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1 **Defining standard and high dosages for beta-lactam agents administered by**
2 **intermittent, prolonged or continuous infusion: a PK/PD simulation study**

3

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8 the French committee on antimicrobial susceptibility testing (CA-SFM)

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30

31 **Running title:** Standard and high dosages of beta-lactams

32

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38

39 **Synopsis**

40 **Background.** The new definitions of antimicrobial susceptibility categories proposed by
41 EUCAST in 2020 require the definition of standard and high dosages of antibiotic. For
42 injectable beta-lactams, standard and high dosages have been proposed for short-infusion
43 regimens only.

44 **Objectives.** To evaluate dosages for beta-lactams administered by prolonged (PI) and
45 continuous infusion (CI).

46 **Methods.** Monte-Carlo simulations were performed for seven injectable beta-lactams:
47 aztreonam, cefepime, cefotaxime, ceftazidime, piperacillin, and temocillin. Various
48 dosage regimens based on short, PI or CI were simulated in virtual patients. Pharmacokinetic
49 (PK) profiles and PTA were obtained based on reference population PK models, as well as
50 pharmacokinetic/pharmacodynamic (PK/PD) targets and MIC breakpoints proposed by
51 EUCAST. Alternative dosage regimens associated with PTA values similar to that of
52 recommended dosages up to the breakpoints were considered acceptable.

53 **Results.** Adequate PTA was confirmed for most EUCAST short-infusion dosage regimens. A
54 total of 9 standard and 14 high dosages based on PI (3 to 4h) or CI were identified as
55 alternatives. For cefepime and aztreonam, only PI and CI regimens could achieve acceptable
56 PTA for infections caused by *Pseudomonas spp* : 2 g q8h as PI of 4h or 6 g /24h CI for
57 cefepime; 2 g q6h as PI of 3h or 6 g /24h CI for aztreonam.

58 **Conclusion.** Those alternative standard and high dosage regimens are expected to provide
59 antibiotic exposure compatible with EUCAST new definitions of susceptibility categories and
60 associated MIC breakpoints. However, further clinical evaluation is necessary.

61 **Introduction**

62 In 2020, EUCAST changed the definitions of the three susceptibility categories, S
63 (susceptible), I (formerly defined as intermediate) and R (resistant).^{1,2} The new definitions
64 emphasize the importance of pharmacokinetic/pharmacodynamic principals (PK/PD), i.e., the
65 relationships between the susceptibility of the bacteria and the antibiotic exposure at the site
66 of infection. A bacteria should be categorised as S – “Susceptible, standard dosing regimen”,
67 when there is a high likelihood of therapeutic success using a standard dosing regimen of the
68 antibiotic. It should be categorized as I – “Susceptible, increased exposure”, when there is a
69 high likelihood of therapeutic success considering that exposure to the antibiotic is increased
70 by adjusting the dosing regimen or by its elevated concentration at the site of infection. It
71 should be defined as R – “Resistant”, when there is a high likelihood of therapeutic failure
72 even when exposure is increased.

73
74 Those new definitions of susceptibility categories require the definition of standard and high
75 dosages of antibiotic. Those have been examined and are provided by EUCAST in a specific
76 document in its breakpoint table that is updated each year
77 (https://www.eucast.org/clinical_breakpoints).

78 However, EUCAST provides only one standard and high dosage for most agents. For
79 injectable agents, this means that only a specific dose amount, infusion duration and dosing
80 interval is considered. For example, the standard and high daily dosages defined for IV
81 cefotaxime are 1 g q8h and 2 g q8h, respectively, assuming short intermittent infusion. While
82 the EUCAST document states that alternative dosage regimens may result in equivalent
83 exposure and thus may be appropriate, those alternative regimens are not specified. This is
84 a limitation for clinical application of new susceptibility categories, especially for injectable
85 beta-lactam agents, because various administration schedules are used in clinical practice.³
86 Prolonged (PI) and continuous infusion (CI) regimens of beta-lactams regimens are
87 associated with increased time during which the free antibiotic concentration is above the
88 MIC (fT>MIC) - which is the PK/PD driver of the antibacterial effect of beta-lactams.⁴ Such

89 regimens result in a higher probability to achieve a defined target value of $fT > MIC$).^{5, 6} There
90 is clinical evidence of the benefits of PI and CI of beta-lactam, especially for severe infections
91 in critically ill patients.^{7, 8}

92 Standard and high dosage regimens associated with susceptibility categories defined by
93 EUCAST have not been defined for beta-lactam agents when administered by PI or CI, in
94 most cases.

