

1 **MANUSCRIPT INFORMATION**

2 **Title:** Quantitative analysis of gentamicin exposure in neonates and infants calls into question
3 its current dosing recommendations

4

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50 **ABSTRACT**

51 Optimal dosing of gentamicin in neonates is still a matter of debate despite its common use.
52 We identified gentamicin dosing regimens from 8 international guidelines and 7 Swiss
53 Neonatal Intensive Care Units. Dose per administration, dosing interval, total daily dose and
54 demographic characteristics between guidelines were compared. There was considerable
55 variability with respect to dose (4 to 6 mg/kg), dosing interval (24 h to 48 h), total daily dose
56 (2.5 to 6 mg/kg/day) and patient demographic characteristics which were used to calculate
57 individualized dosing regimens. A model-based simulation study in 1071 neonates was
58 performed to determine achievement of efficacious peak gentamicin concentrations according
59 to predefined minimum inhibitory concentrations (MICs) ($C_{\max} / \text{MIC} \geq 10$) and safe trough
60 concentrations ($C_{\min} \leq 2 \text{ mg/L}$) with recommended dosing regimens. MIC targets of 0.5 and 1
61 mg/L were used. Dosing optimization was performed giving priority to the first day of
62 treatment and with the goal of simplifying dosing. Current gentamicin neonatal guidelines,
63 achieve effective peak concentrations if MIC is 0.5 mg/L but not for MICs $\geq 1 \text{ mg/L}$. Model-
64 based simulations indicate that to attain peak gentamicin concentrations $\geq 10 \text{ mg/L}$, a dose of
65 7.5 mg/kg should be administered using an extended dosing interval regimen. Trough
66 concentrations $\leq 2 \text{ mg/L}$ can be maintained with a dosing interval of 36 to 48 hours in
67 neonates according to gestational and postnatal age. For treatment beyond 3 days, therapeutic
68 drug monitoring is advised to maintain adequate serum concentrations.

69 **INTRODUCTION**

70 In 2015, about 1.4 million children died worldwide of infections such as pneumonia or
71 sepsis/meningitis in the first 5 years of their life, most of them during the neonatal period (1).
72 The most common cause of Gram-negative early-onset neonatal sepsis (EONS) is *Escherichia*
73 *coli* (2). Other Gram-negative and Gram-positive microorganisms are involved in early or late
74 neonatal sepsis including *Klebsiella spp.* and *Pseudomonas aeruginosa* (3, 4). By virtue of
75 their bactericidal activity and their low costs, aminoglycosides, such as gentamicin, remain
76 the first-line therapy in combination with a β -lactam antibiotic for confirmed or suspected
77 neonatal sepsis (5, 6). However, gentamicin has a narrow therapeutic index and optimal,
78 personalized dosing in neonates is still debated (7). Based on *in vitro* studies, optimal
79 gentamicin efficacy is associated with a plasma peak concentration over minimum inhibitory
80 concentration (MIC) ratio (C_{max}/MIC) $\geq 8 - 10$ (8-10). It has been suggested that the area
81 under the curve (AUC) over MIC ratio (AUC/MIC) could represent another
82 pharmacodynamic predictor of efficacy of aminoglycosides (11). Achieving this optimal
83 efficacy *in vivo* needs to be balanced against nephrotoxicity and ototoxicity associated with
84 high trough concentrations of gentamicin. Nephrotoxicity of aminoglycosides affect both the
85 glomerular and tubular functions (12). While nephrotoxicity is generally temporary and
86 reversible upon treatment discontinuation, ototoxicity might be permanent (13, 14). It has
87 been suggested that trough plasma concentrations of gentamicin should not exceed 1 to 2
88 mg/L to minimize potential toxic effects (15, 16, 17). Further, it has been reported that
89 multiple daily dosing and long duration of treatment are more likely to increase the risk of
90 toxicity (18).

