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1 **TITLE PAGE - Brief Report**

2

3 **Title:**

CSF concentration of cefotaxime in adult patients with pneumococcal meningitis: a multicentre retrospective study

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6

7 **Authors**

8 Paul LE TURNIER^{1*}, Najoua EL HELALI², Romain GUILHAUMOU³, Benoit PILMIS⁴, Matthieu
9 REVEST⁵, Lionel VELLY⁶, Anne-Gaëlle LEROY⁷, Xavier DUVAL⁸, Florian LEMAITRE⁹, Matthieu
10 GREGOIRE¹⁰ on behalf of the DIFCEFO study group†

11 ¹ Department of Infectious Diseases, Nantes University Hospital, Nantes, France - INSERM CIC 1413,
12 Nantes University Hospital, Nantes, France

13 ² Plateforme de Dosages des Anti-infectieux, Groupe Hospitalier Paris Saint-Joseph, Paris, France

14 ³ Aix Marseille Univ, Department of Clinical Pharmacology and Pharmacovigilance CIC-CPCET,
15 University Hospital Timone - Institut de neurosciences des systèmes, Inserm UMR 1106, Marseille,
16 France

17 ⁴ Equipe Mobile de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, Paris, France -
18 Institut Micalis UMR 1319, Université Paris-Saclay, INRAe, AgroParisTech, Châtenay Malabry, France

19 ⁵ Infectious Diseases and Intensive Care Unit, Rennes University Hospital, Rennes, France - University of
20 Rennes, Centre d'Investigation Clinique 1414, INSERM, Bacterial Regulatory RNAS and Medicine,
21 Unité Mixte de Recherche 1230, Rennes, France

22 ⁶ Aix Marseille Univ, Department of Anaesthesiology and Critical Care Medicine, University Hospital
23 Timone - CNRS, INT, Inst Neurosci Timone, UMR7289, Marseille, France

24 ⁷ Department of Microbiology, Nantes University Hospital, Nantes, France

25 ⁸ Paris University, IAME, INSERM, Paris, France - Inserm Clinical Investigation Centre 1425, Paris,
26 France - Inserm, F-CRIN, Innovative Clinical Research Network in Vaccinology (I-REIVAC), Paris,
27 France

28 ⁹ Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et
29 travail), Rennes, France - UMR_S 1085, F- INSERM, Centre d'Investigation Clinique, CIC 1414,
30 Rennes, France

31 ¹⁰ Clinical Pharmacology Laboratory Department Nantes University Hospital, Nantes, France - UMR
32 INSERM 1235, The enteric nervous system in gut and brain disorders, University of Nantes, Nantes,
33 France

34 †Members are listed in the Acknowledgements section

35 *Corresponding author

36

37 **Corresponding author**

38 Paul Le Turnier. Address : Department of Infectious and Tropical diseases, Nantes University Hospital, 1
39 place Alexis Ricordeau 44093, Nantes, France. International phone number/fax : +33 2 40 08 33 47/+33 2
40 40 08 33 30. E-mail : paul.leturnier@gmail.com

41

42 **Running title**

43 Cefotaxime in adult pneumococcal meningitis CSF

44 **Abstract**

45 **Background and objectives:** Pneumococcal meningitis is a devastating disease that requires adequate
46 meningeal antibiotic penetration to limit the mortality. Despite a large usage in this indication, data about
47 CSF concentration of cefotaxime during pneumococcal meningitis in adults are scarce. Therefore we
48 aimed to describe the CSF concentration obtained after high-dose cefotaxime administration in adult
49 patients treated for *Streptococcus pneumoniae* meningitis.

50 **Patients and methods:** In this multicentre, observational, retrospective study, cases of adult patients with
51 *S. pneumoniae* meningitis hospitalized between January 2013 and October 2019 for whom cefotaxime
52 concentration was measured in CSF were reviewed.