95 The objective of the study was to evaluate alternative dosage regimens for seven beta-
96 lactam agents administered by PI or CI by using a PK/PD simulation approach.

97

98 **Material and methods**

99 PK/PD Monte Carlo simulations were performed for seven injectable beta-lactams:
100 aztreonam, cefepime, cefotaxime, ceftazidime, piperacillin (with or without
101 tazobactam), and temocillin.

102 As this simulation study was based on literature data only, no ethics approval was required.

103 First, we selected a population PK model for each agent. To replicate the EUCAST reference
104 simulations, details were necessary about the population PK model e.g. number of
105 compartments, parameter distribution, covariance, influential covariates. Most of the time, the
106 EUCAST rationale documents (RD) do not provide enough details to replicate the population
107 PK model indicated, but a published reference is provided. When available, the published
108 population model mentioned in the EUCAST rationale documents (RD) was used, as it was
109 the basis for defining EUCAST MIC breakpoint as well as the standard and high dosages
110 (<https://www.eucast.org/publications-and-documents/rd>). When no published model was
111 cited in the EUCAST rationale documents, we search for another model in the literature.
112 When several published population PK models were available, we excluded models
113 developed only in special populations (e.g., critically ill patients, patients with renal
114 impairment, neutropenic patients, obese patients, patients under surgical procedure). Models
115 developed in non-infected subjects were also excluded, unless no alternative was available.
116 We selected the published model developed in the largest number of subjects or patients,
117 not pertaining to special populations described above.

118 The selected models were imported into the Pmetrics or the NONMEM programs to perform
119 dosing simulations. For each drug, the reference standard and high dosages provided by
120 EUCAST were simulated. Alternative dosage regimens with PI (e.g., infusion over 50% of the
121 dosage interval) or CI were simulated as well. Model covariates (e.g. renal function, body
122 weight) were taken into account. For renal function, we only simulated patients with normal
123 renal function, because reference dosages are only defined in such conditions. Covariance
124 between PK parameters was also considered when it was clearly described in the EUCAST
125 RD or in publications. This was the case for the ceftazidime model only.⁹

126 Simulations results at steady-state were analyzed to compute PTA. For each beta-lactam,
127 we used the target indicated in the EUCAST rationale documents, which is a percentage of
128 time during which free antibiotic concentration is above the MIC over 24h or the dosing
129 interval (fT>MIC). Free concentration was calculated based on plasma protein binding
130 specified in EUCAST RD or in publications. For each antibiotic, we checked that the PTA
131 obtained with EUCAST standard and high dosage regimens were in accordance with values
132 reported in EUCAST RD, and that PTA \geq 90% was achieved up to the MIC breakpoint
133 proposed by EUCAST. A higher PTA threshold of \geq 95% was also considered in the analysis.
134 This was a way to confirm that the models used in the simulations were adequate. We
135 considered the clinical MIC breakpoints for *Enterobacterales* and/or *Pseudomonas spp* which
136 are the main pathogens targeted with those antibiotics. PTA for the PK/PD MIC breakpoints
137 defined by EUCAST were also checked, although they were consistent with the above-
138 mentioned species-related breakpoints for those agents (see Table 1). Of note, PK/PD
139 breakpoints are defined as non-species related breakpoints that should be used to
140 categorize susceptibility for pathogens without defined clinical, species-related breakpoints.
141 They are based on PK/PD rationale and MIC distributions only, not clinical evidence. Mouton
142 *et al.* have covered this topic and the overall EUCAST approach of setting MIC breakpoints
143 in details.¹⁰

144 For all agents except ceftazidime, several MIC breakpoints were available. For example, for
145 aztreonam, the values (Susceptible \leq / Resistant $>$) were as follows: 1/4, 0.001/16, and 4/8
146 for the *Enterobacterales*, *Pseudomonas spp* and PK/PD breakpoints, respectively. We
147 considered that the standard dosages should be associated with PTA \geq 90% up to the lower
148 PK/PD breakpoint to cover all possible pathogens (4 mg/L in the case of aztreonam), while
149 the high dosages should be associated with PTA \geq 90% up to the highest values, either
150 PK/PD or species-related (16 mg/L for aztreonam).

151

152 Alternative regimens associated with PTA greater than or equal to those obtained with the
153 reference dosages up to the MIC breakpoints were considered as acceptable. Because
154 tazobactam is currently not considered in the EUCAST PK/PD rationale and PTA results of
155 piperacillin/tazobactam, only piperacillin exposure was considered in the analysis. The
156 results are supposed to hold true for both piperacillin alone and in combination with
157 tazobactam.