91

92 In the neonatal population, development and organ maturation is a dynamic process that
93 influences gentamicin pharmacokinetics. Variability in kidney function and body composition
94 in particular is responsible for the large interpatient variability in clearance and volume of

95 distribution of gentamicin in this population. Clearance of gentamicin is indeed almost
96 entirely dependent on glomerular filtration (19). Nephrogenesis is completed after 34-35
97 weeks of gestation and preterm neonates present a lower glomerular filtration rate (GFR) as
98 compared to late preterm and term neonates (20). Birth is marked by major hemodynamic
99 changes that are responsible for a rapid postnatal increase in GFR in all neonates (21-24).
100 Gentamicin distribution is mostly limited to the extracellular fluid compartment. Neonates
101 have a body water content that is proportionally larger compared to adults and older children.
102 Therefore, an increased gentamicin volume of distribution is often observed and explains why
103 a relatively higher dose per kilogram in neonatal dosing is recommended in order to achieve
104 an effective peak concentration (25).

105
106 Pharmacokinetic (PK) understanding of gentamicin in neonates has increased throughout the
107 years. However, this newly acquired knowledge has resulted in many different gentamicin
108 dosing regimens rather than one consistent, optimal dosing regimen for use in daily clinical
109 care (26). Pharmacometric analyses, including pharmacokinetic-pharmacodynamic (PK/PD)
110 modeling and simulation, facilitate evaluation of existing dosing regimens with respect to
111 target attainment and can provide a quantitative rationale for optimizing and personalizing
112 dosing approaches in neonates (27, 28).

113
114 The key objectives of this study were to (1) assess the variability in dosing of gentamicin in
115 international guidelines and Swiss Neonatal Intensive Care Units (NICUs), (2) evaluate and
116 compare target achievement of current dosing recommendations with respect to efficacy and
117 safety and (3) provide a quantitative rationale for an optimal, personalized gentamicin dosing
118 approach to be implemented in a high resource setting such as Swiss NICUs in light of
119 currently relevant MIC breakpoints.

120

121 **RESULTS**

122 **Variability in National and International Guidelines**

123 Considerable variability in dosing regimen recommendations provided by international
124 guidelines and in Swiss NICUs was observed with respect to dose (4 to 6 mg/kg), dosing
125 interval (24 h to 48 h), total daily dose (2.5 to 6 mg/kg/day) and patient characteristics'
126 (qualitative and quantitative) which are used to individualize dosing regimens (Table 1).
127 While two Swiss NICUs did not use any demographic characteristics for *a priori* selection of
128 dosing regimens, most guidelines suggested individualized dosing regimens based on a single
129 or a combination of patient demographic characteristics. Gestational age (GA) combined with
130 postnatal age (PNA) was the most frequently observed regimen. Three different dosing
131 intervals were observed (24 h, 36 h and 48 h), with the longest interval used in the most
132 preterm neonates. Although the same demographic characteristics were mostly used, the cut-
133 off values to define the patient subgroups varied between recommendations. The variability in
134 gentamicin dosing used in Swiss NICUs and proposed in international guidelines is illustrated
135 for two typical patients (preterm and term neonates) at different postnatal ages in Table 2.

136

137 **Achievement of Efficacious and Safe Gentamicin Exposure**

138 Considering achieving target gentamicin exposure in at least 90% of neonatal patients (90%
139 probability of target attainment, PTA) as an appropriate outcome, simulations suggested that
140 all recommendations were adequate in terms of efficacy for pathogens with an MIC of 0.5
141 mg/L, but appeared inadequate for pathogens with an MIC of 1.0 mg/L (Table 1). Gentamicin
142 peak concentrations ≥ 5 mg/L were achieved in $> 96\%$ of neonates whereas a peak
143 concentration ≥ 10 mg/L was found in $< 60\%$ of neonates. Recommendations were successful
144 in maintaining trough concentrations < 2 mg/L in more than 95% of the patients, with one
145 exception (Center 7).

146

147 **Dosing Optimization**

148 **Efficacy target attainment**

149 None of the reviewed guidelines was an obvious candidate for optimal and simplified
150 gentamicin dosing. Therefore, dosing optimization was undertaken for MICs of 0.5 and 1
151 mg/L ($C_{\max} \geq 5$ mg/L and ≥ 10 mg/L, respectively). A dose per administration of 4 mg/kg
152 appeared sufficient to achieve a C_{\max} concentration of at least 5 mg/L with PTA $\geq 96\%$.
153 Simulations suggest that the dose needs to be increased to 7.5 mg/kg to achieve target peak
154 concentrations ≥ 10 mg/L in $\geq 90\%$ neonates (Figure 1).

