Should we reconsider cefazolin for treating staphylococcal meningitis? A retrospective analysis of cefazolin and cloxacillin cerebrospinal fluid levels in patients treated for staphylococcal meningitis

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Title: Should we reconsider cefazolin for treating staphylococcal meningitis? A retrospective analysis of cefazolin and cloxacillin CSF levels in patients treated for staphylococcal meningitis

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Objectives: The main objective of the study was to assess the meningeal penetration of cefazolin and cloxacillin in patients treated for methicillin-susceptible staphylococcal meningitis.

Methods: We retrospectively identified patients treated for *Staphylococcus* meningitis with measurements of cefazolin or cloxacillin concentrations in cerebrospinal fluid (CSF) using a liquid-chromatography coupled with mass-spectrometry validated assay at the Nantes University Hospital between January 2009 and October 2019. *Staphylococcus* meningitis was defined by a compatible clinical presentation and a microbiological confirmation (positive CSF culture or positive specific polymerase chain reaction). Medical charts were retrospectively reviewed to collect microbiological, clinical data and to assess therapeutic success.

Results: Among the 17 included patients, 8 (47%) were treated with cefazolin and 9 (53%) with cloxacillin. Median daily dosages of cefazolin and cloxacillin were 8 (range 6-12) and 12 (range 10-13) grams respectively. Cefazolin and cloxacillin were mainly administered via continuous infusion. Eleven patients (65%) were males, median (IQR) age was 54 years (50;70), 14 (82%) had post-operative meningitis and 3 (18%) hematogenous meningitis. Median (IQR) antibiotic CSF concentrations were 2.8 (2.1;5.2) and 0.66 (0.5;0.9) mg/L for cefazolin and cloxacillin groups respectively. Cloxacillin was discontinued in 2 patients for therapeutic failure.

Conclusions: Patients with staphylococcal meningitis treated with high-dose continuous intravenous infusion of cefazolin achieved therapeutic concentrations in CSF. Cefazolin appears to be a therapeutic candidate which should be properly evaluated in this indication.

Keywords: *Staphylococcus aureus, Staphylococcus epidermidis,* meningitis, cefazolin, cloxacillin, CSF antibiotic dosage, therapeutic drug monitoring

Introduction

Staphylococcus spp. is a rare but challenging cause of meningitis which can occur following hematogenous or direct meningeal inoculation, especially after neurosurgery. Anti-staphylococcal penicillins are recommended for the treatment of methicillin-susceptible *Staphylococcus* meningitis [1], even though their CSF penetration is a matter of debate [2]. Cefazolin is not recommended in this indication because of a presumed poor CSF penetration [3].

The main objective of the herein study was to assess the CSF penetration of cefazolin and cloxacillin in patients treated for methicillin-susceptible staphylococcal meningitis. We present a series of patients treated for *Staphylococcus* meningitis either with high-dose cefazolin or cloxacillin and report the CSF and plasma concentrations of antibiotics as well as clinical outcomes.

Materials and Methods

Patients with positive culture of CSF for *Staphylococcus* spp. (at least two samples in case of Methicillin-susceptible coagulase-negative staphylococci (MSCNS)) or a positive polymerase chain reaction (PCR) in CSF sample were retrospectively identified between January 2009 and October 2019 in 3 French hospitals. Among them, patients with CSF concentrations of cefazolin or cloxacillin measured for therapeutic drug monitoring (TDM) were identified. Finally only patients with proven staphylococcal meningitis (CSF parameters and clinical picture compatible with the diagnosis of meningitis as defined by Tunkel and colleagues [1]) were selected. Medical charts were retrospectively reviewed to collect clinical and microbiological data and outcomes. CSF parameters were reported at the time of meningitis diagnosis and of cefazolin or cloxacillin concentration measurements in CSF. Concomitant antibiotic plasma concentrations were collected when available. All CSF concentrations were measured within 48h following CSF sampling and were systematically stored at -80°C if they were not immediately performed. Antibiotic concentrations were measured in CSF and plasma using a liquid-chromatography coupled with mass-spectrometry validated assay [4]. Limit of quantitation was 0.5 mg/L for cloxacillin and cefazolin. A steady state plasmatic concentration (Css) was defined by a concentration measured at least after 24 hours of anti-staphylococcal betalactams treatment.

