were negative. After 48 hours of CPT, fever resolved and blood cultures obtained on day 7 after antibiotic switch were negative. She was discharged on day 23 of CPT therapy to continue oral trimethoprim-sulfamethoxazole and rifampicin.

Clinical case 3

A 57-year-old man with psoriasis was admitted with fever, back pain and MSSA bacteremia. An epidural abscess was diagnosed and required surgical drainage on day 5 after admission. Spinal specimen grew MSSA. He was treated with CFZ (2 g every 8 hours). Three days after surgery he remained febrile with positive blood cultures, and a TEE informed a 4 mm aortic valve vegetation. Therapy was changed to daptomycin (10 mg/kg/day) but 72 hours later the patient was still febrile with positive blood cultures. No further surgery was considered necessary for the epidural abscess. On day 11, CPT was added and 48 hours later, patient's clinical status improved and blood cultures were negative. Daptomycin was stopped after 8 days and CPT continued for 4 more weeks stepping-down to oral trimethoprim-sulfamethoxazole with clinical recovery.

Clinical case 4

A 51-year-old man was admitted with fever. He received vancomycin for 48 hours, changed to CFZ (2 g every 8 hours) when blood cultures showed growth of MSSA. Due to persistent fever and new onset back pain, an MRI on day 6 showed an epidural abscess that required laminectomy and surgical drainage on day 8. MSSA grew again on intraoperative samples. After surgery, patient remained febrile and blood cultures obtained 48 hours later were again positive for MSSA. On day 10, CPT replaced CFZ, and 48 hours later blood culture cleared and he became afebrile. Aortic valve endocarditis was diagnosed on day 10 based on a TEE showing two small vegetations. Patient showed significant improvement. On day 23 of CPT therapy, CFZ replaced CPT due to neutropenia. During hospital stay, he was diagnosed of catheter-associated candidemia. After completion of a 6-week and 3-week course treatment for MSSA endocarditis and candidemia, respectively, he was discharged home.

Clinical case 5

A 49-year-old woman with history diabetes was admitted with back pain, fever, and positive blood cultures for MSSA. She was started on CFZ 2 g every 8 hours; 4 days after admission lumbar MRI showed no signs of infection. Patient had positive blood cultures for MSSA on days 3, 6, and 9 after treatment initiation. A TEE showed no valve vegetations, but a repeated MRI displayed signs of pyomyositis of right gluteal muscle and L5-S1 discitis. On day 10, treatment was switched to CPT and blood cultures were negative within 72 hours. CPT was

administered for 3 weeks followed by oral levofloxacin plus rifampin for 4 more weeks with good clinical outcome.

Discussion

The impact of MSSA infections on the health system is substantial⁴. During the study period, MSSA accounted for 67% of the *S. aureus* BSI documented at this institution. Five of these patients failed CFZ therapy (24%) for a median of 10 days (range: 5-11 days). Four patients developed a metastatic site of infection and 2 had definitive diagnosis of aortic valve endocarditis. CPT was administered in a dose of 600 mg every 12 hours in 3 patients, and every 8 hours in 2 cases. One patient discontinued CPT due to neutropenia after 23 days of treatment, an adverse event reported in 21% of those treated for more than 3 weeks¹¹.

Effective therapeutic options are needed for severe MSSA infections and CPT could be an attractive agent. All patients included here received CPT for the off label indication persistent MSSA bacteremia, as reported in a real world study, which showed the effectiveness of CPT for patients with MRSA bacteremia¹⁰. For example, in combination with daptomycin, CPT was highly successful in an open-label randomized trial of MRSA bacteremia¹². Studies for combination therapy for MSSA BSI are scarce. The addition of daptomycin (6 mg/kg/day) to the anti-staphylococcal β -lactam did not affect the duration of bacteremia nor the 90-days mortality rate, although it did decrease the rate of ongoing MSSA infections among deaths¹³. CFZ plus ertapenem was successfully combined in 11 patients with persistent MSSA bacteremia and in an endocarditis model using an MSSA strain with CFZ IE¹⁴. These authors proposed that the inhibitory effect of ertapenem on penicillin-binding protein (PBP)-1 would complement CFZ activity, that primarily binds to PBP-2¹⁴.

Several reports have documented CFZ failure in severe MSSA infections, presumably due to the IE⁶⁻⁸. A high prevalence of CFZ IE (54%) have been observed among MSSA isolates in Argentina causing significant increase in the 30-day mortality rate¹⁵. Unfortunately, the infecting strains from this report are not available for IE determination. Of note, a test to identify MSSA isolates harboring the CFZ IE trait has been recently developed¹⁶, and might be useful to better define an effective therapy.

In conclusion, we describe a 24% rate of patients with MSSA BSI failing CFZ therapy that were successfully treated with CPT. This cephalosporin could be a therapeutic option for these cases since it is not affected by the IE in vitro, it was effective in the endocarditis model, and it is currently used for diverse MRSA infections.

Conflict of interest: Esteban C. Nannini reports personal fees from Merck Sharp & Dohme, and grants from Pfizer, Janssen, and Basilea, outside the submitted work. The other authors none to declare.

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