

29 **Abstract**

30 **Objectives:** To investigate the population pharmacokinetics (PK) of amoxicillin in ICU burn
31 patients and the optimal dosage regimens.

32

33 **Methods:** Prospective study involving 21 consecutive burn patients receiving amoxicillin. PK
34 data were analysed using non-linear mixed effects modelling. Monte-Carlo simulations
35 assessed the influence of various amoxicillin dosage regimens with identified covariates on
36 the probability to achieve a target (PTA) value of time during which free amoxicillin
37 concentrations in plasma exceeded the minimal inhibitory concentration ($fT > MIC$).

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39 **Results:** A two-compartment model best described the data. Creatinine clearance (CL_{CR}) and
40 body weight (BW) influenced amoxicillin CL and central volume of distribution (V1),
41 respectively. The median CL_{CR} (Cockcroft-Gault formula) was high (128 mL/min) with 25%
42 of patients having $CL_{CR} > 150$ mL/min. The CL, V1 and $t_{1/2}$ values at steady-state for a patient
43 with a CL_{CR} of 110 mL/min and BW of 70 kg were 13.6 L/h, 9.7 L and 0.8 h, respectively.
44 Simulations showed that a target $fT > MIC \geq 50\%$ was achieved ($PTA > 90\%$) with standard
45 amoxicillin dosage regimens (1-2 g q6-8 h) when the MIC was low (< 1 mg/L). However,
46 increased dosages of up to 2 g/4 h were necessary in patients with augmented CL_R or higher
47 MIC. Prolonging amoxicillin infusion from 30 min to 2 h had a favourable effect on target
48 attainment.

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50 **Conclusion:** This population analysis shows an increased amoxicillin CL and substantial CL
51 PK variability in burn patients compared to literature data with non-burn patients. Situations
52 of augmented CL_{CR} and/or high bacterial MIC target values may require dosage increases and
53 longer infusion durations.

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55 **Keywords:** Amoxicillin, pharmacokinetics, burn patients.

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62 **Introduction**

63 Treating sepsis promptly and adequately in burn patients is crucial as it is still the
64 predominant cause of morbidity and mortality despite major advances in hemodynamic and
65 respiratory support (1-5). In this context, optimizing antibiotic dosage regimens to improve
66 clinical outcomes and to avoid antibiotic resistance is desirable (6). However, this task is
67 highly complex as it not only requires a well-trained multidisciplinary team but also extended
68 knowledge of pharmacokinetic (PK) alterations due to burn trauma (7-9). Therapeutic drug
69 monitoring (TDM) appears to be a useful intervention to ensure attainment of
70 PK/pharmacodynamic (PD) surrogate indicators of antibiotic efficacy to counteract the well
71 documented intervariability PK observed in this population (10-15). Moreover, TDM might
72 also potentially improve burn patient outcomes (10, 12, 16, 17). Currently, the Bayesian
73 forecasting approach for estimation of individual PK parameters represents the gold-standard
74 approach for TDM (18, 19).

75 Amoxicillin is frequently used as a first-line antibiotic treatment in burn patients
76 during the first weeks of hospitalization (14). It is partially metabolized by the hepatic system
77 and lowly protein-bound (18%) (20). As this antibiotic is excreted in the urine (60%
78 unchanged), its elimination is slowed in case of renal impairment. TDM of amoxicillin is
79 available but rarely used in our institution, including in the Burn Centre, as beta-lactam
80 antibiotics are often thought to have few dose-dependent side effects and a wide therapeutic
81 margin (21).

82 Because significant PK changes of antibacterial agents have been reported in burn
83 patients, such patients are considered as a special population in clinical PK studies (9, 22). For
84 beta-lactams, most reports indicate increased values of drug CL and volume of distribution in
85 burn patients compared to healthy subjects (9). Because of these alterations, dose
86 requirements of antibiotics may be increased in this population. However, few reports have

87 addressed the PK profile in burn patients and are based on a small number of individuals. The
88 use of a population approach to characterize amoxicillin PK and its variability and identify
89 sources of variability has rarely been performed in burn patients.

90 In this context, our study aimed at determining the PK profile of intravenous
91 amoxicillin given to adult patients with severe burns hospitalized in the Burn Centre of our
92 hospital. The population model served to evaluate the PK/PD target attainment using standard
93 and alternative dosage regimens of amoxicillin.

94

95 **Materials and Methods**

96 ***Ethics***

97 This study was approved by the Institutional Review Board of the Centre Hospitalier
98 Universitaire Vaudois and the Ethics Committee of the State of Vaud, Switzerland (protocole
99 195/13). Written informed consent was obtained from each patient.

100

101 ***Study design and setting***

102 We prospectively and consecutively enrolled all burn patients admitted to the Burn Centre of
103 our hospital who received a course of intravenous amoxicillin administered either alone or in
104 combination with clavulanic acid from October 2013 to October 2016. The Burn Centre is a
105 five-bed Swiss tertiary ICU nested in a 35-bed medical surgical ICU. This study was
106 registered on the <https://clinicaltrials.gov/> platform (Trial Registration: NCT01965340).

107

108 ***Data collection***

109 Age, sex, weight, CL_{CR} (Cockcroft-Gault formula) and burn characteristics (including total
110 burnt body surface area and Ryan score (23)) were collected from medical records for each

111 burn patient hospitalized during the study period. Data regarding amoxicillin administration
112 (including date and time of administration, dose administered and duration of infusion) were
113 prospectively collected from our computerized information system (Metavision; IMDsoft, Tel
114 Aviv, Israel). For each episode of infection, the microorganism was systematically identified,
115 if possible. The susceptibility of amoxicillin was determined using E-Test for each patient in
116 whom the microorganism was identified (24, 25).