158

159 **Results**

160 The models used, simulation settings, targets considered, and supporting references are
161 summarized in **Table 1**.^{9, 11-15} The population PK models mentioned in EUCAST RD were
162 used for cefotaxime, ceftazidime and temocillin. For cefotaxime and piperacillin, the EUCAST
163 RD did not provide published references for the model. However, for cefotaxime, no
164 appropriate model was identified in the literature, so the model from EUCAST RD was
165 eventually used, assuming a one-compartment model without covariates and gaussian
166 distribution of the volume of distribution and half-life. For piperacillin, the model of Li *et al.*¹⁵
167 was preferred, as the study population and model characteristics were better explained than
168 in EUCAST RD. For cefepime, cefoxitin, and aztreonam, models from the literature were
169 used, because no published model was cited in EUCAST RD, or no RD was available
170 (cefoxitin). There were differences in the PK population study size, and model characteristics
171 between drugs. One- and two-compartment models with and without covariates were
172 reported and used.

173

174 Plots of PTA are shown in **Figure 1** for cephalosporin agents (cefepime, cefotaxime,
175 cefoxitin, ceftazidime) and in **Figure 2** for aztreonam, piperacillin and temocillin.

176 Except in two cases, simulations performed with the EUCAST standard and high dosages
177 confirmed that $PTA \geq 90\%$ was achieved up to the MIC breakpoints defined above. For
178 cefepime, the two EUCAST standard dosage of 2 g q12h and 1 g q8h (as 30 min infusion for
179 both) were associated with $PTA = 85\%$ and 89% , respectively, for a $MIC = 4 \text{ mg/L}$ (the

180 resistance clinical breakpoint for *Enterobacterales* and susceptible PK/PD (non-species-
181 related) breakpoint). For aztreonam, the EUCAST standard dosage was also associated with
182 PTA slightly below the acceptance value (PTA = 88%) for a MIC of 4 mg/L (resistance clinical
183 breakpoint for *Enterobacterales* and susceptible PK/PD (non-species-related) breakpoint).
184 For cefoxitin, none of the investigated regimens, ranging from 6 to 12 g daily with various
185 infusion times provided a PTA $\geq 90\%$ at the MIC value of 8 mg/L. The highest PTA (82 %)
186 was obtained for 2g q4h with 2h infusion. Regimens based on short infusion showed very
187 poor PTA results, even for MIC values lower than 8 mg/L.

188

189 Except for cefoxitin, several dosages with PI and CI of beta-lactam were found to have PTA
190 profiles similar to that of standard and high dosages based on short infusion proposed by
191 EUCAST. For a given dose, prolonging the infusion time to half of the dosing interval (e.g.,
192 infusing over 4h for a 8h-dosing interval) was associated with PTA equal to or greater than
193 that of a short infusion. For CI regimens, achievement of the PK/PD target up to the MIC
194 breakpoint was possible despite a lower total daily dose compared with short-infusion
195 regimens.

196 **Figure 3** illustrates the effect of prolonging the infusion time on the PK/PD index $fT_{>MIC}$ for
197 ceftazidime. Regimens associated with similar PTA (see Figure 1) showed variable $fT_{>MIC}$.

198 **Table 2** summarizes proposed standard and high dosage regimens based on EUCAST
199 recommendations and our PK/PD simulations.

200

201

202 **Discussion**

203 Standard and high antibiotic dosages suggested by EUCAST are useful but may not be
204 relevant in all clinical settings. For injectable antibiotics, the infusion regimen (dose amount,
205 dose interval, infusion duration) may vary across countries and clinical units, especially for
206 beta-lactams.¹⁶ For this group, there is a PK/PD rationale for using PI or CI to optimize drug
207 exposure, but dosages suggested by EUCAST were only provided for short-infusion
208 regimens, except for a few drugs. There is a need to define several standard and high
209 dosages for injectable beta-lactams, for short, prolonged and continuous infusion.

210

211 Monte Carlo simulations and PTA analysis based PK/PD properties of antibiotics play a
212 major role in setting clinical MIC breakpoints.¹⁰ We used those techniques to identify dosage
213 regimens associated with adequate drug exposure and PTA for seven beta-lactams
214 administered by PI or CI.

