

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

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1	Defining standard	and high dosag	es for beta-lactam agent	s administered by

2 intermittent, prolonged or continuous infusion: a PK/PD simulation study

- 3
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39 Synopsis

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

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

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

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

(susceptible), I (formerly defined as intermediate) and R (resistant).^{1, 2} The new definitions 63 64 emphasize the importance of pharmacokinetic/pharmacodynamic principals (PK/PD), i.e., the relationships between the susceptibility of the bacteria and the antibiotic exposure at the site 65 of infection. A bacteria should be categorised as S – "Susceptible, standard dosing regimen", 66 when there is a high likelihood of therapeutic success using a standard dosing regimen of the 67 antibiotic. It should be categorized as I – "Susceptible, increased exposure", when there is a 68 high likelihood of therapeutic success considering that exposure to the antibiotic is increased 69 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

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 (<u>https://www.eucast.org/clinical_breakpoints</u>).

However, EUCAST provides only one standard and high dosage for most agents. For 78 injectable agents, this means that only a specific dose amount, infusion duration and dosing 79 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 the EUCAST document states that alternative dosage regimens may result in equivalent 82 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 beta-lactam agents, because various administration schedules are used in clinical practice.³ 85 86 Prolonged (PI) and continuous infusion (CI) regimens of beta-lactams regimens are associated with increased time during which the free antibiotic concentration is above the 87 88 MIC (fT>MIC) - which is the PK/PD driver of the antibacterial effect of beta-lactams.⁴ Such

- 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

102

99 PK/PD Monte Carlo simulations were performed for seven injectable beta-lactams:

aztreonam, cefepime, cefotaxime, cefoxitin, ceftazidime, piperacillin (with or withouttazobactam), and temocillin.

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

First, we selected a population PK model for each agent. To replicate the EUCAST reference 103 104 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 population model mentioned in the EUCAST rationale documents (RD) was used, as it was 108 109 the basis for defining EUCAST MIC breakpoint as well as the standard and high dosages (https://www.eucast.org/publications-and-documents/rd). When no published model was 110 cited in the EUCAST rationale documents, we search for another model in the literature. 111 When several published population PK models were available, we excluded models 112 113 developed only in special populations (e.g., critically ill patients, patients with renal impairment, neutropenic patients, obese patients, patients under surgical procedure). Models 114 developed in non-infected subjects were also excluded, unless no alternative was available. 115 116 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 dosing simulations. For each drug, the reference standard and high dosages provided by 119 120 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

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

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

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

158

159 Results

160 The models used, simulation settings, targets considered, and supporting references are summarized in **Table 1**.^{9, 11-15} The population PK models mentioned in EUCAST RD were 161 used for cefotaxime, ceftazidime and temocillin. For cefotaxime and piperacillin, the EUCAST 162 163 RD did not provide published references for the model. However, for cefotaxime, no appropriate model was identified in the literature, so the model from EUCAST RD was 164 eventually used, assuming a one-compartment model without covariates and gaussian 165 distribution of the volume of distribution and half-life. For piperacillin, the model of Li et al. ¹⁵ 166 167 was preferred, as the study population and model characteristics were better explained than in EUCAST RD. For cefepime, cefoxitin, and aztreonam, models from the literature were 168 used, because no published model was cited in EUCAST RD, or no RD was available 169 (cefoxitin). There were differences in the PK population study size, and model characteristics 170 171 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 $PTA \ge 90\%$ was achieved up to the MIC breakpoints defined above. For

cefepime, the two EUCAST standard dosage of 2 g q12h and 1 g q8h (as 30 min infusion for

both) were associated with PTA = 85% and 89%, respectively, for a MIC = 4 mg/L (the

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

188

Except for cefoxitin, several dosages with PI and CI of beta-lactam were found to have PTA 189 190 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 breakpoint was possible despite a lower total daily dose compared with short-infusion 194 195 regimens. Figure 3 illustrates the effect of prolonging the infusion time on the PK/PD index fT>MIC for 196

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.

