



**HAL**  
open science

## Empirical Treatment in Acute Bacterial Meningitis: a Plea for High Doses of Cefotaxime or Ceftriaxone

Paul Le Turnier, Pierre Tattevin, Emmanuelle Varon, Xavier Duval

► **To cite this version:**

Paul Le Turnier, Pierre Tattevin, Emmanuelle Varon, Xavier Duval. Empirical Treatment in Acute Bacterial Meningitis: a Plea for High Doses of Cefotaxime or Ceftriaxone. *Antimicrobial Agents and Chemotherapy*, 2023, 67 (4), pp.e00012-23. 10.1128/aac.00012-23 . hal-04059600

**HAL Id: hal-04059600**

**<https://hal.science/hal-04059600>**

Submitted on 9 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Title**

2 Empirical treatment in acute bacterial meningitis: a plea for high doses of cefotaxime or ceftriaxone

3

4 **Authors**

5 Paul Le Turnier <sup>1\*</sup>, Pierre Tattevin <sup>2,3</sup>, Emmanuelle Varon <sup>4</sup>, Xavier Duval <sup>5,6</sup>

6 <sup>1</sup> Infectious diseases department, Centre Hospitalier de Cayenne, Cayenne, French Guiana

7 <sup>2</sup> Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France

8 <sup>3</sup> ESCMID Study Group for Infectious Diseases of the Brain (ESGIB), Basel, Switzerland

9 <sup>4</sup> Centre National de Référence des Pneumocoques (CNRP), Centre de Recherche Clinique et  
10 Biologique, Centre Hospitalier Intercommunal de Créteil, Créteil, France

11 <sup>5</sup> Inserm CIC 1425, Centre d'Investigation Clinique, AP-HP, Hôpital Bichat, Paris, France

12 <sup>6</sup> Université de Paris, IAME, INSERM, Paris, France.

13

14 \* corresponding author : Paul Le Turnier, Infectious diseases department, Centre Hospitalier de  
15 Cayenne, Avenue des Flamboyants, 97300 Cayenne, French Guiana

16 email : paul.leturnier@gmail.com, Fax. : +594 594 39 50 40

17

18

19 **MANUSCRIPT**

20 Sir,

21 We read with great interest the article by Cabellos et al. (1) who provide real-life data on antibiotic  
22 treatment of acute bacterial meningitis (ABM) due to *Streptococcus pneumoniae*, including those  
23 with reduced susceptibility to 3<sup>rd</sup> generation cephalosporin (3GC). Notably, the authors reported no  
24 clinical failure when empirical therapy was high-dose cefotaxime (HDCTX), i.e. 300 mg/kg/day. They  
25 also reported initial clinical failures in 4 cases due to *S. pneumoniae* isolates with CTX MIC of 1 to 2  
26 mg/L, finally cured with HDCTX (1). They concluded that HDCTX is an interesting option as empirical  
27 therapy for pneumococcal meningitis even with MICs up to 2 mg/L, contrarily to European guidelines  
28 (2). In fact, using HDCTX or high dose ceftriaxone (100 mg/kg/day) - without maximum daily dose - as  
29 empirical therapy pending MIC determination has been recommended in France since 2008 for  
30 adults with ABM (3). However, among the 157 *S. pneumoniae* strains isolated from adults with  
31 pneumococcal meningitis in 2021 in France, 19 (12.1%) had a CTX MIC > 0.5 mg/L, with a MIC90 of 1  
32 mg/L. This was the highest level of reduced susceptibility to 3GC recorded since 2009 (4) which may  
33 challenge the strategy of single-drug empirical treatment with HD3GC, but Cabellos and coll. provide  
34 reassuring data. In addition, we demonstrated that HDCTX (> 280 mg/kg/day) ensure CSF levels that  
35 would be effective on most *S. pneumoniae* strains with reduced susceptibility to CTX, with median  
36 CTX CSF concentrations of 10.3 mg/L (interquartile range, 4.8-19.3) (5). Besides, using HDCTX by  
37 continuous infusion should be preceded by a loading dose of 50 mg/kg over 1 hour for early  
38 attainment of PK/PD target (6). Unfortunately, Cabellos and coll. did not provide any data on  
39 antibiotic concentrations in CSF, nor in the proportion of patients with persistent positive CSF  
40 cultures among those with clinical failure; despite repeating lumbar puncture to assess CSF  
41 sterilization and monitor CSF antibiotic level has been recommended in case of clinical failure and/or  
42 meningitis due to *S. pneumoniae* with CTX MIC > 0.5 mg/L (2, 3).