215 The standard and high dosage suggested by EUCAST were associated with adequate PTA
216 up to the breakpoint in our simulations. This supports the validity of the model selected and
217 simulations conducted. In some cases (e.g. temocillin, ceftazidime), for a given dose and
218 dosing interval, both short and prolonged infusion of the same dose were associated with
219 acceptable PTA $\geq 90\%$. One may question the clinical relevance of PI as suggested in Table
220 2, considering that short infusions appear as effective and more convenient in clinical
221 practice. However, it should be reminded that target attainment is a binary result, based on a
222 continuous variable, the PK/PD index ($fT > MIC$). Regimens associated with acceptable PTA
223 can yet be associated with different values of $fT > MIC$. As illustrated with ceftazidime in
224 Figure 3, for a given dose, prolonging the infusion time results in higher $fT > MIC$. This may be
225 of interest in clinical situations requiring drug exposure higher than the PK/PD target
226 considered in EUCAST RD. Our results add to many other reports supporting the interest of
227 performing PI or CI of beta-lactam from a PK/PD perspective.^{5, 17} EUCAST dosages for
228 piperacillin/tazobactam were revised in 2021, and those for aztreonam and cefepime for
229 *Pseudomonas spp.* in 2023, with the introduction of PI, based in part on this rationale. Our

230 results support the generalizability for other beta-lactams. However, considerations about
231 loading dose and stability should be examined for practical implementation of PI and CI.¹⁸

232

233 For cefepime dosing, the study group distinguished infections caused by *Pseudomonas spp.*
234 and those caused by other pathogens (see Table 2). Indeed, *Pseudomonas spp.* are only
235 susceptible to high cefepime exposure, and a single resistance clinical breakpoint is defined
236 by EUCAST. While other agents share this feature (ceftazidime, piperacillin), the study group
237 considered that it was adequate to suggest a high dosage very clearly in this case, because
238 cefepime is a first line agent for pseudomonal infections. Moreover, a PK/PD target higher
239 than that mentioned in EUCAST RD (about 60-70% versus 50%) has been suggested for
240 cefepime in several clinical reports.¹⁹⁻²¹ This also justifies the special need for a high dosage
241 for this pathogen. This has been considered by EUCAST in its 2023 breakpoint table, which
242 now suggests a dosage of 2g q8h as a 4h infusion for severe *P. aeruginosa* infections.

243 Aztreonam dosing for infections caused by *Pseudomonas spp.* was especially considered in
244 the same way. High aztreonam dosages of 2 g q6h over 30 min and 2g q8h over 4h were
245 still associated with PTA of 79% and 87% for a MIC of 16 mg/L, respectively. So, those
246 appear insufficient for infections caused by *Pseudomonas spp.* Dosages of 2 g q6h as a 3h
247 infusion and 6 g q24h CI were associated PTA > 90% and should be recommended in this
248 case. This is also in line with EUCAST 2023 breakpoint table, which now suggests a dosage
249 of 2g q6h as a 3h infusion for severe *P. aeruginosa* infections.

250 Indeed, for all first-line antipseudomonal agents (piperacillin + tazobactam, ceftazidime,
251 cefepime, aztreonam), it important to remind that all wild-type *Pseudomonas spp.* organisms
252 are always categorized by EUCAST as “susceptible, increased exposure”, whatever the
253 measured MIC is. An arbitrary “off-scale” susceptibility breakpoint of 0.001 has been fixed to
254 enforce this categorization (see Table 1 and

255 [https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf)
256 [Breakpoint Tables.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf), accessed July 26, 2023). So, only high dosages of those agents

257 should be used for this pathogen. By contrast, standard dosages may still be adequate for
258 *Enterobacterales* with low MICs.

259

260 Cefoxitin is a cephamycin derivative, second-generation cephalosporin. It is widely used as a
261 prophylaxis therapy in various surgical procedures, but it can also be used for treating
262 documented infections. The labelled dosage is 1-2 g q8h in France, but dosages up to 2 g
263 every 4-6h are approved in UK and Northern America. Cephamycins have shown resistance
264 to ESBL enzymes and cefoxitin has been considered as a carbapenem-sparing agent for
265 infections caused by ESBL-producing Gram negative pathogens, especially urinary tract
266 infections.^{22, 23}

267 There is no breakpoint and no dosage suggested by EUCAST for cefoxitin. In France, CA-
268 SFM has proposed a MIC breakpoint of 8/8 mg/L for *E. coli* only. Our simulations indicate
269 that recommended dosages of 2g q8h and even larger dosages up to 12g per day fail to
270 achieve acceptable PTA $\geq 90\%$ up to a MIC of 8 mg/L. Nevertheless, dosages are suggested
271 in Table 2, with a warning about insufficient PTA for high MIC values. Our results are in
272 agreement with previous PK studies that reported considerable dosage requirements in
273 patients with normal renal function.^{24, 25} This raises questions about the MIC breakpoint,
274 approved dosages (especially in France) and overall role of this agent in therapy. Further
275 clinical evaluation is necessary.