155

156 **Safety target attainment**

157 **First dose.** For a dosing regimen of 7.5 mg/kg, only 6% of the patients would present trough
158 concentrations ≥ 2 mg/L after the dosing interval has been increased to 36 hours for all
159 neonates (Table S1). However, it was observed that neonates with PNA < 7 days showed
160 more frequently high trough concentrations (9%) than neonates with PNA ≥ 7 days (4%) (data
161 not shown). If neonates with PNA < 7 days were dosed every 48 hours only 1% reached these
162 high concentrations (Table 3).

163 **After one week of treatment.** A dosing regimen of 7.5 mg/kg every 36 hours for neonates
164 with PNA ≥ 7 days and every 48 hours for those with PNA < 7 days would result in some
165 accumulation after one week of treatment in the oldest subgroup (PNA ≥ 7 days), with 13% of
166 them reaching trough concentrations ≥ 2 mg/L (data not shown). Additional subgroup
167 stratification for patients in the oldest subgroup (PNA ≥ 7 days) who received 7.5 mg/kg
168 every 36 hours if their GA ≥ 28 weeks and every 48 hours if their GA ≤ 28 weeks, would
169 allow target achievements of trough concentrations below the predefined safety threshold in
170 both groups in more than 90% of neonates (Table 3). Neonates with PNA < 7 and GA ≤ 28
171 weeks would require a dosing interval of 60 hours. However, with a 48 hours dosing interval,
172 93% would show trough concentrations < 2 mg/L after the second dose (96 hours after the

173 start of treatment while most treatment courses will be discontinued at 72 hours) (data not
174 shown). Similar subgroup stratification, based on PNA and GA, were required for a dose of 4
175 mg/kg (Table 3).

176
177 In the scope of simplifying the dosing regimen of gentamicin in high resource settings, a
178 standard dose of 7.5 mg/kg to achieve an effective exposure ($C_{\max} / \text{MIC} \geq 10$) is favored
179 from the first dose, irrespective of any demographic factors, when an MIC of 1 mg/L is
180 considered. Individual dosing intervals for the following doses from 36 to 48 hours are
181 suggested according to PNA and GA (Table 3 & Figure 2). TDM should be considered for
182 treatment periods beyond 3 days to fine-tune dosing intervals at the individual level,
183 particularly in the most preterm neonates.

184
185 **Sensitivity analysis.** The proposed dosing regimen would not suffice in ascertaining a trough
186 concentration < 1 mg/L in $\geq 90\%$ of the patients (Table 3). For an initial gentamicin dose of
187 7.5 mg/kg, 90% of the patient would achieve a trough concentration < 1 mg/L after one week
188 of treatment by increasing the dosing interval by 72 hours (or more) for patients with $\text{GA} \leq 28$
189 weeks and by 48 hours or 60 hours for patients with $\text{GA} > 28$ and $\text{PNA} < 7$ days or $\text{PNA} \geq 7$
190 days, respectively. Following an initial dose of 4 mg/kg, dosing intervals should be increased
191 by 12 hours for each subgroup except for patients $\text{PNA} < 7$ days and $\text{GA} \leq 28$ weeks that
192 would require a dosing interval of 60 hours (data not shown). Predicted concentrations and
193 area under the curve (AUC) distributions are provided in the supplemental content (Table S2,
194 Figures S1-S3).

195
196 **DISCUSSION**
197 Considerable variability in gentamicin dosing recommendation is observed in current
198 international guidelines as well as in Swiss NICUs, in agreement with other studies (30).

199 According to simulations of neonatal exposure, results suggest that a dose of 4 mg/kg, as
200 frequently used in current recommendations, would be sufficient when an MIC breakpoint of
201 0.5 mg/L is considered. A higher MIC breakpoint of 1 mg/L requires a dose of 7.5 mg/kg to
202 achieve efficacious gentamicin exposures in at least 90% of treated neonates. Maintaining
203 trough concentrations ≤ 2 mg/L requires a dosing interval of 36 to 48 hours in neonates
204 according to postnatal age and gestational age.