117

118 *Antimicrobial treatment*

119 Amoxicillin [Clamoxyl[®] (GlaxoSmithKline AG, Münchenbuchsee) or Co-Amoxi-Mepha[®]
120 (Mepha Schweiz AG, Basel)] was dosed in accordance with the manufacturer's
121 recommendations (1-2 g every 6–8 h in patients with normal renal function) and infused over
122 2 h (amoxicillin) or 1 h (amoxicillin/clavulanic acid) starting from the second dose (over 30
123 min for the first dose) according to our local guidelines. Indeed, amoxicillin/clavulanic acid
124 solutions (diluted with 0.9% NaCl) have limited stability and, therefore, the maximal infusion
125 time was set to 1 h. In contrast, as amoxicillin alone is more stable (stability of 3 h or 6 h
126 when diluted in Ringer's lactate solution or 0.9% NaCl, respectively (20)), an extended
127 perfusion (2 h) could be used. For patients with renal insufficiency, the dosage was adjusted
128 according to the renal function estimated by the Cockcroft-Gault equation (eGFR < 30
129 ml/min: 500 mg–2 g q8-12 h; eGFR < 15 ml/min: 750 mg–2 g q24 h).

130

131 *Blood concentration measurements*

132 Blood samplings for the amoxicillin assay were performed at various time points. Trough
133 levels were sampled on days 2, 4, 6 and 8. Additional samples were obtained every 2 days in
134 a few patients who received a course longer than 8 days. Random levels were sampled on day
135 6 and day 8. A rich amoxicillin kinetic profile was obtained on one occasion for most patients

136 (18 out of 21, including one patient with two rich profiles) at the following sampling times: 0,
137 1, 2, 3, 4 and 5 h after the end of the infusion. The exact times were adjusted according to the
138 infusion duration.

139

140 *Determination of amoxicillin concentrations*

141 Amoxicillin plasma levels were determined using a multiplex assay by ultra-performance
142 liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) requiring 100
143 μL of plasma for the simultaneous quantification within 9 min of 12 most recommended and
144 frequently used antibacterial drugs (see **Supplemental Material**)(26). As no assay method
145 was available for clavulanic acid, its concentration was not determined in this study. Blood
146 samples were directly sent to the laboratory after sampling and were stored at -80°C until the
147 analysis. Analyses were performed within 6 hours during the week. Samples collected over
148 the weekend were analyzed the following Monday afternoon.

149

150 *Population PK model building*

151 NONMEM version 7.1.0 (ICON Development Solutions, Ellicott City, MD, USA) was used
152 to analyse amoxicillin plasma concentrations versus time data using a non-linear mixed-
153 effects modelling approach. The first-order conditional estimation with the interaction
154 algorithm was selected for all runs. We assumed log-normal distributions of PK parameters,
155 i.e. an exponential model for interindividual variability. First, the best structural model and
156 residual error models were identified. One-, two- and three-compartment open linear models
157 were evaluated. For the residual error, proportional, additive and combined (additive plus
158 proportional) error models were tested.

159 Next, covariate model building was performed using the Stepwise Covariate Model
160 building tool of Perl Speaks to NONMEM (27). This tool permits forward selection and

161 backward deletion of covariates in a model in a comprehensive manner. The following
162 covariates were investigated: sex, total body surface area, serum albumin, serum creatinine,
163 CL_{CR} (estimated by the Cockcroft-Gault equation), actual body weight (BW), BW on
164 admission (BW_{ADM}), BW gain (defined as $BW - BW_{ADM}$ when $BW > BW_{ADM}$ and zero
165 otherwise), and BW loss (defined as $BW_{ADM} - BW$ when $BW_{ADM} > BW$ and zero otherwise).
166 Linear relationships were tested for categorical covariates, while linear and power functions
167 were tested for continuous covariates. The change in the objective function value (OFV) was
168 used to assess the influence of covariates, assuming a chi-squared distribution of the OFV,
169 with one degree of freedom for each addition of a linear power relation. Statistical
170 significance was set at a p-value of 0.05 for forward selection and 0.01 for backward deletion.

171

172 ***Final model evaluation***

173 Internal model validation was based on standard criteria (28): the OFV as described
174 above, parameter estimates along with their standard errors, plots of observed amoxicillin
175 concentration versus population and individual predictions, and plots of conditional weighted
176 residuals (29). A bootstrap analysis ($n = 1000$ samples with replacement from the original
177 dataset) was carried out with the PsN tool kit to check the uncertainty of parameter estimates
178 and derive the 95% CI. A visual predictive inspection was also performed by comparing the
179 observed amoxicillin concentration with model-based simulations ($n = 1000$ samples for each
180 patient)(30).

181

182 ***Dosing simulations***

183 PK/PD simulations were performed based on the final model to investigate the influence of
184 amoxicillin dose, dose interval, infusion duration and covariates (renal function) on the
185 probability to achieve a target exposure for amoxicillin. All simulations and calculations of

186 probabilities of target attainment were done with the Pmetrics R package (31). Mean and
187 variance of parameters of the final model estimated with NONMEM were imported into
188 Pmetrics. We tested three amoxicillin doses (0.5, 1 and 2 g), five dosing intervals (4, 6, 8, 12
189 and 24 h), and two infusion times (30 min and 2 h). As CL_{CR} was found to influence
190 amoxicillin CL, we considered six levels of renal function: 15, 30, 60, 100, 150 and 200
191 mL/min. For each condition, 500 virtual patients were created based on parameter estimates
192 and covariates retained in the final NONMEM model. Amoxicillin CL values were randomly
193 sampled based on the final estimates of mean and variance. The Q and V2 values were fixed
194 to their final NONMEM estimates for all subjects. Since BW influenced V1, this value
195 changed as a function of BW. BW was sampled from a log-normal distribution in the form of
196 $89 \times \exp(\eta_{BW})$, with $\eta_{BW} \sim N(0, 0.184^2)$. These values were representative of the average BW
197 (89 kg) during antibiotic therapy and variability in a group of 39 burn patients from our Burn
198 Centre who received a beta-lactam antibacterial agent (data not shown), including the 21 burn
199 patients involved in this study.