276 The case of cefoxitin is interesting from a PK/PD perspective. For such agent with a very
277 short half-life, a low PK/PD objective (50% fT>MIC) and a high MIC upper bound, the dosing
278 schedule associated with best PTA was not continuous, but prolonged infusion (e.g. 2g q4h
279 (2h) versus 12 g q24h CI, see figure 1). This is because prolonged infusion is associated with
280 a peak that permits to exceed the MIC for some time. By contrast, continuous infusion
281 produces in a steady concentration (C_{ss}), and the result in terms of fT>MIC is binary, it can
282 only be 0 or 100%. So, for high MIC values, many patients have C_{ss} below the MIC over the
283 entire dosing interval, and the overall PTA is low.

284

285 This study has several limitations. We only used one model for each drug for performing
286 dosing simulations. While this is consistent with the current EUCAST approach, it would be
287 interesting to consider various models to better appraise the uncertainty in PTA analysis.
288 Some models referenced by EUCAST were developed in a very low number of healthy
289 subjects (e.g., ceftazidime). We believe that large models built in patients would be more
290 relevant. Typical values of PK parameters may be different between healthy volunteers and
291 patients, and variability is usually larger in patients. So, when simulating from models based
292 on a low number of healthy subjects, there is a risk of overestimating PTA because of the
293 underestimation of inter-individual variability. This issue has been discussed by Lodise *et al.*
294 about ceftobiprole.²⁶

295 Regarding PK/PD targets, we only considered values suggested in EUCAST RD, i.e. $fT > MIC$
296 ranging from 35 to 60%. Higher target values have been suggested for some agents such as
297 cefepime,²¹ and in some patient populations, especially critically ill patients.^{27, 28} It is
298 important to distinguish antibiotic targets and dosages used to define MIC breakpoints and
299 those recommended to treat patients. Our aim was to examine alternative dosages used to
300 define MIC breakpoints. Our PTA results are based on specific PK/PD target values that are
301 described in the manuscript. They may not be relevant when considering other targets. It
302 seems relevant to consider higher antibiotic dosage for deep-seated infections (e.g., bone
303 and joint infection), immunocompromised or severely ill patients, even for an infection caused
304 by a susceptible strain. Also, we did not consider special population that would require
305 dosage adjustment (e.g., patients with renal impairment, obese patients), as it was out of the
306 scope of this work. In line with EUCAST, standard and high dosages suggested in the
307 present report should not be considered as therapeutic guidance. Those are dosages
308 associated with a drug exposure compatible with the definition of bacterial susceptibility and
309 associated breakpoints. Finally, the main limitation of this work is the lack of clinical data
310 supporting alternative dosage regimens.

311

312 **Conclusion**

313 Alternative standard and high dosage regimens based on PI and CI have been identified for
314 seven injectable beta-lactams by Monte Carlo simulations. Those regimens are expected to
315 provided antibiotic exposure compatible with EUCAST new definitions of susceptibility
316 categories and associated MIC breakpoints. However, further clinical evaluation is
317 necessary.

318

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333

334 **Contribution**

335 All authors contributed to study design and data review. SG and VJ performed PK/PD
336 simulations and drafted the manuscript. All authors performed critical review of the
337 manuscript draft and approved the final version of the manuscript.

338

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Table 1. PK/PD rationale and setting of Monte Carlo simulations.

Antibiotic	Simulation size	PK program	Population PK model	Original population	Model covariates	PK/PD target	Free fraction	MIC breakpoints in mg/L (S ≤ / R >)	Simulated regimens Dosage (infusion time)
Aztreonam	N = 1000	Pmetrics	2 compartments ¹¹	N = 42 (30 HV, 12 patients)	CL _{CR} (fixed at 90 mL/min) on CL BW on V1	60% fT> MIC	48.5%	1/4 (E) 0.001/16 (P) 4/8 (PK/PD)	1, 2 g q8h (30 min) 1, 2 g q8h (4h) 1, 2 g q6h (30 min) 1, 2 g q6h (3h) 2, 4, 6, 8g q24h (CI)
Cefepime	N = 1000	NONMEM	2 compartments ¹²	N = 36 Patients with suspected infection	CL _{CR} (fixed at 100 mL/min)	50% fT> MIC	80%	1/4 (E) 0.001/8 (P) 4/8 (PK/PD)	2 g q12h (30 min) 1, 2g q8h (30 min) 1, 2 g q8h (4h) 2 g q6h (30 min) 2 g q6h (3h) 4, 6, 8 g q24h (CI)
Cefotaxime	N = 1000	Pmetrics	1 compartment [EUCAST]	Not specified	None	50% fT> MIC	64%	1/2 (E) 1/2 (PK/PD)	1, 2 g q8h (30 min) 0.5, 1, 2 g q8 h (4h) 2, 4, 6 g q24h (CI)
Cefoxitin	N = 1000	NONMEM	2 compartments ¹³	N = 16 (HV)	None	50% fT> MIC	30%	8/8 (E) ^a	2 g q6h (1h) 2 g q6h (3h)