43 In our opinion, the ceftriaxone daily dosage used by Cabellos and coll. in the 2 patients with  
44 therapeutic failures (4 g/day) was sub-optimal for the following reasons: first, not trespassing the  
45 ceftriaxone manufacturers advices should definitively not be a major concern when dealing with  
46 ABM, a devastating disease. Second, as reminded by the authors, a satisfying tolerability was yet  
47 demonstrated for ceftriaxone regimens above 4 g/day (7). Third, it has been shown that a daily dose  
48 of 4 g ceftriaxone may be associated with subtherapeutic levels in case of augmented renal  
49 clearance, as reported during sepsis, a common finding with invasive pneumococcal disease (8).  
50 Therefore, we suggest that ceftriaxone monotherapy should not be discarded as empirical therapy  
51 for ABM in settings with high prevalence of *S. pneumoniae* with reduced susceptibility to 3GC,  
52 provided that high doses are used (100 mg/kg/day), with no maximum daily dose.

53 Finally, considering that only half of empirical regimens prescribed for ABM in France complied with  
54 the national guidelines, the most common error being the use of insufficient doses of 3GC (9), the  
55 main take-home message would be to rigorously apply the guidelines, with a special caution on the  
56 3GC doses selected for the primary prescription.

57

## 58 **References**

- 59 1. Cabellos C, Guillem L, Pelegrin I, Tubau F, Ardanuy C, Gudiol F, Ariza J, Viladrich PF. 2022.  
60 Penicillin- and Cephalosporin-Resistant Pneumococcal Meningitis: Treatment in the Real World  
61 and in Guidelines. *Antimicrob Agents Chemother* e00820-22.
- 62 2. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B,  
63 Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC. 2016. ESCMID guideline:  
64 diagnosis and treatment of acute bacterial meningitis. *Clinical Microbiology and Infection*  
65 22:S37–S62.

- 66 3. Hoen B, Varon E, de Debroucker T, Fantin B, Grimprel E, Wolff M, Duval X, expert and reviewing  
67 group. 2019. Management of acute community-acquired bacterial meningitis (excluding  
68 newborns). Long version with arguments. *Med Mal Infect* 49:405–441.
- 69 4. Plainvert C, Varon E, Viriot D, Kempf M, French Regional Pneumococcal Observatories (ORP)  
70 network. 2022. Invasive pneumococcal infections in France: Changes from 2009 to 2021 in  
71 antibiotic resistance and serotype distribution of *Streptococcus pneumoniae* based on data from  
72 the French Regional Pneumococcal Observatories network. *Infect Dis Now* S2666-  
73 9919(22)00270–6.
- 74 5. Le Turnier P, El Helali N, Guilhaumou R, Pilmis B, Revest M, Velly LJ, Leroy A-G, Duval X, Lemaitre  
75 F, Gregoire M, DIFCEFO study group. 2021. CSF concentration of cefotaxime in adult patients  
76 with pneumococcal meningitis: a multicentre retrospective study. *J Antimicrob Chemother*  
77 76:2352–2355.
- 78 6. Aardema H, Bult W, van Hateren K, Dieperink W, Touw DJ, Alffenaar J-WC, Zijlstra JG. 2020.  
79 Continuous versus intermittent infusion of cefotaxime in critically ill patients: a randomized  
80 controlled trial comparing plasma concentrations. *J Antimicrob Chemother* 75:441–448.
- 81 7. Le Turnier P, Navas D, Garot D, Guimard T, Bernard L, Tattevin P, Vandamme YM, Hoff J,  
82 Chiffolleau A, Dary M, Leclair-Visonneau L, Grégoire M, Pere M, Boutoille D, Sébille V, Dailly E,  
83 Asseray N, High-Dose Ceftriaxone CNS Infections Study Group. 2019. Tolerability of high-dose  
84 ceftriaxone in CNS infections: a prospective multicentre cohort study. *J Antimicrob Chemother*  
85 74:1078–1085.
- 86 8. Grégoire M, Dailly E, Le Turnier P, Garot D, Guimard T, Bernard L, Tattevin P, Vandamme Y-M,  
87 Hoff J, Lemaitre F, Verdier M-C, Deslandes G, Bellouard R, Sébille V, Chiffolleau A, Boutoille D,  
88 Navas D, Asseray N. 2019. High-Dose Ceftriaxone for Bacterial Meningitis and Optimization of  
89 Administration Scheme Based on Nomogram. *Antimicrob Agents Chemother* 63:e00634-19.

90 9. Maurin A, Escaut L, Gueit I, Gorenne I, Hoen B, Ploy M, Mourvillier B, Varon E, Duval X, Tubiana S.  
91 2017. Antibiothérapie de 1 re ligne des méningites bactériennes aiguës communautaires au sein  
92 de la cohorte COMBAT : adéquation aux recommandations SPILF 2008. Médecine et Maladies  
93 Infectieuses 47:S17.

94