Ceftaroline versus standard therapy for pneumococcal meningitis in critically ill patients

Ceftarolina frente a terapia antibiótica estándar para meningitis pneumocócica en pacientes críticos

Dear Editor:

Community-acquired bacterial meningitis (CABM) remains an important health problem due to its morbidity and mortality, specially in critical care units (CCU) where the severity of the disease increases mortality from 15 up to 47%.[1]

Streptococcus pneumoniae is the most frequent aetiology for CABM in adults, reaching to 75–80% of all bacterial meningitis cases,[2] but despite a high mortality, guidelines keep on recommending the same empirical antibiotic pattern since 2004.

Recently, ceftaroline, a fifth-generation cephalosporine with an approved indication for community-acquired bacterial pneumonia, has shown potential benefits for meningitis, opening the possibility for its use in CABM. The objective of our study was to evaluate the effectiveness of cetaroline in critically ill patients with CABM.

A retrospective, observational study including patients admitted to our CCU because of *S. pneumoniae* CABM from 2014–2019 was conducted. Participants received ceftaroline or standard therapy according to medical criteria. Primary outcome was 30-day mortality. Secondary outcomes were clinical response (if all signs and symptoms present at the time of diagnosis had improved or disappeared), need for invasive mechanical ventilation (IMV), length of stay and meningitis complications.

The quantitative variables were obtained as median (IQR), the qualitative as percentages. For the comparison, chi-square or Fisher's exact test was used for categorical variables and Student *t*-test or Mann–Whitney *U* for continuous variables. The hospital's ethic committee approved the project; informed consent was waived due to the retrospective nature of the study.

Twenty-five patients were included, five received ceftaroline, twenty were treated with other drugs. The demographical date are depicted in Table 1. Ceftaroline patients presented in a more severe condition by APACHE II (24 [22–33] vs. 18 [13–22], $p = 0.035$) and SAPS III scores (82 [60–88] vs. 51 [43–65], $p = 0.024$), septic shock rate at CABM diagnosis (60% vs. 10%, $p = 0.038$) and need for IMV (100% vs. 50%, $p = 0.041$). Biochemical and microbiological results from cerebrospinal fluid (CSF) and blood at diagnosis were similar in both groups, except for serum procalcitonin which was significantly higher in the ceftaroline group (21.16 [16.81–25.50] vs. 2.80 [1.84–7.25] ng/mL, $p = 0.039$).

All patients received appropriate empirical treatment. In the standard group, 19 (95%) patients received ceftriaxone (2 g/12 h) for a median of 14 days [9–20.5], in combination with linezolid (600 mg/12 h) for a median of 5 days [3–13] in 13 patients (65%) or vancomycin (15 mg/kg/day) for a median of 4 days [2–14] in 7 patients (35%). In 5 patients (25%) ampicillin (2 g/6 h) was added to the combination. One patient was treated with clindamycin, linezolid and levofloxacin due to beta-lactam allergy. All *Streptococcus pneumoniae* isolated in microbiological culture were susceptible to ceftriaxone (CMI $\leq$ 0.25 mg/L) or cefotaxime (CMI $\leq$ 1 mg/L). Nineteen patients (95%) were also treated with steroids for a median of 4 days [3–5.5].

All patients treated with ceftaroline had previously received standard empiric antibiotic treatment. Most of these patients were treated after less than 24 h in the hospital because of *S. pneumoniae* aetiology confirmation. Only in one patient treatment was switched to ceftaroline due to a lack of response to standard treatment. In this patient, the ceftaroline CMI was 0.047 mg/L. All patients were treated for a median of 11 [8–15] days, in combination with linezolid (600 mg/12 h) for a median of 6 [6–7] days and with steroids for 4 days, except for one patient who received steroids during all CCU stay.

Although not statistically significant, 30-day mortality was higher in the standard group (40% vs. 0%, $p = 0.116$) in similar way to clinical response at the end of treatment (100% vs. 60%, $p = 0.086$). CCU length of stay was longer for ceftaroline group (18 [14–28] vs. 4 [3–13] days, $p = 0.040$). Other complications related to CABM are depicted in Table 2.