53 **Results:** Cefotaxime concentration was analysed in 44 CSF samples collected among 31 patients...
54 Median (IQR) age was 61 years (52;69). Dexamethasone was administered in 27 subjects. Median (IQR)
55 cefotaxime daily dosage was 15 g (12;19) corresponding to 200 mg/kg (150;280). CSF samples were
56 collected 5 days after cefotaxime initiation roughly. Median (IQR, range) cefotaxime CSF concentration
57 was 10.3 mg/L (4.8;19.3, 1.2-43.4). Median (range) MIC of *Streptococcus pneumoniae* was 0.25 mg/L
58 (0.008-1) (n=22). The median (IQR, range) CSF/MIC ratio was 38 (12;146, 4-1844). Twenty-five CSF
59 concentrations (81 %) were above 10 times the MIC. Cefotaxime was discontinued in 2 patients for
60 toxicity. In-hospital mortality rate was 29%.

61 **Conclusions:** Adult patients with pneumococcal meningitis treated with high dose of cefotaxime (200
62 mg/kg/day) had elevated CSF concentrations with satisfying pharmacokinetics/pharmacodynamics
63 parameters and tolerability profile. This study brings reassuring pharmacological data regarding the use of
64 high dose cefotaxime monotherapy for treating pneumococcal meningitis with susceptible strains to
65 cefotaxime.

66

67 **TEXT (1217 words)**

68 **Introduction**

69 *Streptococcus pneumoniae* meningitis is a devastating disease with the highest morbidity and mortality
70 among community-acquired bacterial meningitis. ¹ Cefotaxime is a third-generation cephalosporin (3GC)
71 widely recommended for the treatment of pneumococcal meningitis. French guidelines for management
72 of acute bacterial meningitis recommend dosage of cefotaxime to be weight-based without any upper
73 limit whereas international guidelines recommend a maximum daily dosage of 12 g. ²⁻⁴ The adequacy
74 between antibiotic penetration in CSF and antibiotic susceptibility of *Streptococcus pneumoniae* is a
75 cornerstone to achieve satisfying pharmacokinetics/pharmacodynamics (PK-PD) targets in this lethal
76 disease. The increasing incidence of *Streptococcus pneumoniae* isolates with reduced susceptibility to
77 3GC is therefore a matter of concern. ⁵ Given these epidemiological changes, data about cefotaxime
78 penetration in CSF might offer relevant information. ⁶ However, very limited data exist about CSF
79 penetration of cefotaxime when meningeal dose are used in adults treated for pneumococcal meningitis.
80 We aimed to describe the CSF penetration of cefotaxime in adult patients treated for *S. pneumoniae*
81 meningitis.

82 **Patients and methods**

83 We conducted a multicentre, observational, retrospective study. Adult patients hospitalized between
84 January 2013 and October 2019 for whom cefotaxime concentration was measured in CSF as part of the
85 routine care were identified in the participating centres and among the participants of the COMBAT
86 cohort (NCT02916732). Among them, individuals treated for proven pneumococcal meningitis, with
87 either positive CSF culture or CSF PCR assay for *Streptococcus pneumoniae*, were included. Medical
88 charts were retrospectively reviewed to collect clinical, pharmacological and microbiological data. CSF
89 parameters were reported at the time of cefotaxime concentration measurements in CSF. Concomitant
90 cefotaxime plasma concentrations (same day) were collected when available. All CSF concentrations
91 were measured within 48h following CSF sampling and were systematically stored at -80°C if they were

92 not immediately performed. Antibiotic concentrations were measured in CSF and plasma using a liquid-
93 chromatography coupled with mass-spectrometry or diode-array detector validated assay. Limit of
94 quantitation was 1 mg/L. A steady-state plasma concentration was defined by a cefotaxime concentration
95 measured at least 24 hours after treatment initiation. Plasma concentrations were considered as trough
96 levels when continuous infusion was used or when discontinued infusion was used and plasma samples
97 collected just before infusion.

98 Cefotaxime MIC were determined using an Etest strips or Vitek 2 automated system (bioMérieux,
99 France) depending on usual practices of the different centres and according to the European Committee
100 on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The study received ethical approval from
101 the Research Ethics Committee on Infectious and Tropical Diseases (CERMIT2019-0706,
102 IRB00011642). Participants were informed of the study in accordance with French legal standards.