									2 g q6h (4h) 2 g q4h (30 min) 2 g q4h (2h) 6 g q24h (CI) 8 g q24h (CI) 12 g q24h (CI)
Ceftazidime	N = 1000	Pmetrics	2 compartments [EUCAST and ⁹]	N = 8 (HV)	None	50% fT> MIC	90%	1/4 (E) 0.001/8 (P) 4/8 (PK/PD)	1, 2 g q8h (30 min) 1, 2 g q8h (4h) 1 g q6h (30 min) 2, 4 or 6 g q24h (CI)
Piperacillin (alone or in combination with tazobactam)	N = 1000	Pmetrics	1 compartment ¹⁵	N = 56 (patients)	CL _{CR} (fixed at 90 mL/min) on CL Body weight (random) on V1	40% fT>MIC	81%	8/8 (E) 0.001/16 (P) 8/16 (PK/PD)	4 g q8h (30 min or 4h) 4 g q6h (30 min, 3h, or 4h) 8, 12, 16, 20 g q24h (CI)
Temocillin	N = 1000	Pmetrics	2 compartments [EUCAST and ¹⁴]	N = 29 (patients)	None	35% fT>MIC	41%	0.001/16 (E) 8/8 (PK/PD)	2 g q12h (30 min or 4h) 2 g q8h (30 min or 4h) 2, 4, 6 g q24h (CI)

^aCefoxitin MIC breakpoint defined in France by CA-SFM for *E. coli* only. EUCAST has not defined any breakpoint for this agent.

Abbreviations: CI, Continuous infusion, CL_{CR}, creatinine clearance, E, EUCAST clinical breakpoint for *Enterobacterales*; HV, healthy volunteers; P, EUCAST clinical breakpoint for *Pseudomonas*; PK/PD, EUCAST pharmacokinetic/pharmacodynamic breakpoint; S, susceptible; R, resistant.

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Table 2. Proposed standard and high dosages of injectable beta-lactams.

Beta-lactam	Standard dosage	High dosage
Aztreonam	1 g q8h (30 min) ^a 2 g q24h (CI) ^d	2 g q6h (30 min) ^{a,d} 2 g q8h (4h) ^d 6 g q24h (CI) ^d
Aztreonam (<i>Pseudomonas spp</i>)	NA	2g q6h (3h) ^{b,d} 6 g q24h (CI) ^d
Cefepime	1 g q8h (30 min) ^a	2 g q8h (30 min) ^a 2 g q8h (4h) ^d 4 g q24h (CI)
Cefepime (<i>Pseudomonas spp</i>)	NA	2 g q6h (30 min) ^d 2 g q8h (4h) ^{b,d} 6g q24h (CI) ^d
Cefotaxime	1 g q8h (30 min) ^a 0.5 g q8h (4h) ^d 2 g q24h (CI) ^d	2 g q8h (30 min) ^a 2 g q8h (4h) ^d 4 g q24h (CI) ^d
Cefoxitin	2 g q6h (4h) ^c 2 g q4h (2h) ^c 8-12 g q24h (CI) ^c	NA
Ceftazidime	1 g q8h (30 min) ^{a,d} 1 g q8h (4h) ^d 2 g q24h (CI) ^d	2 g q8h (30 min) ^{a,d} 2 g q8h (4h) ^d 4 g q24h (CI) ^d
Piperacillin (alone or in combination with tazobactam)	4g q6h (30 min) ^{a,d} 4 g q8h (4h) ^d 8 g q24h (CI) ^d	4g q6h (3h) ^{a,d} 12 g q24h (CI) ^d
Temocillin	2 g q12h (30 min) ^{a,d} 2 g q12h (4h) ^d 4 g q24h (CI) ^d	2 g q8h (30 min) ^a 2 g q8h (4h) ^d 6 g q24h (CI) ^d

^a Dosages suggested by EUCAST (The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 13.0, 2023.

https://www.eucast.org/clinical_breakpoints)

^b Dosages suggested by EUCAST for severe *P. aeruginosa* infections only

^c Those dosages are suggested as guidance for therapy, but they are associated with PTA < 90% for MIC values > 4 mg/L.