200 Steady-state (i.e. after 10 days of therapy) amoxicillin concentration profiles were
201 simulated for each condition. Then, we derived probabilities of target attainment (PTA) using
202 the dedicated function in Pmetrics. The PK/PD target was defined as a percentage of time
203 during which the free amoxicillin concentration in plasma exceeds the MIC ($fT>MIC$). Two
204 targets were considered: a target of $fT>MIC \geq 50\%$ usually recognized as efficient for β -
205 lactams (such as penicillins and carbapenems) (32-35), and a more conservative target of
206 $fT>MIC = 100\%$, which seems to be associated with better outcomes in critically ill patients
207 (11, 36). We considered MIC values of 0.25, 0.5, 1, 2, 4, 8 and 16 mg/L as 8 mg/L is the
208 highest amoxicillin MIC breakpoint value for several Gram-negative organisms, including
209 *Escherichia coli*, according to the European Committee on Antimicrobial Susceptibility
210 Testing (37). We assumed a free fraction of 82% for amoxicillin (38). In addition, we

211 considered 90% as an optimal PTA to be achieved, as suggested by the European Medicines
212 Agency (39).

213 The influence of BW on PTA was also examined using the same approach. We
214 considered situations of low weight (50 kg), standard weight (70 kg), overweight (100 kg) and
215 obesity (150 kg) as well as three levels of renal function (30, 100 and 200 mL/min) for each
216 weight. A dosage regimen of 1 g q8h (infused over 30 min) was simulated in 500 virtual
217 patients in all 12 conditions, and steady-state concentrations were analysed.

218

219 **Results**

220 *Patient characteristics and microbiological data*

221 A total of 185 amoxicillin concentrations were obtained from 21 burn patients aged from 16
222 to 93 years. The patients' body weight on admission ranged from 60 to 132 kg. **Table 1**
223 presents the characteristics of the population. There was a large majority of male patients. The
224 median CL_{CR} was high (128 mL/min), with 25% of patients having $CL_{CR} > 150$ mL/min. The
225 median BW on admission was 72.4 kg, with a coefficient of variation of 22%. Limited intra-
226 individual variability was observed in BW during the course of amoxicillin (\pm clavulanic acid)
227 therapy, with a median change in BW of -2.3% (minimum, -11.4%; maximum, +10.6%). Of
228 note, some patients had several episodes of infection that were treated by amoxicillin (\pm
229 clavulanic acid). Microorganism identification with susceptibility was obtained at least once
230 for 16 out of 21 patients. Two different bacteria were identified in the same sample for three
231 patients, and one patient presented the same bacteria (*Staphylococcus aureus*) in two distinct
232 tissue samples. As a result, a total of 20 susceptibilities were determined. **Table 2** summarizes
233 the microbiological data.

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238 *Population PK model*

239 The final model was a two-compartment model with the following parameters: amoxicillin
240 CL, central (V1) and peripheral (V2) volumes of distribution, and intercompartmental
241 clearance (Q).

242 Residual variability was best described by a combined additive and proportional residual error
243 model. The stepwise covariate modelling approach identified CL_{CR} and BW as covariates
244 influencing amoxicillin CL and V1, respectively. CL_{CR} was found to influence amoxicillin CL
245 in a linear manner, and V1 was allometrically scaled to the actual BW. Amoxicillin CL was
246 the only random PK parameter, while the others had a fixed, estimated value. Models
247 incorporating between subject variability on V1, V2 and Q were tested. As they either did not
248 improve the model fit or poorly estimated the corresponding random effects (high standard
249 errors), interindividual variabilities were not estimated for those parameters in the final
250 model. Interoccasion variability could not be tested owing to the sampling design, which
251 prevented from discriminating between interoccasion and inpatient variabilities. **Table 3**
252 displays the final estimates of population PK parameters, bootstrap estimates as well as
253 parameter-covariate relationships. All parameters were estimated with acceptable precision.

254 **Figure 1** shows the plots of conditional weighted residuals versus population
255 predictions and time. Most residuals were within the expected range (-2; +2), and no major
256 trend was observed versus prediction or time. The prediction-corrected visual predictive
257 check obtained with the final model is shown in **Figure 2**. As a good agreement was observed
258 between measured amoxicillin concentrations and model-based predictions (**Figure 3**), the
259 model was deemed to be appropriate for further dosing simulations.

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263 *Dosage regimen simulations*

264 The Monte-Carlo simulation results are summarized in **Figure 4**. As expected, when all other
265 factors were kept constant, the values of $fT>MIC$ and PTA decreased with increasing renal
266 function and MIC values.

267 Considering $fT>MIC \geq 50\%$ as the target, in patients with normal renal function (CL_{CR}
268 = 100 mL/min), the standard dosage regimens with a 30-min infusion of 1-2 g q6-8 h were
269 adequate for MIC values ≤ 2 mg/L but failed to achieve 90% PTA for higher MIC values. For
270 a MIC of 8 mg/L, such a PTA was only achieved with the most intensive dosage of 2 g/4 h
271 and extended infusion (2 h) of 1 g/4 h or 2 g/6 h. The results were quite similar in patients
272 with moderately impaired renal function ($CL_{CR} = 60$ ml/min), with 2 g/8 h administered as a
273 2-h infusion also being effective for high MIC values. In order to achieve the target of
274 $fT>MIC = 100\%$, regimens of 1 to 2 g administered every 4 h were necessary for MIC values
275 ≤ 2 mg/L. However, for a high MIC of 8 mg/L, even an extended infusion of 2 g q4 h failed to
276 achieve 90% PTA in simulated patients with $CL_{CR} = 100$ ml/min.

277 In patients with augmented renal clearance (200 mL/min), the minimum dose to
278 achieve the desired 90% PTA for the low target ($fT>MIC \geq 50\%$) with MIC values ≤ 1 mg/L
279 was 1g q6 h (**Figure 4**). For higher MIC values, prolonging the infusion duration was
280 effective for obtaining a higher PTA, and a 2-h infusion of 2 g every 4 h was the only regimen
281 associated with PTA $> 90\%$ for a MIC of 8 mg/L. None of the tested regimens was associated
282 with acceptable PTA for the high target when the MIC was > 2 mg/L.