205

206 Observed sources of variation in Swiss and international guidelines include differences in
207 dose per administration, dosing interval, total daily dose and/or patient characteristics used for
208 dose individualization. Complex dosing recommendations for personalized treatment increase
209 the risk of prescription errors and are factors triggering suboptimal patient management (31,
210 32), highlighting the potential benefit of using dosing harmonization and simplification for a
211 large number of patients. Variation between recommendations did not result in improved
212 efficacy and/or safety of gentamicin use. All recommendations managed to achieve
213 gentamicin peak concentrations ≥ 5 mg/L (MIC of 0.5 mg/L), but failed to achieve peak
214 concentrations of ≥ 10 m/L (MIC of 1 mg/L) in a high proportion of neonates. Except for one
215 recommendation, all lead to a relatively small proportion of neonates (< 5 %) with potentially
216 unsafe trough levels ≤ 2 mg/L.

217

218 It is likely that guidelines were established considering lower MICs and therefore lower peak
219 concentrations. Dosing strategies should ideally rely on individual MICs, but in NICUs, the
220 majority of neonates are treated empirically at the stage when infection cannot yet be
221 definitively confirmed and in many cases, it cannot be identified. Treatment should therefore
222 target the most likely and the most virulent pathogens involved in neonatal infections and
223 MIC targets are based upon standard MIC breakpoints from antimicrobial susceptibility
224 testing databases (33, 34). By using this approach, it is possible that the MIC breakpoint used

225 is higher than observed gentamicin MIC in individual patients' isolates (35). In this study,
226 MICs up to 1 mg/L are addressed. While MICs for many *Enterobacteriaceae* were
227 historically 0.5 mg/L, MICs of 1 mg/L are increasingly observed, especially for the spectrum
228 of pathogens encountered in late neonatal onset sepsis (*Pseudomonas spp.*, *Klebsiella spp.*)
229 (36). EUCAST sensitivity breakpoint for *Escherichia coli* is currently 2 mg/L, although this is
230 rather rarely observed in Switzerland (37). In addition, rates of multidrug resistance of Gram-
231 negative infections to empiric treatment are increasing, especially in resource limited settings
232 where MICs up to 4 mg/L are now encountered (Table S3) (33). Accordingly, peak
233 concentrations of 20 - 40 mg/L would be required, but are very challenging to achieve (Figure
234 1) and could result in unacceptable toxicity.

235
236 The pre-defined exposure target for efficacy was set to $C_{\max}/MIC \geq 10$. This is more
237 conservative compared to a ratio of 8 (9, 38), but was preferred as C_{\max}/MIC ratio of 10 was
238 associated with peak efficacy according to a pooled analysis of the 1980s data reported by
239 Turnidge *et al.* (39), and $C_{\max}/MIC \geq 10$ ratio has been shown to be necessary if deep tissue
240 penetration for infections is required (40-42). It is also reported that attainment of a PD target
241 ($C_{\max}/MIC > 10$) within 48 h of therapy is associated with an early therapeutic response (39).
242 In addition, the impact of the immature neonatal immune system on the appropriate efficacy
243 target is unknown, and this slightly higher target might be more suitable in this population
244 (43).

245
246 Finally, although $PTA \geq 90\%$ was considered as an appropriate outcome, the acceptable level
247 of PTA is still under debate with values from ranging 90% to 99% (44). However, the
248 definition of a target PTA has not been applied in a majority of previous gentamicin studies
249 and dosing recommendations from previous analysis are based on much lower proportions of
250 infants achieving target exposure (45-53).

251

252 As for many drugs, solid trial data supporting the use of specific doses associated with good
253 clinical outcome *in vivo* in this vulnerable population are lacking. As a result, current dosing
254 recommendations for gentamicin are variable and often complex. More evidence-based
255 dosing recommendations are required (26). However, trials for (suspected) infections are
256 difficult to design due to endpoint definitions, the low number of actual confirmed infections
257 in the neonatal population and obvious ethical reasons. Dosing optimization and possibly
258 simplification can benefit from pharmacometric modeling and simulations techniques. We
259 have used exposure simulations in 1071 neonatal patients leveraging an existing neonatal
260 gentamicin PK model to identify dosing regimens with a high probability of reaching pre-
261 defined efficacy and safety targets in a high proportion of patients. Priority was given to
262 optimizing and simplifying the first dose of gentamicin in order to maximize the
263 microorganism clearance as early as possible during infection (hit hard and hit fast paradigm)
264 (54).