^d Dosages associated with PTA ≥ 95%

Abbreviations: NA, not applicable

Infusion durations are indicated in brackets.

Figure 1. Probabilities of target attainment for various cephalosporin dosage regimens

Standard and high dosage regimens suggested by EUCAST are shown in light green.

The horizontal dashed line represents PTA = 90%.

The vertical dashed lines represent clinical breakpoint for *Enterobacterales* or *Pseudomonas spp.* or PK/PD MIC breakpoints. The latter should be used for pathogens without defined clinical, species-related breakpoints (see Table 1 and methods section).

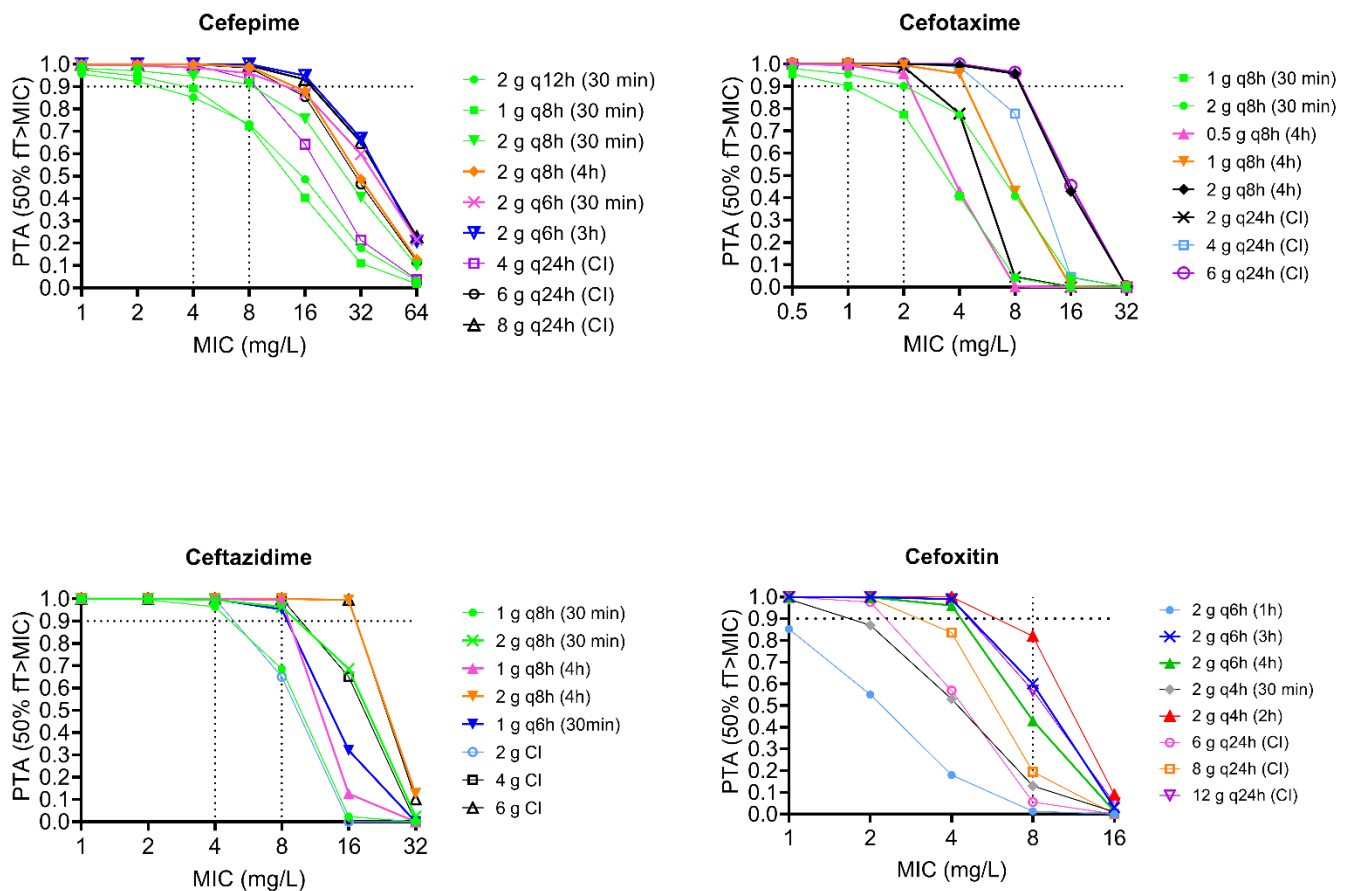


Figure 2. Probabilities of target attainment for various dosage regimens of piperacillin, temocillin, and aztreonam

Standard and high dosage regimens suggested by EUCAST are shown in light green.