Bacterial antibiotic susceptibilities, including oxacillin minimum inhibitory concentrations (MICs) were determined using a Vitek 2 automated system (bioMérieux, France) and AST-P631 cards. Because

cefazolin is not included in AST-P631 cards, MICs of cefazolin were specifically determined by broth microdilution (BMD) antimicrobial susceptibility testing according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. CSF concentrations were analyzed with respect to the latest epidemiological cut-off (ECOFF) values for cefazolin (2 mg/L) and cloxacillin (0.5 mg/L). The study received ethical approval from the University of Nantes Human Research Ethics Committee. Patients were informed of the study in accordance with French legal standards.

Results

Study population

Seventeen patients met inclusion criteria during the study period (**Figure S1**). Patient characteristics are reported in **Table 1**. Eleven (65%) were males and median (interquartile range [IQR]) age was 54 years (50-70). Fourteen (84%) patients had post-operative meningitis and 3 (18%) hematogenous meningitis. Eight (47%) patients were treated by cefazolin all with continuous intravenous infusion and nine (53%) by cloxacillin mainly with continuous intravenous infusion (missing data for 3 patients). Daily dosages and dosing times are detailed in **Table 1** and **Figure S2**. Median MICs were 0.5 mg/L for cefazolin (range 0.125-0.5) and oxacillin (range $\leq$ 0.25-0.5) for patients treated by cefazolin and cloxacillin respectively.

Pharmacokinetics-pharmacodynamics of cefazolin and cloxacillin in CSF

Twenty eight CSF concentrations were measured in the 17 patients: 14 in cefazolin group (range 1-4 per patient) and 14 in cloxacillin group (range 1-5 per patient). All CSF samples were drawn at least 24 hours after the initiation of antibiotic so steady state was achieved in CSF. CSF samples reported as below the limit of quantitation were fixed at 0.5 mg/L for analysis (n=5 for cloxacillin and n=2 for cefazolin). Median (IQR) CSF concentration was 2.8 mg/L (2.1;5.2) for cefazolin and 0.66 mg/L (0.5;0.9) for cloxacillin. The median (IQR) CSF/plasma ratio was 4.3% (2.9;8.4) for cefazolin and 1.8 % (1.7;2.8) for cloxacillin. The median (IQR) CSF/MIC ratio was 7.38 (2.1;20.04) for cefazolin and 2.0 (1.34;3.4) for cloxacillin (**Table 1**). The median (IQR) CSF/ECOFF value ratio was 1.4 (1.05;2.6) for cefazolin and 1.33 (1;1.805) for cloxacillin. CSF concentration of antibiotic was above ECOFF in 11 (79%) samples corresponding to 6 (75%) patients receiving cefazolin and 8 (57%) samples corresponding to 6 (67%) patients receiving cloxacillin (**Figure 1**).

Clinical outcomes

All patients were cured without any recurrences. In 2 patients treated with cloxacillin for external ventricular drain-associated *S. aureus* meningitis, CSF culture remained positive 2 days and 4 days after cloxacillin initiation respectively. They were considered by the physicians in charge as therapeutic failures leading to cloxacillin discontinuation and its replacement by another antibiotic. Of note in both cases the infected CSF drains had not been removed between diagnosis and antibiotic change.

Discussion

In this study, cefazolin demonstrated levels of CSF penetration higher than previously expected in patients with staphylococcal meningitis and achieved therapeutic concentrations confirming preliminary results [5]. Cefazolin has become a first line option for the management of methicillin-susceptible *Staphylococcus* bacteraemia because of a good efficacy [6], favourable pharmacokinetics [4] and a good tolerability profile when compared with anti-staphylococcal penicillins [7]. Gelfand *et al* recently pointed out the lack of evidence regarding the treatment of CNS infections due to MSSA [8].

To the best of our knowledge the herein study reports the largest series of CSF measurements of cefazolin and cloxacillin in patients treated for staphylococcal meningitis. CSF penetration of cefazolin appeared as good as cloxacillin.