103 A Wilcoxon rank sum test was used to compare the cefotaxime CSF levels between patients with and
104 without dexamethasone with a significance level of 0.05.

105 **Results**

106 *Study population*

107 In total, 31 individuals were included. Their characteristics are reported in **Table 1**. Median (IQR) age
108 was 61 years (52;69). Dexamethasone was administered in 27 subjects (87 %). Median (IQR) cefotaxime
109 daily dosage was 15 g (12;19) corresponding to 200 mg/kg (150;280). Sixteen out of 28 patients received
110 cefotaxime by continuous intravenous infusion (3 missing data).

111 *Pharmacokinetics-pharmacodynamics analysis*

112 Forty-four CSF concentrations (from 1 to 4 per patient) and 28 plasma concentrations (from 0 to 4 per
113 patient) were measured. The median (IQR) time between cefotaxime initiation and CSF sampling was
114 121 hours (78-194), all above 24 hours (2 missing data). For patients who did not receive continuous
115 infusion, the median (IQR) time between cefotaxime preceding infusion and CSF sampling was 3.3 (1.5-

116 5.3) hours. Median (IQR, range) CSF concentration was 10.3 mg/L (4.8;19.3, 1.2-43.4) (see **Table 1**).
117 Median (IQR) plasma concentration was 60.5 mg/L (31.3-81.7). Plasma concentrations were trough levels
118 in 75% (21/28) of patients. For paired CSF and plasma cefotaxime measurements (n=28 paired samples),
119 the median (IQR) calculated CSF/plasma ratio was 21.6 % (8.6-28.5). The cefotaxime MIC of *S.*
120 *pneumoniae* was reported for 22 (71%) subjects. Median (IQR, range) MIC was 0.25 mg/L (0.036;0.5,
121 0.008-1). Based on the cefotaxime MIC of each patient's pneumococcal strain the median (IQR, range)
122 CSF/MIC ratio was 38 (12-146, 4-1844) (n=31 CSF samples). Twenty-five CSF concentrations (81 %)
123 were above 10 times the corresponding MIC. CSF cefotaxime levels did not differ between
124 dexamethasone- and non-dexamethasone-treated patients (p=0.59). Considering the weight-based daily
125 dosage and the associated CSF concentration, 6 patients received less than 150 mg/kg/day (n=9 samples),
126 6 between 150 and 199 mg/kg/day (n=8 samples), 11 between 200 and 280 mg/kg/day (n=13 samples), 6
127 above 280 mg/kg/day (n=10) with a median (IQR) CSF concentration of 7.5 mg/L (1.2;29.3), 10.3 mg/L
128 (2.2;15.4), 5.4 mg/L (1.6;23.8), and 18.3 mg/L (3.0;43.4) respectively (see **Table 2**).

129 *Clinical outcomes*

130 Cefotaxime was discontinued because of toxicity in 2 patients (8.0 %, 6 missing data). One with acute
131 kidney injury experienced a neurological degradation with electroencephalogram abnormalities while
132 having elevated cefotaxime concentrations in CSF (19.3 mg/L) and plasma (254.9 mg/L). The details on
133 toxicity were not available for the other patient. In hospital mortality rate was 29 % (9/31).

134 **Discussion**

135 Previous studies assessing CSF penetration of cefotaxime were mostly done in children and revealed
136 lower concentrations than in this study,⁷ or variable concentrations similarly to those observed here.⁸
137 Interestingly, a previous PK/PD modelling study suggested that cefotaxime dosages of 4g/6h would be
138 sufficient to achieve CSF levels above the MIC for 90% of time, even for pneumococcal strains with an
139 MIC of 2, which appear close to the results observed in the current study.⁹

140 The IDSA and the ESCMID guidelines for acute bacterial meningitis treatment in adults recommend a
141 cefotaxime daily dosage from 8 to 12 g, in association with vancomycin or rifampicin when reduced
142 susceptibility to penicillin is suspected, which is the case in France.^{3,4} Meanwhile, French guidelines
143 promote a monotherapy of cefotaxime with a dose-weighted adjustment without any upper limit dosage
144 and recommend dosages based on cefotaxime susceptibility which range from 200 mg/kg when MIC is
145 below 0.5 mg/L (susceptible strain) to 300 mg/kg when MIC is between 0.5 mg/L and 2 mg/L
146 (intermediate strain) or unknown.²