The horizontal dashed line represents PTA = 90%.

The vertical dashed lines represent clinical or PK/PD MIC breakpoint (see Table 1)

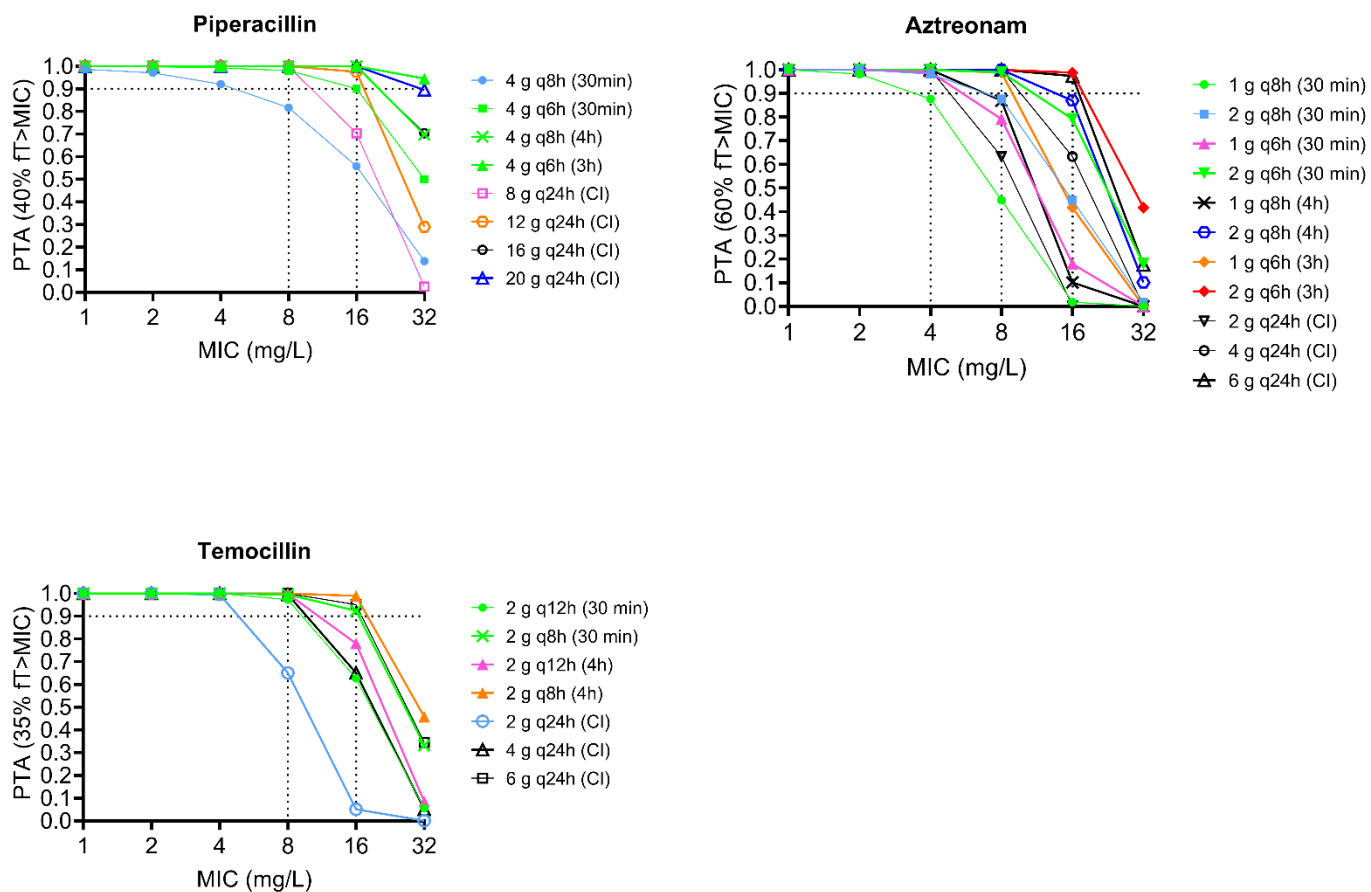


Figure 3. Value of the pharmacodynamic index ($fT > MIC$) as a function of dosage regimen for ceftazidime.

The colored bars represent mean values and black error bars represent standard deviations of the percentage of time during which the free concentration of ceftazidime is above the MIC ($fT > MIC$)