The increased CSF protein levels observed in our patients is suggestive of meningeal inflammation, a major determinant of blood-brain barrier permeability and antibiotic penetration in CSF [9,10]. Of note, six cefazolin CSF concentrations measured in 4 patients without meningitis were collected during study period. Median (IQR) concentrations were 0.95 mg/L (0.5; 1.4) in CSF and 47.7 mg/L (42.3; 52.1) in plasma with a median (IQR) CSF/plasma ratio of 2.1% (0.9;5.2). Knowing that meningeal inflammation can vary a lot in nosocomial meningitis, we suggest performing systematic TDM in CSF when using cefazolin in this indication. Naturally, this statement should also be applied to cloxacillin considering the poor CSF penetration observed here, despite assigning the value of 0.5 mg/L to the assays below the limit of quantification.

In general a concentration measured in CSF above ECOFF should be targeted throughout the treatment (100% $fT_{>MIC}$) [11]. The therapeutic failure of the 2 patients treated with cloxacillin who still had positive CSF culture at least 2 days after antibiotic therapy is hard to ascertain because of the retention of the

infected CSF drain in those patients. The limitations of our study include (i) its retrospective design, (ii) the small number of patients included, especially those who received cefazolin or cloxacillin as a monotherapy, and the variability of co-administered antibiotics limiting the comparison of clinical outcomes between the two groups, (iii) single dosage in most patients yielding the data insufficient to ascertain the stability of cefazolin concentrations in CSF.

In conclusion, continuous high-dose intravenous infusion of cefazolin achieved targeted concentrations in CSF for a large majority of patients with staphylococcal meningitis. Based on our results this regimen may be a suitable option in this indication. If chosen, we recommend associating cefazolin regimen with a systematic therapeutic drug monitoring directly in CSF to check target attainment.

Competing interests

All authors report no conflicts of interest relevant to this article.

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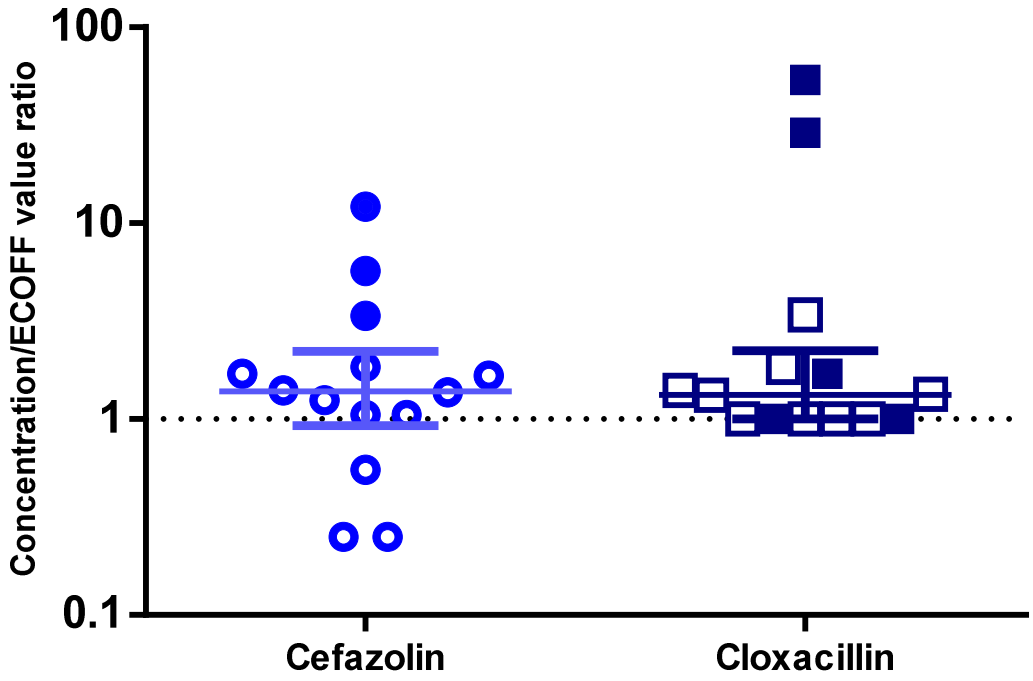

Figure 1: Cerebrospinal fluid concentrations (CSF) of cefazolin and cloxacillin in meningitis. Concentrations are represented in function of EUCAST epidemiological cut-off (ECOFF) values. Median (Interquartile range) CSF concentration was 2.8 mg/L (2.1;5.2) for cefazolin and 0.66 mg/L (0.5;0.9) for cloxacillin. External ventricular drain are represented by circles (for cefazolin) and squares (for cloxacillin) and lumbar puncture by filled circles and squares.