147 Recently, Mizrahi and coll. reported a case of therapeutic failure in a patient with 3GC-intermediate
148 *Streptococcus pneumoniae* meningitis.¹⁰ After several days of ceftriaxone monotherapy the patient's state
149 worsened and repeated CSF culture revealed a 3GC-resistant *Streptococcus pneumoniae* isolate. This
150 resistance emergence possibly occurred due to insufficient exposition of antibiotics.¹¹ Because a limited
151 exposition to antibiotics can lead to resistant strain selection, it appears necessary to target CSF
152 concentrations far above the MIC although the optimal CSF/MIC ratio target remains uncertain.¹²

153 In France, the incidence of pneumococcal meningitis with decreased 3GC susceptibility reached its lowest
154 point in 2014 when 1.5% of strains were cefotaxime-intermediate and none resistant. Since then, this
155 proportion increased relatively with 6.6% in 2017 with rare resistant strains (0.7%).¹³ The
156 pharmacological results of our study suggest that using high-dose cefotaxime (200 mg/kg) seems a
157 reasonable option to treat cefotaxime-susceptible strains. Notably, the highest CSF concentrations
158 observed in this cohort were found in patients receiving daily dosage above 280 mg/kg with a median of
159 18 mg/L and were higher than previous reports in adults receiving meningeal dose of cefotaxime.^{14,15}
160 Those very high dosages corresponded approximately to the initial empirical dosage proposed by French
161 guidelines and could be sufficient to treat even cefotaxime-intermediate strains.

162 The global satisfying tolerability of cefotaxime despite the high doses used in the study population is in
163 accordance with previous reports of very high doses of other 3GC in patients treated for suspected CNS
164 infections.¹⁶

165 The limitations of our study include: i) the retrospective design, ii) a small sample size, which prevents to
166 analyse the factors associated with CSF cefotaxime penetration and patients' outcomes, iii) some missing
167 data regarding the indication of CSF antibiotic dosing and the dosage of dexamethasone (although it is
168 likely that the recommended dosage of 10 mg/q6h was administered), iv) a possible selection bias because
169 repeated CSF analysis is not systematically recommended but only in case of elevated MIC or
170 unfavourable outcome.²

171 High dose cefotaxime regimens (200 mg/kg) used in adults during pneumococcal meningitis lead to
172 elevated CSF levels associated with satisfying PK-PD parameters in CSF. Despite its limitations this
173 study brings reassuring pharmacological and clinical data regarding the use of high dose cefotaxime as
174 recommended in France for treating pneumococcal meningitis with 3GC susceptible strains.

175 **Authors' contributions**

176 Paul Le Turnier (Conceptualization, Methodology, Investigation, Data curation, Formal analysis,
177 Visualization, Methodology, Writing – original draft), Najoua El Helali (Investigation, Writing – review
178 and editing), Romain Guilhaumou (investigation), Benoit Pilmis (Investigation, Writing – review and
179 editing), Lionel Jean Velly (Investigation) Matthieu Revest (Investigation), Anne Gaele Leroy
180 (Methodology, Writing – original draft), Xavier Duval (Conceptualization, Investigation, Writing –
181 review and editing), Florian Lemaitre (Investigation, Writing – review and editing), Matthieu Grégoire
182 (Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft).

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188 DIFCEFO study group: (Nantes University Hospital) Paul Le Turnier, Matthieu Gregoire, Anne-Gaëlle
189 Leroy; (Saint-Joseph group) Najoua El-Helali, Benoît Pilmis; (Rennes University Hospital) Matthieu
190 Revest, Florian Lemaitre; (Marseille University Hospital) Romain Guilhaumou, Lionel Velly (Quimper
191 Hospital) Jean-Philippe Talarmin; (Amiens University Hospital) Jean-Luc Schmit, Youssef Bennis;
192 (Nancy University Hospital) Alexandre Charmillon, Julien Scala-Bertola; (Strasbourg University
193 Hospital) Joy Mootien; (Cochin University Hospital) Solen Kernéis; (Reims University Hospital) Firouze
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199 **Transparency declarations**