Ceftaroline was approved for community-acquired pneumonia treatment, after the results of FOCUS I and II clinical trials.[3,4] The potential efficacy in meningitis has been studied in animal models. Ceftaroline showed higher bacterial killing rate in rabbit models than the comparator (cefepime or ceftriaxone). For *S. pneumoniae* meningitis model the change in bacterial load was -0.71 $\pm$ 0.06 $\log_{10}$ vs. -0.59 ± 0.11 $\log_{10}$ every hour in favour of ceftaroline ($p < 0.009$).[5] Besides this, they observed a good ceftaroline CSF penetration achieving enough antibiotic concentration to be effective.

Despite these promising results, clinical experience in *S. pneumoniae* CABM is scarce. Sakoulas et al. reported four patients treated with ceftaroline; all cases responded successfully except one who received an insufficient dossage (600 mg every 12 h instead of 600 mg every 8 h).[6] In a population-based epidemiologic study performed in the USA, 18 of 764 patients treated with ceftaroline corresponded to meningitis, with a mortality rate of 6% and a 22% rate of CCU admission.[7]

All our patients received 600 mg/8 h of ceftaroline except one who received 300 mg/12 h because of renal failure. Pharmacokinetic characteristics in the critically ill patients suggest to use higher or different dosage regimens in various antibiotics. Specifically in central nervous infections, a one-dose pharmacokinetic study of ceftaroline for patients with an external ventricular drainage showed a CSF ceftaroline exposure of 9% of systemic exposure. Therefore, as ceftaroline is a time-dependent antibiotic, maximum dose and extended infusions seems to be the most advisable management.[8]

Our study presents a complex *S. pneumoniae* CABM cohort. Mortality rate for CABM has been identified to be 14–17%, but for those admitted to the CCU, it can reach up to 47%.[1] In this line, our 30-day mortality was 40%, but surprisingly, despite a higher severity score indexes and a higher rates of septic shock presentation and need for invasive mechanical ventilation, none of the patients treated with ceftaroline died.

Table 1 Patient's demographic and clinical characteristics.

	Ceftaroline ($n = 5$)	Standard therapy ($n = 20$)	p
Age (years) (mean, sd)	65.2 (11.8)	59.4 (15.7)	0.451
Female gender, (N, %)	3 (60%)	9 (45%)	0.645
Comorbidities, (N, %)			
Arterial hypertension	3 (60%)	11 (55%)	1.000
Diabetes mellitus	1 (20%)	7 (35%)	1.000
Chronic heart disease	1 (20%)	2 (10%)	0.504
Immunosuppression	1 (20%)	4 (20%)	1.000
Onco-haematological malignancy	1 (20%)	2 (10%)	0.504
Backgrounds, (N, %)			
Prior neuorological symptomatology	0	2 (10%)	1.000
Otitis media	0	11 (55%)	0.046
Sinusitis	0	1 (5%)	1.000
Vaccine against pneumococcus	2 (40%)	1 (5%)	0.091
Clinical data at diagnosis			
Glasgow score, (median, IQR)	8 (7–8)	10 (8–12)	0.229
APACHE II score, (median, IQR)	24 (22–33)	18 (13–22)	0.035
SAPS3 score, (median, IQR)	82 (60–88)	51 (43–65)	0.024
Septic shock, (*N*, %)	3 (60%)	2 (10%)	0.038
Mechanical ventilation, (*N*, %)	5 (100%)	10 (50%)	0.041

Table 2 Clinical response and complications.