283 In patients with renal impairment (15 and 30 mL/min), reduced dosages (0.5 or 1 g
284 q12h) appeared to be adequate for low MIC values but were not sufficient for MIC values as
285 high as 8 mg/L. In this case, a standard dosage (1-2 g q6-8 h) appeared necessary to achieve

286 $fT>MIC \geq 50\%$, while regimens of 1 g q4 h and 2 g q4 h were necessary to achieve $fT>MIC =$
287 100% with acceptable PTA in patients with CL_{CR} of 15 and 30 ml/min, respectively.

288 BW had a limited influence on $fT>MIC$ and PTA, as shown in **Table 4**. The index
289 $fT>MIC$ slightly increased with an increasing BW as a result of a decrease in the distribution
290 ($K_{12} = Q/V$) and elimination rate constants ($K_e = CL/V$). However, even a three-fold increase
291 in BW only had a modest effect on PTA.

292

293 **Discussion**

294 Although amoxicillin is frequently prescribed in patients with severe burns, to the best
295 of our knowledge, this is the first population analysis carried out in this population. Literature
296 regarding the PK of amoxicillin in non-burn patients exists but is scarce (36, 40-42). Our
297 study provides several insights regarding the PK and dosage requirements of amoxicillin in
298 this population with known distinct PK characteristics. The PK of burn patients is indeed
299 altered due to different phenomena, such as capillary leak syndrome, mechanical ventilation,
300 hypoalbuminemia, extracorporeal circuits and post-surgical drains; in addition, significant
301 burn injuries themselves might increase the volume of distribution of hydrophilic drugs (43-
302 48).

303 Our results are in good agreement with a recent population PK study of
304 amoxicillin/clavulanic acid in 13 ICU adult patients (36), with comparable patient
305 characteristics (except for burns). While the typical values of volumes of distribution were
306 similar (V_1 and V_2), patients in the present study showed a 21% increased CL and a 22%
307 increased Q in patients with normal renal function (CL_{CR} of 110 mL/min) compared to the
308 ICU patients without burns. Our results confirm the increase in CL reported for other beta-
309 lactam agents in burn patients, irrespective of renal function (10, 15). We did not observe any
310 difference in amoxicillin volume of distribution in comparison to the non-burn population

311 (36, 49, 50). The covariate analysis confirmed that CL_{CR} influences amoxicillin CL, as
312 previously described (36). We also found that BW influences V1, suggesting an approximate
313 doubling of this value from 70 kg to 132 kg. This will reflect in a slightly longer elimination
314 half-life in overweight patients. Renal function explained 35% of the initial estimated
315 interpatient variability on amoxicillin clearance, which remains still largely unexplained. This
316 large variability could be due to several factors related to patients' characteristics, burn
317 consequences and medical support that can affect drug concentrations.

318 In critically ill patients (including burn patients), evidence suggests that patients may
319 have a higher CL_{CR} even in the presence of normal plasma creatinine concentrations (51, 52).
320 An augmented CL_R (i.e. $CL_{CR} > 130$ mL/min) has been reported to occur in 15–65% of ICU
321 patients including burn patients and therefore increasing the risk of subtherapeutic
322 concentrations in this population (15, 53). Based on our simulations, our data showed that in
323 patients with a $CL_{CR} = 150$ to 200 mL/min, the standard dosage achieved the desired 90%
324 PTA only for cock values < 1 mg/L. In those patients, dosages as high as 2 g or 4 g appear
325 necessary to achieve $fT > MIC \geq 50\%$ for the highest MIC breakpoint (8 mg/L). Prolonging the
326 amoxicillin infusion from 30 min to 2 h was also a way to increase the target attainment. As
327 more aggressive pathogens are commonly found in the ICU, the prescription of antibiotics has
328 to be adapted and carefully monitored among burn patients (10). The standard amoxicillin
329 dose of 1-2 g q6-8 h results in adequate exposure ($fT > MIC \geq 50\%$) for both low and normal
330 CL_{CR} in the case of MIC values of ≤ 2 mg/L. However, a higher dosage regimen should be
331 used to treat burn patients infected by microorganisms with higher MIC. This may be
332 especially relevant for the treatment of infection caused by Enterobacteriaceae with
333 amoxicillin/clavulanic acid, as those bacteria often display high MIC values ranging from 2 to
334 8 mg/L.

335 Achieving $fT>MIC = 100\%$ with acceptable PTA for MIC values as high as 8 mg/L
336 was only possible in patients with severe renal impairment. In burn patients with normal or
337 augmented renal clearance, our results showed that achieving this target was hardly possible
338 even with the highest dosage of amoxicillin (12 g/day) and repeated extended infusions. Yet,
339 the clinical benefits of targeting $fT>MIC = 100\%$ remains unclear. In the DALI study
340 performed in critically ill patients who received intravenous beta-lactams, there was no
341 difference in the predictive value of positive clinical outcomes following either $fT>MIC =$
342 100% or $fT>MIC \geq 50\%$ (11). In addition, targeting $fT>MIC = 100\%$ in all burn patients
343 would require larger doses and concentrations of amoxicillin that could increase its toxicity
344 without a thorough monitoring by TDM. Indeed, adverse reactions such as crystalluria have
345 been reported with the use of high doses of amoxicillin (54, 55). Unlike renal function, inter-
346 individual changes in BW did not appear to have a clinically relevant influence on amoxicillin
347 PD in adult burn patients.

348 Our simulation results are somewhat different from those described by *Carlier et al*
349 (36). They reported that a $fT>MIC$ of 50% or even 100% would be achieved in most ICU
350 patients treated with standard doses of amoxicillin (3–4 g in three or four administrations per
351 day), except for the conditions of augmented CL_R combined with the highest bacterial MIC.
352 Our less optimistic results in burn patients are likely due to the increased Q and CL values
353 discussed above. In addition, the proportion of simulated patients associated with successful
354 treatment was not clearly stated in the work by *Carlier et al*.

