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1 **Research note V2: CLM-19-16649**

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

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25

26 **Main text- 1189/1200 words**

27 **Abstract- 246/250 words**

28

29 **Abstract- 225/250 words**

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

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

39 **Results:** Among the 17 included patients, 8 (47%) were treated with cefazolin and 9 (53%) with
40 cloxacillin. Median daily dosages of cefazolin and cloxacillin were 8 (range 6-12) and 12 (range 10-13)
41 grams respectively. Cefazolin and cloxacillin were mainly administered via continuous infusion. Eleven
42 patients (65%) were males, median (IQR) age was 54 years (50;70), 14 (82%) had post-operative
43 meningitis and 3 (18%) hematogenous meningitis. Median (IQR) antibiotic CSF concentrations were
44 2.8 (2.1;5.2) and 0.66 (0.5;0.9) mg/L for cefazolin and cloxacillin groups respectively. Cloxacillin was
45 discontinued in 2 patients for therapeutic failure.

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

49

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

52

53 **Introduction**

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

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

63 **Materials and Methods**

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

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

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

87 **Results**

88 *Study population*

89 Seventeen patients met inclusion criteria during the study period (**Figure S1**). Patient characteristics are
90 reported in **Table 1**. Eleven (65%) were males and median (interquartile range [IQR]) age was 54 years
91 (50-70). Fourteen (84%) patients had post-operative meningitis and 3 (18%) hematogenous meningitis.
92 Eight (47%) patients were treated by cefazolin all with continuous intravenous infusion and nine (53%)
93 by cloxacillin mainly with continuous intravenous infusion (missing data for 3 patients). Daily dosages
94 and dosing times are detailed in **Table 1** and **Figure S2**. Median MICs were 0.5 mg/L for cefazolin
95 (range 0.125-0.5) and oxacillin (range \leq 0.25-0.5) for patients treated by cefazolin and cloxacillin
96 respectively.

97 *Pharmacokinetics-pharmacodynamics of cefazolin and cloxacillin in CSF*

98 Twenty eight CSF concentrations were measured in the 17 patients: 14 in cefazolin group (range 1-4
99 per patient) and 14 in cloxacillin group (range 1-5 per patient). All CSF samples were drawn at least 24
100 hours after the initiation of antibiotic so steady state was achieved in CSF. CSF samples reported as
101 below the limit of quantitation were fixed at 0.5 mg/L for analysis (n=5 for cloxacillin and n=2 for
102 cefazolin). Median (IQR) CSF concentration was 2.8 mg/L (2.1;5.2) for cefazolin and 0.66 mg/L
103 (0.5;0.9) for cloxacillin. The median (IQR) CSF/plasma ratio was 4.3% (2.9;8.4) for cefazolin and 1.8
104 % (1.7;2.8) for cloxacillin. The median (IQR) CSF/MIC ratio was 7.38 (2.1;20.04) for cefazolin and 2.0
105 (1.34;3.4) for cloxacillin (**Table 1**). The median (IQR) CSF/ECOFF value ratio was 1.4 (1.05;2.6) for
106 cefazolin and 1.33 (1;1.805) for cloxacillin. CSF concentration of antibiotic was above ECOFF in 11
107 (79%) samples corresponding to 6 (75%) patients receiving cefazolin and 8 (57%) samples
108 corresponding to 6 (67%) patients receiving cloxacillin (**Figure 1**).

109 *Clinical outcomes*

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

115 **Discussion**

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

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

125 The increased CSF protein levels observed in our patients is suggestive of meningeal inflammation, a
126 major determinant of blood-brain barrier permeability and antibiotic penetration in CSF [9,10]. Of note,
127 six cefazolin CSF concentrations measured in 4 patients without meningitis were collected during study
128 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
129 plasma with a median (IQR) CSF/plasma ratio of 2.1% (0.9;5.2). Knowing that meningeal inflammation
130 can vary a lot in nosocomial meningitis, we suggest performing systematic TDM in CSF when using
131 cefazolin in this indication. Naturally, this statement should also be applied to cloxacillin considering
132 the poor CSF penetration observed here, despite assigning the value of 0.5 mg/L to the assays below the
133 limit of quantification.