200 None to declare

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241

242

243 TABLES

244 Table 1: Description of study population's characteristics and outcomes, antibiotic therapy
 245 characteristics, CSF parameters and pharmacological results (n=31 patients)

Study population characteristics

Age, years, median (IQR)	61 (52;69)
Weight, Kg, median (IQR) ^a	75.5 (60.7;90.2)
Glomerular filtration (CKD-EPI) at each CSF samples, mL/min/1.73 m ² , median (IQR) ^b	91 (78;105.3)
Dexamethasone, n (%)	27 (87)
In-hospital mortality, n (%)	9 (29)
<i>S. pneumoniae</i> MIC, mg/L, median (min;Q1;Q3;max) ^c	0.25 (0.008;0.032;0.5;1)

Characteristics of the cefotaxime therapy

Daily dosage, g, median (IQR) ^d	15 (12;19)
Daily dosage, mg/Kg, median (IQR) ^e	200 (150;280)
Continuous infusion, n (%) ^f	16 (57)
Frequency in intermittent infusion, n/24h, median (IQR)	6 (4;6)
Discontinuation for toxicity, n (%) ^g	2 (8)

CSF parameters in samples used for pharmacological measurements

CSF samples with antibiotic dosing, n	44
---------------------------------------	----

CSF sampling via LP, n (%)	33 (75)
White blood cells/mm ³ , median (IQR) ^h	111 (32;565)
Protein g/L, median (IQR) ⁱ	2.2 (1.2;2.7)
Glucose mmol/L, median (IQR) ^j	3.28 (1.65;6.11)

Pharmacological results of cefotaxime measurements

CSF concentration, mg/L, median (min;Q1;Q3;max)	
- All patients (n=44)	10.5 (1.2;4.9;19.3;43.4)
- Patients with dexamethasone (n= 33)	9.3 (1.6;4.5;15.4;39.1)
- Patients without dexamethasone (n=11)	12.3 (1.2;6.5;20.4;43.4)
Plasma concentration, mg/L, median (min;Q1;Q3;max) ^k	60.5 (13.5;31;81.7;254.9)
CSF/Plasma concentration ratio, %, median (min;Q1;Q3;max) ^k	21.6 (1.4;8.6;28.5;183.8)
CSF/MIC ratio, median (min;Q1;Q3;max) ^l	38 (4;12;146;1844)
CSF/MIC > 10, n (%) ^l	25 (81)

246 CTX, Cefotaxime; CKD-EPI, Chronic Kidney Disease EPIdemiology collaboration, LP, Lumbar
 247 puncture; PK-PD, Pharmacokinetics-pharmacodynamics; min, minimum; Q1, first quartile; Q3, third
 248 quartile; max, maximum.

249 ^amissing data: n=3/31; ^bcreatinin clearance values were collected for each CSF sample, missing data:
 250 n=4/44; ^cmissing data: n=9/31; ^d missing data: n=1/44; ^e missing data: n=4/44; ^f missing data: n=3/31;

251 ^gmissing data: n=6/31; ^hmissing data: n=11/44; ⁱmissing data: n=12/44; ^jmissing data: n=13/44; ^kmissing
 252 data: n=17/44; ^lmissing data: n=14/44.

253 **Table 2. CSF concentrations of cefotaxime according to weight-based daily dosage (n=40 dosages, 4**
 254 **missing data)**

Daily dosage (mg/kg/day)	<150	[150-199]	[200-280]	>280
Number of patients	6	6	11	6
Number of dosages	9	8	13	10
Time since CTX initiation, hours, median	120	144	96	193
Creatinin clearance, ml/min, median	51	77.5	86.0	96.5
Creatinin clearance < 30ml/min, n	4 (1 md)	0	1 (2 md)	0
CSF concentration, mg/L, median (range)	7.5 (1.2;29.3)	10.3 (2.2;15.4)	5.4 (1.6;23.8)	18.3 (3.0;43.4)

255 Md, missing data; CTX, Cefotaxime