Table 1: Description of study population characteristics, CSF parameters, pharmacological data and outcomes.

	Cefazolin group (n=8)	**Cloxacillin group (n=9)**
Study population characteristics		
Age, years, median (IQR)	58.4 (50.3;74)	54 (50;67)
Male gender, n (%)	6 (75)	5 (55)
BMI, Kg/m^2, median (IQR)	25.9 (24.2;26.9)	22.3 (21;30.2)
Glomerular filtration (MDRD) on diagnosis, median (IQR)[a]	136 (115;146)	102 (93;114)
Mechanism of the meningitis, n (%)		
Post-operative meningitis	7 (88)	7 (78)
EVD associated meningitis	5 (62)	6 (66)
Hematogenous meningitis	1 (12)	2 (22)
Microbiological diagnosis of meningitis, n (%)		
S. aureus	4 (44)	6 (66)
S. epidermidis	3 (33)	3 (34)
S. lugdunensis	1 (11)	-
CSF parameters on diagnosis, median (IQR)		
White blood cells/mm^3	440 (92;6022)	370 (181;1166)
Protein, g/L	1.52 (0.81;2.47)	1.76 (0.59;2.41)
Glucose mmol/L[b]	3.15 (0.17;4.75)	2.95 (1.42;4.1)
Lactate (mmol/L)[c]	4.5 (3.8;9.7)	5 (3.1;9.8)
CSF parameters in samples used for pharmacological measurements		
CSF samples with antibiotic dosing, n	14	14
CSF sampling via EVD, n (%)	11 (79)	9 (64)
White blood cells/mm^3, median (IQR) [d]	31.5 (6.75;68.5)	3 (2;21)
Protein g/L, median (IQR)[e]	0.86 (0.67;1.27)	0.76 (0.54;1.13)
Glucose mmol/L, median (IQR)[f]	3.9 (2.27;4.75)	2.7 (1.8;3.5)
Lactate mmol/L, median (IQR)[g]	2.7 (2.1;3.3)	3.55 (3;4.1)
Pharmacological results, median (IQR)		
CSF antibiotic concentration, mg/L	2.8 (2.1;5.2)	0.66 (0.5;0.9)
Plasma antibiotic concentration, mg/L	58.1 (55.5;70.4)	47.7 (46 ;51.1)
Ratio concentration CSF/Plasma, %[h]	4.3 (2.9;8.4)	1.8 (1.7;2.8)
CSF/MIC ratio	7.38 (2.1;20.04)	2.0 (1.34;3.4)
Characteristics of the antibotic therapy		
Daily dosage, g [median (IQR) (min-max)]	8 (7.88;8) (6-12)	12 (12;12) (10-13)
Co administered antibiotic, n (%)	6 (75)	7 (77.8)
Levofloxacin	4 (50)	4 (44.4)
Clindamycin	1 (12.5)	-
Rifampin	-	2 (22.2)
Other[i]	2 (25)	3 (33)
Reason for discontinuation of antibiotic therapy, n(%)[j]		
Therapeutic failure	-	2 (22)

BMI, body mass index; IQR, Interquartile range; MIC, Minimum Inhibitory Concentration; EVD, external ventricular drain; CSF, Cerebrospinal fluid

[a]missing data: cloxacillin group (n=1) [b]missing data: cloxacillin group (n=1) [c]missing data: cefazolin group (n=3), cloxacillin group (n=1) [d] missing data : cefazolin group (n=4), cloxacillin group (n=4) [e] missing data : cefazolin group (n=6), cloxacillin group (n=3) [f] missing data : cefazolin group (n=6), cloxacillin group (n=3) [g]missing data : cefazolin group (n=9), cloxacillin group (n=8) [h] missing data: cefazolin group (n=4), cloxacillin group (n=5) [i]Other antibiotics were linezolid (n=1 in the cefazolin group and n=1 in cloxacillin group), fosfomycin (n=1) in the cloxacillin group, acid fusidic (n=1) in the cefazolin group, gentamycin (n=1) in the cloxacillin group. [j]2 failures with positive culture above 48 h of antibiotic therapy and 1 underdosing in the cloxacillin group.