355 As shown for other time-dependent beta-lactam agents (56, 57), increasing the
356 infusion time of amoxicillin may be a simple way to optimize $fT>MIC$ and drug response.
357 Amoxicillin combined with clavulanic acid is less stable than amoxicillin alone due to the
358 degradation of clavulanic acid catalysed by both acids and bases when dissolved in aqueous
359 solution (58). However, a recent study has demonstrated that amoxicillin alone is stable

360 enough to be administered as a continuous infusion and that the combination of amoxicillin
361 and clavulanic acid is stable for 2 h (58). As our data showed that prolonging the infusion
362 duration was effective for obtaining a higher PTA in burn patients treated with amoxicillin,
363 we therefore recommend that an extended infusion of 2 h could be used in cases of infections
364 caused by microorganisms with high MIC values.

365 Optimizing antibiotic exposure in the burn population is of high importance as 60% of
366 these patients fail to reach the PK/PD target of $fT>MIC = 100\%$ while receiving betalactams
367 (12). In order to counteract the PK variability observed in this frail population, it has now
368 been demonstrated that TDM is a valuable intervention that should be widely used in order to
369 reach and maintain the antibiotic therapeutic target (10, 12, 14, 15).

370 Our study had a prospective design and included all burn patients admitted consecutively to a
371 tertiary hospital. Nevertheless, this study has several limitations. First, as burn patients
372 constitute a specific and difficult population to study, the sample size is limited compared
373 with population PK standards. However, quite rich amoxicillin concentration data were
374 available, and PK parameters were precisely estimated. Second, as our laboratory could not
375 dose clavulanic acid, only the amoxicillin concentration could be analysed and studied for this
376 work. Further research is necessary to investigate the potential PK changes of clavulanic acid
377 in burn patients and to define the PK/PD in this population. However, amoxicillin is
378 considered as the main therapeutic agent as clavulanic acid has a very weak antibacterial
379 activity and literature suggests that clavulanic acid has no influence on amoxicillin PK and
380 vice-versa (59). Third, even though research is active on the field, it is still unclear which
381 PK/PD target should be aimed for in critically ill patients (including the burn population)(11,
382 12, 14) and experimental studies have shown that the values of $fT>MIC$ required to produce a
383 given effect may vary between beta-lactams (35). Fourth, this work focused only on efficacy
384 targets and no upper threshold for toxicity endpoints was evaluated. Owing to the large

385 therapeutic window of amoxicillin, this should not present an important limitation to our
386 results. Finally, simulations performed outside the data range of data should be handle
387 cautiously. Nevertheless, this may be an adequate approach when the covariate-parameter
388 relationships have a rational basis. Regarding body weight, the use of allometric scaling to
389 describe the relationship between V1 and BW is a reasonable approach for simulating the
390 effect of weight on the PK based on the theories of allometry and scaling (60). Regarding
391 renal function, the simulation was based on the linear correlation found between amoxicillin
392 clearance and creatinine clearance which is in accordance with renal clearance concepts.

393 In conclusion, to the best of our knowledge, this is the first population analysis of
394 amoxicillin PK data in burn patients showing increased typical values and important
395 variability in amoxicillin CL compared to literature data with non-burn patients. This work
396 highlights the need for a higher dosage and a longer infusion of amoxicillin in burn ICU
397 patients with augmented CL_R infected by microorganisms with high MIC values.

398 **List of Abbreviations**

399	BW	Body weight
400	BW_{ADM}	Body weight on admission
401	CL	(Body) clearance
402	CL_{CR}	Creatinine clearance
403	ECOFFs	Epidemiological cut-off values
404	HPLC-MS/MS	High-performance liquid chromatography coupled with tandem mass
405		spectrometry
406	ICU	Intensive care unit
407	MIC	Minimum inhibitory concentration
408	OFV	Objective function value
409	PK	Pharmacokinetic
410	PD	Pharmacodynamic
411	Q	Intercompartmental clearance
412	TDM	Therapeutic drug monitoring
413	V1	Central volume of distribution
414	V2	Peripheral volume of distribution

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429 **Author contributions**

430 CC, YQ, EP, PV and AF designed the study. AF and OP collected the data. CC, AF and SG

431 analysed the data. AF, SG, CC, YQ, PE, OP and FS wrote the manuscript. All authors

432 contributed to and approved the final version of the manuscript.

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613 **Figure Legends**

614

615 **Figure 1.** Model-derived conditional weighted residuals versus population predictions (upper
616 panel) and time (lower panel).

617

618 **Figure 2.** Prediction-corrected visual predictive check obtained with the final model. The
619 open circles represent the observed concentrations. The grey solid and dashed lines represent
620 the median and the 5th/95th percentiles of the observed concentrations, respectively. The dark
621 and light grey areas represent the 95% CI of the simulated median and 5th/95th percentiles,
622 respectively. Of note, three observations greater than 100 mg/L are not shown for ease of
623 graphical display (105.7, 134.4 and 198 mg/L).

624

625 **Figure 3.** Observed vs. population/individual predictions (linear scale). Circles represent
626 population predictions and black dots individual predictions. The line is $y = x$.

627

628 **Figure 4.** Probability of target attainment as a function of the MIC and dosage regimen for six
629 stages of renal function. IT indicates infusion time. The left and right panel shows the results
630 for the low ($fT>MIC \geq 50\%$) and high ($fT>MIC = 100\%$) pharmacodynamic target
631 respectively.

632

633

634 **Table 1. Characteristics of the burn patients who received amoxicillin**
635

Characteristic	Value
Number of patients	21
Male, <i>n</i> (%)	16 (76.2)
Age (years), mean (\pm SD)	50.1 (24.3)
Body weight at admission (kg), median (IQR)	72.4 [67.0–83.6]
Initial CL _{CR} (mL/min), median (IQR)*	128 [65–150]
TBSA affected (%), median (IQR)	23 [12.5–44]
	< 20 (n, %)
	7 (33.3)
	20–40 (n, %)
	9 (42.9)
	41–60 (n, %)
	2 (9.5)
	> 60 (n, %)
	3 (14.3)
SAPS II, mean (\pm SD)	35.9 (18.6)
Ryan score, median (IQR)	1 [1–2]
Inhalation lesions, <i>n</i> (%)	16 (76.2)
Length of ICU stay, median (IQR)	23 [13.0–39.5]
Mortality in the burn ICU, <i>n</i> (%)	2 (9.5)

636

637 * Using Cockcroft and Gault formula.