134 In general a concentration measured in CSF above ECOFF should be targeted throughout the treatment
135 ($100\% f_{T>MIC}$) [11]. The therapeutic failure of the 2 patients treated with cloxacillin who still had positive
136 CSF culture at least 2 days after antibiotic therapy is hard to ascertain because of the retention of the

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

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

146

147 **Competing interests**

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

149

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171 Paul Le Turnier (Conceptualization, Investigation, Data curation, Methodology, Writing – original
172 draft), Matthieu Grégoire (Conceptualization, Investigation, Formal analysis, Visualization, Writing –
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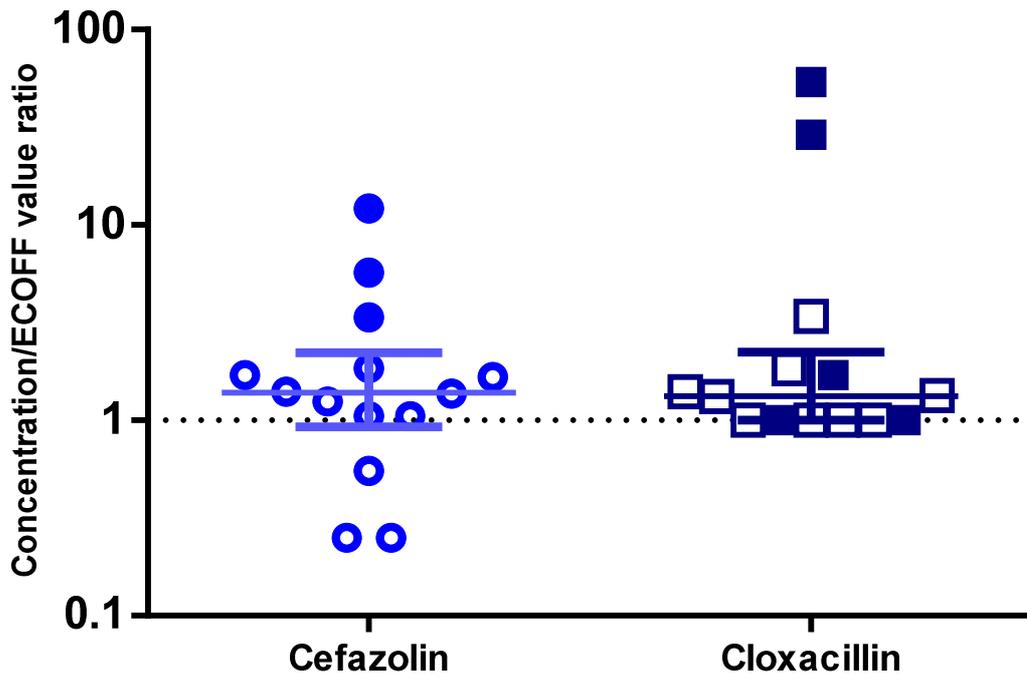


Figure 1: Cerebrospinal fluid concentrations (CSF) of cefazolin and cloxacillin in meningitis. Concentrations are represented in function of EUCAST epidemiological cut-off (ECOFF) values. Median (Interquartile range) CSF concentration was 2.8 mg/L (2.1;5.2) for cefazolin and 0.66 mg/L (0.5;0.9) for cloxacillin. 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 (%)		
<i>S. aureus</i>	4 (44)	6 (66)
<i>S. epidermidis</i>	3 (33)	3 (34)
<i>S. lugdunensis</i>	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 antibiotic 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

^amissing data: cloxacillin group (n=1) ^bmissing data: cloxacillin group (n=1) ^cmissing 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)

^gmissing data : cefazolin group (n=9), cloxacillin group (n=8) ^h missing data: cefazolin group (n=4), cloxacillin

group (n=5) ⁱOther antibiotics were linezolid (n=1 in the cefazolin group and n=1 in cloxacillin group),

fosfomicin (n=1) in the cloxacillin group, acid fusidic (n=1) in the cefazolin group, gentamycin (n=1) in the

cloxacillin group. ^j2 failures with positive culture above 48 h of antibiotic therapy and 1 underdosing in the

cloxacillin group.