Ceftriaxone for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia: a matter of dosages?

Stefano Di Bella[1] · **Milo Gatti**[2,3] · **Luigi Principe**[4]

Sir,

We read with great interest the recent manuscript by Yetmar et al. on different outcomes of ceftriaxone versus antistaphylococcal penicillins or cefazolin for methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. The authors found that ceftriaxone treatment was associated with treatment failure (HR 2.66, 95% CI 1.15–6.12; $p = 0.022$) [1].

As properly discussed by the authors, ceftriaxone was administered most of the time at the dosage of 2 g every 24 h (83.8%). We recognize that this is very common in everyday clinical practice. However, it is noteworthy that the minimum inhibitory concentration (MIC) against MSSA is two- to four-fold higher than other susceptible pathogens, being the MIC_{50} and the MIC_{90} of 4 and 8 mg/L, respectively. Consequently, standard ceftriaxone dosing regimen of 2 g every 24 h could be inadequate for attaining optimal pharmacokinetic/pharmacodynamic target (at least 100%$fT_{>MIC}$).

Usually clinicians use the following dosages for staphylococcal infections: cefazolin 2 g every 8 h, ceftriaxone 2 g every 24 h, and oxacillin 2 g every 4 h. However, the last EUCAST document [2] differentiates standard and high dosage for *S. aureus* as in Table 1.

Moreover, EUCAST specifies that for *S. aureus* infections, only high-dose ceftriaxone should be used. Notably, several preclinical and clinical pharmacokinetic/pharmacodynamic models suggested the use of high-dose ceftriaxone for maximizing bacterial killing and target attainments against MSSA [3–5]. In a hollow-fiber infection model in which a clinical isolate of MSSA was used (ceftriaxone MIC = 4 mg/L), Heffernan et al. [5] found that the likelihood of achieving bacterial growth stasis, a 1-log_{10} kill, and a 2-log_{10} kill within the first 24 h of ceftriaxone administration are negligible for doses less than 2 g twice daily at any renal function, whereas only high-dose therapy (2 g q12h) attained either bacterial stasis or a ≥ 1-log_{10} reduction in the total bacterial burden over the first 24 h of therapy. Notably, high-dose ceftriaxone consisting of 2 g q8h should be administered for ensuring bacterial stasis over 24 h in patients with normal renal function [5]. Similarly, in an in vitro PD model in which the activity of ceftriaxone was assessed against five clinical MSSA strains, Zelenitsky et al. found that the standard ceftriaxone dosing of 2 g/day showed bacterial growth or bacteriostasis in 54% of cases with bactericidal effects in only 17%, whereas bactericidal activity (at least 100%$fT_{>MIC}$) was attained in 95% of cases when high-dose ceftriaxone (i.e., 2 g q12h) was administered [4]. However, it is noteworthy that the proposed ceftriaxone dosages are based only on preclinical evidence, and currently, no clinical studies investigating the efficacy of high-dose ceftriaxone in MSSA bacteremia exist. Furthermore, which is the best ceftriaxone dosing against MSSA in challenging real-life scenarios (e.g., critically ill patients, obesity) still remains an unmet clinical need, considering that no pharmacokinetic or pharmacokinetic/pharmacodynamic have assessed this issue.

The indication of the high dose for ceftriaxone is available at the EUCAST breakpoint tables, starting from 2019 (version 9.0). Currently, there are no specific staphylococcal breakpoints for ceftriaxone, and testing of individual isolates for clinical purposes, including MIC determination, is strongly discouraged by EUCAST. *S. aureus* susceptibility to ceftriaxone could be inferred from the susceptibility to cefoxitin. Moreover, EUCAST recommends that if

✉ Stefano Di Bella
stefano932@gmail.com

[1] Clinical Department of Medical, Surgical and Health Sciences, Trieste University, Trieste, Italy

[2] Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

[3] Clinical Pharmacology Unit, Department for Integrated Infectious Risk Management, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[4] Clinical Pathology and Microbiology Unit, "San Giovanni di Dio" Hospital, Crotone, Italy

Table 1 EUCAST dosages used to define breakpoints

Antibiotic	Standard dose	High dose
Cefazolin	1 g q8h	2 g q8h
Ceftriaxone	2 g q24h	2 g q12h or 4 g q24h
Oxacillin	1 g q6h	Dosages vary by indication

ceftriaxone is reported for MSSA, this should be reported "Susceptible, increased exposure" (I) [2]. It is of note that the number of observations for cefazolin MIC distribution available at the EUCAST database [6] is more than 100-fold higher than those reported for ceftriaxone against *S. aureus*. Nevertheless, the proportion of strains with MIC values above the ECOFF is comparable (5% of strains for cefazolin vs 4% for ceftriaxone).

In light of this, we are likely facing a comparison between 2 drugs given at "high dose" versus 1 drug given at "standard dose." Of course, this is the real-life scenario; however, we believe that from the Yetmar et al. paper it should not be inferred that ceftriaxone is inferior to antistaphylococcal penicillins or cefazolin but that the 2 g daily ceftriaxone administration is inferior. One can speculate that even cefazolin and oxacillin if given at standard dosage would be inferior compared to the same molecules given at high dosage.

We congratulate Yetmar et al. for their meticulous work; however, we believe that the question is still open and would deserve further comparisons using antistaphylococcal ceftriaxone dose.

Author contribution All authors contributed to the conception and writing of the study.

Declarations

Competing interest The authors declare no competing interests.

References

1. Yetmar ZA, Khodadadi RB, Go JR, Chesdachai S, Abu Saleh OM (2023) Post-treatment outcomes of ceftriaxone versus antistaphylococcal penicillins or cefazolin for definitive therapy of methicillin-susceptible Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis 42:423–430
2. Online document. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf. Accessed 19 Mar 2023
3. Telles JP, Leme RCP, Campos ML, Ito C, Bail L, Nogueira KDS et al (2021) Ceftriaxone and methicillin-susceptible : a perspective from pharmacokinetics/pharmacodynamics studies. Expert Opin Drug Metab Toxicol 17:1039–1048
4. Zelenitsky SA, Beahm NP, Iacovides H, Ariano RE, Zhanel G (2018) Limitations of ceftriaxone compared with cefazolin against MSSA: an integrated pharmacodynamic analysis. J Antimicrob Chemother 1(73):1888–1894
5. Heffernan AJ, Sime FB, Lim SMS, Adiraju S, Wallis SC, Lipman J et al (2022) Pharmacodynamics of ceftriaxone for the treatment of methicillin-susceptible Staphylococcus aureus: is it a viable treatment option? Int J Antimicrob Agents 59:106537
6. Online document. MIC EUCAST. https://mic.eucast.org/. Accessed 19 Mar 2023