638

639 **IQR:** Interquartile range; **SAPS II:** Simplified Acute Physiology Score; **SD:** Standard deviation;

640

TBSA: total body surface area.

641 **Table 2. Microbiological data**

642

643

	Number of isolates	Median MIC (min–max)	Antimicrobial therapy
Gram-negative bacteria	5	2 (1–4) mg/L	Amoxicillin + clavulanic acid (n = 5)
Gram-positive bacteria	15	0.5 (0.016–2) mg/L	Amoxicillin (n = 3) Amoxicillin + clavulanic acid (n = 12)

644 Gram-negative species: *Haemophilus influenzae* (n = 2), *Klebsiella pneumoniae*, *Citrobacter koseri*, *Pantoea*
645 *spp.*646 Gram-positive species: *Staphylococcus aureus* (n = 6), *Streptococcus pneumoniae* (n = 5), *Streptococcus bovis*,
647 *Enterococcus faecalis*, *Granulicatella adiacens*, *Bacillus spp.*

648 **Table 3. Population PK parameters of amoxicillin**

Parameter	Structural model mean estimate (RSE)	Covariate model mean estimate (RSE)	Bootstrap mean estimate (95% CI)
Fixed effects			
CL (L/h)	13.1 (12%)	13.6 (8%)	13.7 (11.5–16.5)
$\theta_{CL_{CR_CL}}$	-	0.57 (25%)	0.53 (0.19–0.79)
V1 (L)	10.1 (25%)	9.73 (20%)	9.6 (4.5–16.4)
Q (L/h)	20.8 (31%)	20.1 (24%)	20.2 (12.6–52.5)
V2 (L)	16.6 (15%)	17.6 (14%)	17.4 (13.0–24.2)
Random effect			
ω_{CL} (CV%)	57.3 (16%)	37.3 (19%)	36.0 (21.7–53.2)
Residual variability			
Proportional error (%)	34.4 (20%)	37 (19%)	34.6 (22.1–47.5)
Additive error (mg/L)	0.59 (31%)	0.08 (10%)	0.08 (0.07–0.93)

649

650 **CL**: clearance, **V1**: central volume of distribution, **RSE**: relative standard error; **95% CI**:651 95% confidence interval, $\theta_{CL_{CR_CL}}$ proportional increase in CL elimination as a function of652 CL_{cr} , ω_{CL} : interpatient variability on CL.

653

654 The final models are as follows:

655
$$TV_{CL} = CL * (1 + \theta_{CL_{CR_CL}} * (CL_{CR} - 110))$$

656
$$TV_{V1} = V1 * (BW/70)$$

657 where CL_{CR} is estimated by the Cockcroft-Gault equation (mL/min), 110 ml/min is average658 CL_{cr} in our population and BW is body weight (kg).

659 **Table 4. Probability of target attainment stratified by body weight and renal function**
 660 **for a dosage of 1 g q8 h and a MIC of 8 mg/L**

661

CL_{CR}	Body weight	$fT>MIC$	PTA $fT>MIC \geq 50\%$	PTA $fT>MIC = 100\%$
30 mL/min	50 kg	0.65 (0.24)	0.69	0.17
	70 kg	0.68 (0.24)	0.73	0.21
	100 kg	0.72 (0.24)	0.77	0.26
	150 kg	0.76 (0.23)	0.82	0.32
100 mL/min	50 kg	0.34 (0.18)	0.16	0.008
	70 kg	0.36 (0.19)	0.19	0.01
	100 kg	0.38 (0.20)	0.22	0.02
	150 kg	0.42 (0.21)	0.27	0.04
200 mL/min	50 kg	0.18 (0.10)	0.012	0
	70 kg	0.19 (0.10)	0.018	0
	100 kg	0.21 (0.11)	0.03	0
	150 kg	0.23 (0.12)	0.04	0

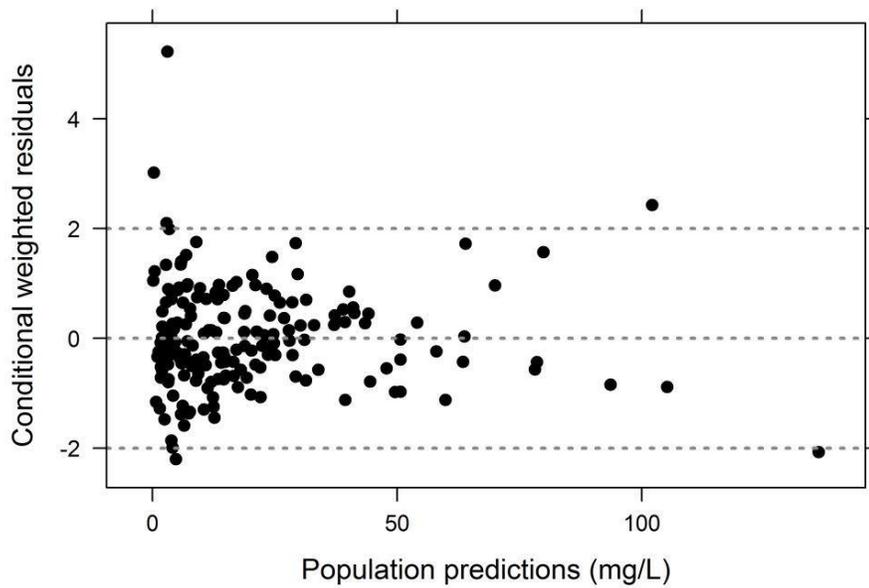
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663 CL_{CR} : Creatinine clearance, $fT>MIC$: Cumulative percentage of a 24 h period that the
 664 unbound fraction of a drug exceeds the MIC at steady-state pharmacokinetic conditions,