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201

202 Discussion

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

210

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

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

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

233 For cefepime dosing, the study group distinguished infections caused by *Pseudomonas spp.* and those caused by other pathogens (see Table 2). Indeed, *Pseudomonas spp.* are only 234 susceptible to high cefepime exposure, and a single resistance clinical breakpoint is defined 235 by EUCAST. While other agents share this feature (ceftazidime, piperacillin), the study group 236 237 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 than that mentioned in EUCAST RD (about 60-70% versus 50%) has been suggested for 239 cefepime in several clinical reports.¹⁹⁻²¹ This also justifies the special need for a high dosage 240 for this pathogen. This has been considered by EUCAST in its 2023 breakpoint table, which 241 242 now suggests a dosage of 2g q8h as a 4h infusion for severe *P. aeruginosa* infections. Aztreonam dosing for infections caused by *Pseudomonas spp* was especially considered in 243 the same way. High aztreonam dosages of 2 g q6h over 30 min and 2g q8h over 4h were 244 245 still associated with PTA of 79% and 87% for a MIC of 16 mg/L, respectively. So, those appear insufficient for infections caused by *Pseudomonas spp.* Dosages of 2 g q6h as a 3h 246 infusion and 6 g q24h CI were associated PTA > 90% and should be recommended in this 247 case. This is also in line with EUCAST 2023 breakpoint table, which now suggests a dosage 248 249 of 2g q6h as a 3h infusion for severe *P. aeruginosa* infections. 250 Indeed, for all first-line antipseudomonal agents (piperacillin + tazobactam, ceftazidime,

cefepime, aztreonam), it important to remind that all wild-type *Pseudomonas spp.* organisms
are always categorized by EUCAST as "susceptible, increased exposure", whatever the
measured MIC is. An arbitrary "off-scale" susceptibility breakpoint of 0.001 has been fixed to
enforce this categorization (see Table 1 and

255 https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_

256 <u>Breakpoint_Tables.pdf</u>, accessed July 26, 2023). So, only high dosages of those agents

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

259

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

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

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

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

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

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

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

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

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

^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, CLCR, 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.

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 q6h (30 min) ^{a,d}
	2 g q24h (CI) ^d	2 g q8h (4h) ^d
		6 g q24h (Cl) ^d
Aztreonam (Pseudomonas spp)	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 (Pseudomonas spp)	NA	2 g q6h (30 min) ^d
		2 g q8h (4h) ^{b,d}
		6g q24h (Cl) ^d
Cefotaxime	1 g q8h (30 min)ª	2 g q8h (30 min) ^a
	0.5 g q8h (4h) ^d	2 g q8h (4h) ^d
	2 g q24h (CI) ^d	4 g q24h (Cl) ^d
Cefoxitin	2 g q6h (4h)°	NA
	2 g q4h (2h)⁰	
	8-12 g q24h (CI)º	
Ceftazidime	1 g q8h (30 min) ^{a,d}	2 g q8h (30 min) ^{a,d}
	1 g q8h (4h) ^d	2 g q8h (4h) ^d
	2 g q24h (CI) ^d	4 g q24h (CI) ^d
Piperacillin (alone or in	4g q6h (30 min) ^{a,d}	4g q6h (3h) ^{a,d}
combination with tazobactam)	4 g q8h (4h) ^d	12 g q24h (CI) ^d
	8 g q24h (CI) ^d	
Temocillin	2 g q12h (30 min) ^{a,d}	2 g q8h (30 min) ^a
	2 g q12h (4h) ^d	2 g q8h (4h) ^d
	4 g q24h (CI) ^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. <u>https://www.eucast.org/clinical_breakpoints</u>)

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

 $^{\rm c}$ Those dosages are suggested as guidance for the rapy, but they are associated with PTA < 90% for MIC values > 4 mg/L.

 $^{\rm d}$ Dosages associated with PTA $\geq 95\%$

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 (*f*T>MIC)

