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Letter to the Editor

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Use of ceftaroline in complex central nervous system infections

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Sir,

Ceftaroline fosamil is a fifth-generation cephalosporin approved for skin and soft tissue infections and pneumonia, but its use in out-off-label indications is increasing, as we have previously reported in this journal [1]. It is particularly valuable in serious infections with participation of resistant gram-positive microorganisms, in which other options as vancomycin, linezolid or daptomycin may be restricted because of adverse effects or low efficacy. Few data are available about its use in central nervous system (CNS) infections.

In the last 5 years, we have recorded 5 CNS infections treated with ceftaroline [1]. We here present two of them which were evaluable.

Case 1

A 67-year-old woman was admitted due to fever and gait instability. She was carrying a ventriculoperitoneal shunt device placed 10 years ago. Blood cultures were obtained, and methicillin-susceptible *Staphylococcus aureus* (MSSA) grew 23 hours later in 2 of 2 sets. MIC to vancomycin was 2 mg/L using microdilution and 1.5 mg/L by E-test. A sample of cerebrospinal fluid (CSF) was obtained from the ventriculoperitoneal shunt reservoir. Gram stain revealed Gram-positive cocci in grape-like clusters and MSSA grew in aerobic culture. Infection of the ventriculoperitoneal shunt was then confirmed and the device was removed. While waiting for definite antibiotic susceptibility testing and confirming microbiological clearance in repeated blood cultures, ceftaroline (600mg every 8 hours) was employed for the first 7 days and then switched to cloxacillin plus linezolid. After 2 weeks of antibiotic treatment, CSF culture was negative, ventriculoperitoneal shunt was replaced, and patient was discharged one week afterwards.

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Case 2

A 77-year-old man was admitted due to traumatic brain injury with a subdural hematoma. A craniotomy was performed. 2 months later cranioplasty with autologous bone was made, and 1 week afterwards patient developed a subdural empyema in surgical site. Re-intervention was performed, collection was removed, and culture showed polymicrobial growth of EBSL-producing *Escherichia Coli, Enterococcus faecalis*, methicillin-resistant and linezolid-resistant (MIC > 4 mg/L) *Staphylococcus epidermidis* and *Corynebacterium amycolatum*. Treatment was initiated with meropenem and vancomycin. Nevertheless, CT scan performed 2 weeks later revealed worsening of the epidural collection with data suggestive of cerebritis. Surgical debridement was made again and autologous bone plasty was removed. Antibiotic therapy was changed to meropenem + ceftaroline (600mg every 8 hours) and maintained for 4 weeks. CT scan then showed resolution of the collection.

These two cases show the usefulness of ceftaroline for complicated CNS infections in which resistant-gram positive microorganisms' participation is suspected. The first case is an infection of ventriculoperitoneal shunt by MSSA with secondary bacteriemia. While waiting for susceptibility test, daptomycin was considered inappropriate as first-line therapy because of its low penetration in CSF, as it was linezolid for its bacteriostatic effect in bacteriemia. The second case is a complex patient with post-surgical epidural empyema with multi-resistant isolations. Here, ceftaroline was used against methicillin-resistant *S. epidermidis* after clinical failure with vancomycin, being linezolid ruled out because of resistance.

Available literature in this scenario is scarce. A large retrospective study conducted by Britt et al. evaluated ceftaroline in 764 patients, 2% of which had meningitis. Mortality was low (6%), but microbiological etiology or causes of death were not provided [2]. Martin-Cerezuela et al performed a retrospective study involving patients with *Streptococcus pneumo-*

niae penicillin-susceptible meningitis, comparing ceftaroline (n=5) and standard therapy (n=20). There was a non-statistically significant lower mortality in ceftaroline group (0% vs 40%, P=0,016) despite of being more severe cases [3]. Most experience comes from case series, including some regarding ceftaroline use in epidural abscess, mainly due to MRSA, with promising results [4-6]. Skoulas et al described 5 patients with gram positive bacterial meningitis (4 due to *S. pneumoniae,* of which one was penicillin-resistant, and 1 MSSA). Four of them treated with 600mg of ceftaroline fosamil every 8 hours were successful whilst the other one with 600mg very 12 hours failed [7]. Both cases reported here were treated with 600mg every 8 hours.

Little is known about CSF penetration of ceftaroline. Chauzy et al reported a mean of 9% in a series of 11 patients with external ventricular drain, but without meningeal inflammation [8]. However, this penetration can be enhanced with meningeal inflammation, as showed by Helfer et alt [9]. In fact, animal models of meningitis show variable rates from 15 to 51%. Ceftaroline was no-inferior to vancomycin in an animal study of meningitis by SARM and was superior to ceftriaxone in meningitis by penicillin-susceptible *S. pneumoniae* and to combination of ceftriaxone plus vancomycin in penicillin-resistant pneumococcal meningitis [10-11].

In summary, ceftaroline fosamil administrated 600mg iv every 8 hours is an attractive option in CNS infections. Although there is little experience in meningitis by penicillin-resistant *S. pneumoniae* or MRSA, its penetration in CSF is like other third-generation cephalosporins and better to vancomycin, which together with its higher in vitro activity makes it an interesting option in this scenario. In neurosurgical infections by linezolid-resistant *S. epidermidis* – an emerging problem with taxes of 17% in our center- ceftaroline could be the best choice, as it was in our second case.

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CONFLICTS OF INTEREST

Authors declare no conflict of interest

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