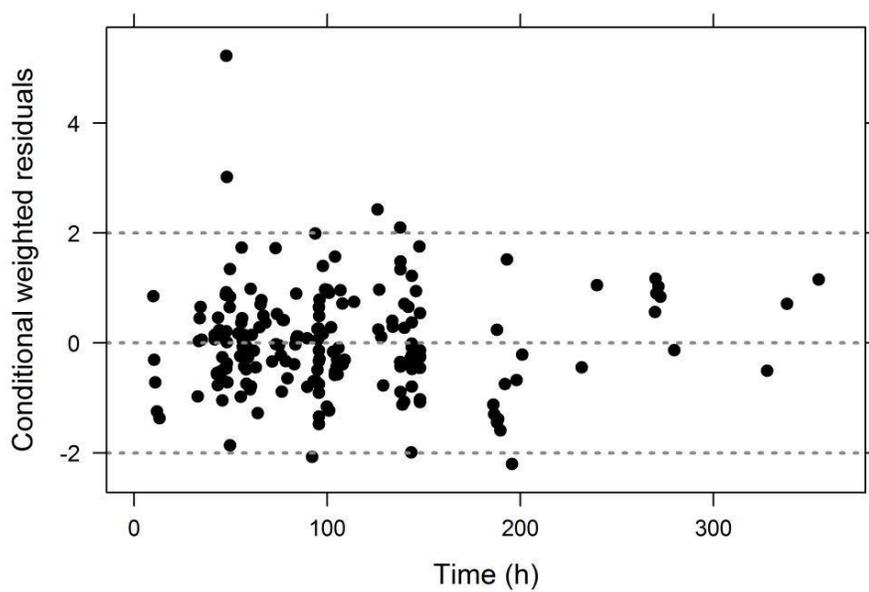
665 **PTA**: probability of target achievement.

666 **Figure 1**

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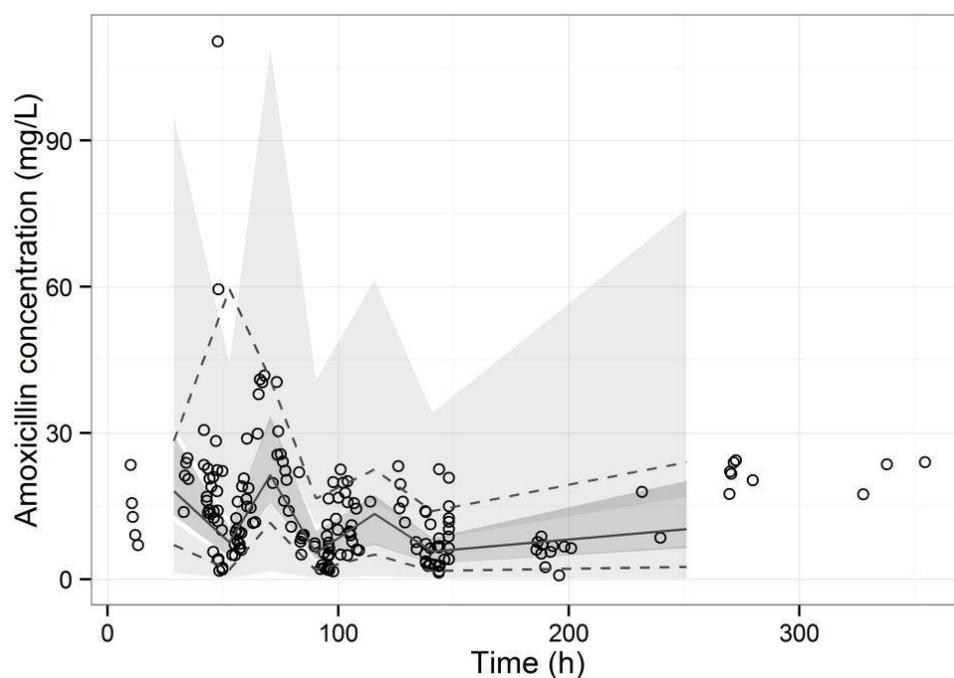
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670 **Figure 1.** Model-derived conditional weighted residuals versus population predictions (upper

671 panel) and time (lower panel).

672 **Figure 2**

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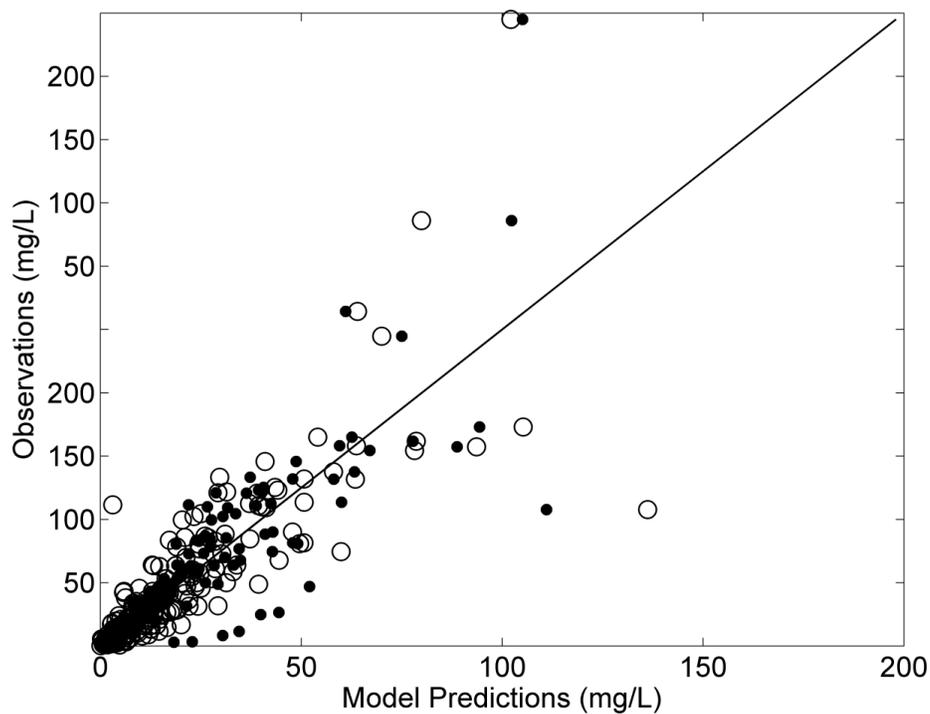
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676 **Figure 2.** Prediction-corrected visual predictive check obtained with the final model. The
677 open circles represent the observed concentrations. The grey solid and dashed lines represent
678 the median and the 5th/95th percentiles of the observed concentrations, respectively. The dark
679 and light grey areas represent the 95% CI of the simulated median and 5th/95th percentiles,
680 respectively. Of note, three observations greater than 100 mg/L are not shown for ease of
681 graphical display (105.7, 134.4 and 198 mg/L).