	Ceftaroline ($n = 5$)	Standard therapy ($n = 20$)	p
Mechanical ventilation, (*N*, %)	5 (100%)	10 (50%)	0.041
Glasgow score (72 h), median (IQR)	7 (3–8)	14 (13–15)	0.015
Clinical response (72 h), (*N*, %)	2 (40%)	12 (60%)	0.623
Symptoms resolution end of treatment (*N*, %)	5 (100%)	12 (60%)	0.140
Cerebral abcess, (*N*, %)	2 (40%)	1 (5%)	0.091
Cerebritis, (*N*, %)	1 (20%)	3 (15%)	1.000
Epilepsy, (*N*, %)	1 (20%)	3 (15%)	1.000
Cerebral ischaemia, (*N*, %)	3 (60%)	4 (20%)	0.113
Cerebral edema, (*N*, %)	0 (0%)	2 (10%)	1.000
Cerebral death, (*N*, %)	0 (0%)	1 (5%)	1.000
Death, (*N*, %)	0 (0%)	8 (40%)	0.140

There are some limitations in this scientific letter. It is a retrospective study with a short number of cases, mainly in the ceftaroline group. We have been able to present an entire cohort and, therefore, collect data from two treatment groups, however, ceftaroline initiation was a microbiological decision (*S. pneumoniae* identification) in most of the cases without a clinical justification. Finally, although the used doses of ceftriaxone were appropriate according to the recommendations of the IDSA[9] and ESCMID[10] guidelines, it is true that French guidelines for meningitis promote higher ceftriaxone doses (75–100 mg/kg/day).[11]

Nevertheless, given the tenuous prognosis of *S. pneumoniae* CABM admitted to CCU, we believe that our results could pioneer the use of ceftaroline for these patients and set the basis for the design of a proper study to demonstrate the efficacy and safety of ceftaroline in *S. pneumoniae* CABM.

In summary, treatment with ceftaroline seems to be a promising therapeutic option for CABM caused by *S. pneumoniae*.

Authors' contributions

All authors contributed to the conception of the study, interpretation of findings or writing of the manuscript. Ramírez has participated in the conception and design of the study and in the critical review of intellectual content. Martín-Cerezuela has participated in the design of the study and the acquisition, statistical analysis and interpretation of the data and has made the draft of the article. Frasquet has participated in the acquisition of microbiologic data. Padrón, Palacios and Barrios performed the initial data extraction and have participated in the acquisition of data and analysis and interpretation of data. All authors read and approved the final manuscript.

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Análisis descriptivo del impacto de la pandemia por SARS-CoV-2 en los ingresos de un servicio terciario de cuidados intensivos pediátricos

Descriptive analysis of SARS-CoV-2 pandemia impact on pediatric intensive care unit admissions

La pandemia por SARS-CoV-2 ha requerido de medidas de salud pública dirigidas a disminuir su expansión. Estas, como el uso de mascarillas obligatorias, la higiene de manos o el distanciamiento social han sido trasladadas a la población pediátrica. Dichas normas han condicionado no solo la transmisibilidad de SARS-CoV-2 sino también la de otros patógenos. Este hecho ha provocado un menor número de infecciones y de ingresos hospitalarios[1,2]. En el caso del paciente pediátrico grave, y según lo descrito en diversos países, parece asociarse a un descenso de cuadros infecciosos de todo tipo con especial impacto sobre los respiratorios[3,4].

Con intención de cuantificar este hecho se revisan en este trabajo los ingresos en una unidad de cuidados intensivos pediátricos (UCIP) de un hospital terciario durante el primer año de pandemia por SARS-CoV-2. Se compara con los tres años anteriores con intención de determinar las posibles diferencias en número y características de los pacientes atendidos. Se realiza un estudio descriptivo retrospectivo aprobado por el comité ético de investigación clínica del centro en el que se realiza. Comprende el periodo enero de 2017 a diciembre de 2020. Se incluyen todos los pacientes ingresados en UCIP y se compara 2020 con la mediana de ingresos para los tres años anteriores. Se recoge el tipo de ingreso hospitalario definido por la causa fundamental del mismo. Para ello se analiza el diagnóstico principal de cada paciente y se agrupan con base en ello.

Se estudian un total de 3.345 ingresos en los cuatro años analizados. Los ingresos por año fueron: 790 en 2020, 894 en 2019, 874 en 2018 y 877 en 2017. La mediana de ingresos previa a 2020 fue de 877, en 2020 se observa un descenso