682 **Figure 3**

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687 **Figure 3.** Observed vs. population/individual predictions (linear scale). Circles represent
688 population predictions and black dots individual predictions. The line is $y = x$.

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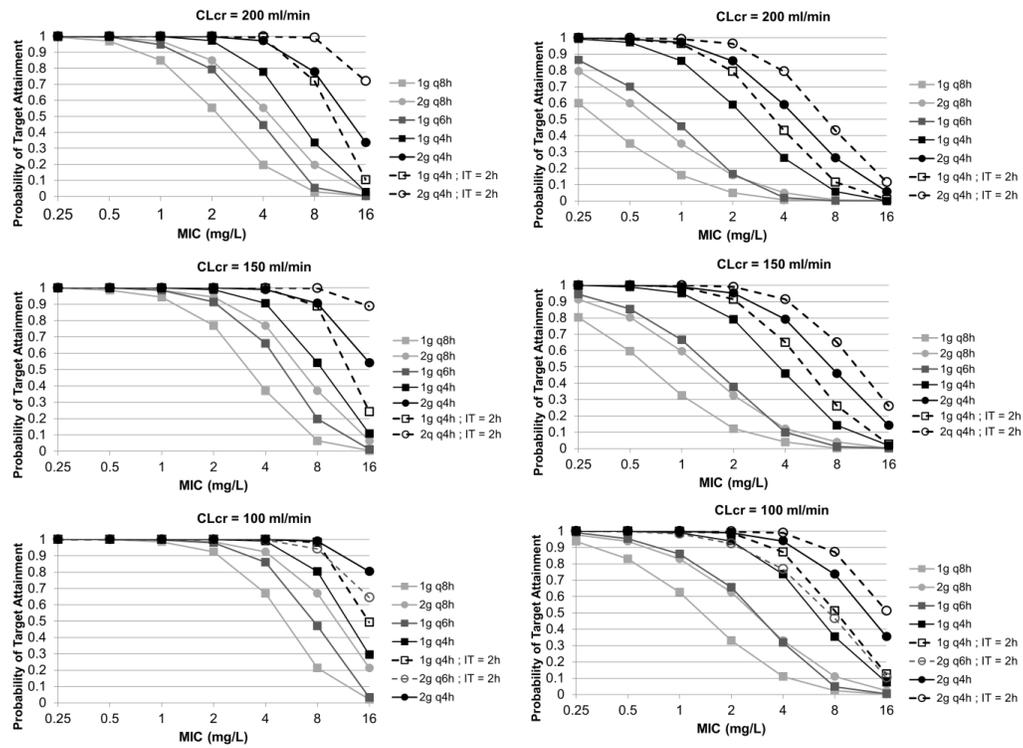
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698 **Figure 4**

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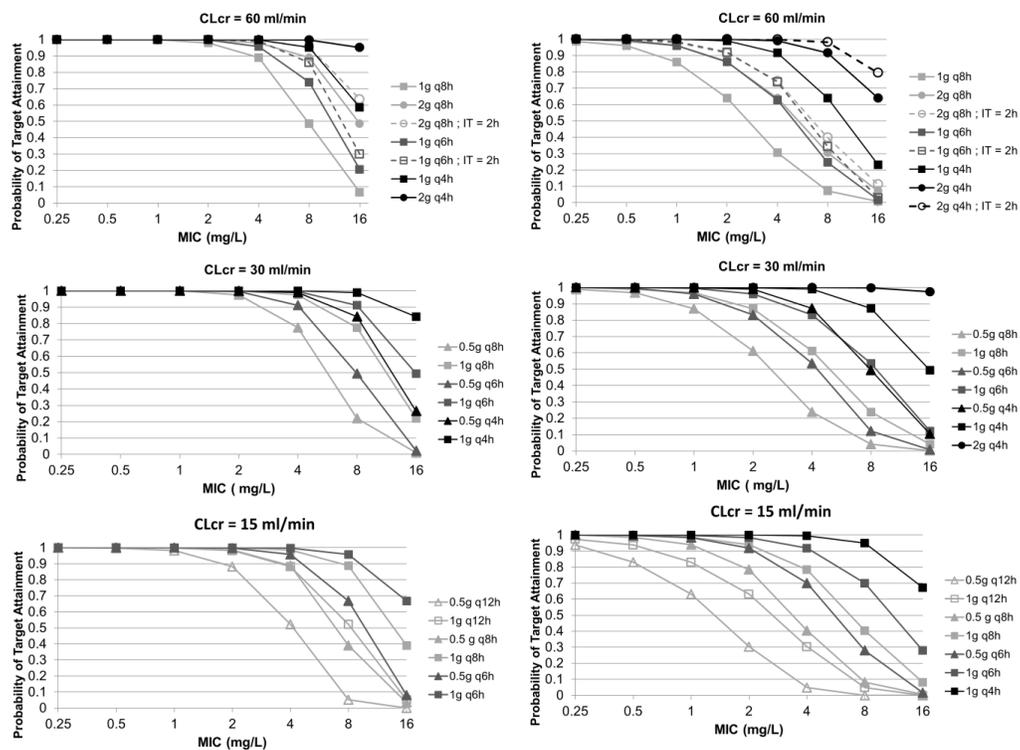
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713 **Figure 4 (continued)**

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717 **Figure 4.** Probability of target attainment as a function of the MIC and dosage regimen for six
 718 stages of renal function. IT indicates infusion time. The left and right panel shows the results
 719 for the low ($fT > MIC \geq 50\%$) and high ($fT > MIC = 100\%$) pharmacodynamic target
 720 respectively.

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