265

266 Combination of higher efficacy criteria and higher PTA set in this study might appear
267 conservative as compared to previous studies, but are in line with the current methodology
268 used in simulation and dosing optimization for other antibiotics and with MICs encountered in
269 NICUs (55-57). Presumably, this explains why our simulations suggest a higher dose (7.5
270 mg/kg) as compared to current international and local guidelines. It is acknowledged that a
271 large number of patients are exposed to gentamicin while not having a true infection, putting
272 them at risk of adverse events with no benefits. However, effective initial therapy to cover
273 pathogens which are difficult to treat is essential for those infants with a true infection to
274 minimize adverse outcome due to the infection (2).

275 Nephro- and oto-toxicity do not seem to be associated with peak concentrations (58), but
276 rather with drug accumulation and prolonged treatment (59). Though, the safety consequences

277 of higher peak concentration to target higher MICs are unknown. Nevertheless, toxicity
278 incidence remains low in the pediatric population and is lower than the rates reported in
279 adults, in particular when extended dosing intervals are used (60). To maintain trough
280 concentrations ≤ 2 mg/L with a dose of 7.5 mg/kg, the dosing interval should be extended to
281 36 – 48 hours. This dosing regimen would also ensure trough concentrations < 1 mg/L in the
282 majority of patients ($> 82\%$), a target sometimes used as a more stringent surrogate for safety.
283 Thomson *et al.* investigated the daily intramuscular administration of an 8 mg/kg gentamicin
284 dose and trough concentrations < 2 mg/L were observed (61). Lopez *et al.* investigated
285 extended intervals (24 and 36 hours) after high gentamicin doses (8 mg/kg) and no
286 nephrotoxicity was observed in this study, although gentamicin was not administered for
287 prolonged periods (no longer than 5 days) (58). Additionally, it was found that a gentamicin
288 dose of 8 mg/kg provided near 100% probability of achieving adequate peak concentrations $>$
289 16 mg/L (for a population that included children up to 4 years old) (58). In a study involving
290 newborns receiving a 6 mg/kg gentamicin dose over various intervals ranging from 24 to 48
291 hours, trough concentrations ≥ 2 mg/L were observed in only 6% of all treatment episodes.
292 No evidence for ototoxicity was observed and potential nephrotoxicity was not assessed in
293 any detail (21).

294

295 Since the first hours of infection are crucial, administration of antibiotics within one hour of
296 identification of sepsis is recommended (62). Therapeutic drug monitoring is recommended
297 for longer courses to evaluate the necessity of adjusting dosing interval on any individual
298 basis (63). Considering that trough gentamicin TDM is cumbersome in neonates and that
299 steady-state definition in neonates is not applicable, a Bayesian-based TDM approach
300 allowing opportunistic TDM at the time of routine blood tests based on one concentration
301 measurement would present numerous advantages (19). For a large proportion of patients,

302 treatment will be discontinued after 48 - 72 hours and most of them would receive only one to
303 two doses and therefore would not require TDM, limiting the burden of blood sampling.

304

305 Another important constraint concerns the selection of the model used to investigate
306 gentamicin drug exposure in neonatal patients in this simulation study. The choice of the most
307 robust model (Germovsek *et al.* model) was evaluated with respect to the population on which
308 the model was built, the data used for model development (number of centers, prospective
309 collection, number of subjects and concentrations measurements), the relevance of covariate
310 effects included in the model, and the assessment of the predictive performance of the model.
311 Simulation results were also compared with those obtained with the two other published
312 models to avoid any systematic bias in the prediction. This sensitivity test yielded similar
313 results as shown in Table S4 and Figure S6.

314

315 **CONCLUSION**

316 This simulation study in 1071 neonatal patients suggests that a gentamicin dose per
317 administration of 7.5 mg/kg is optimal to achieve an efficacious peak concentration
318 corresponding to an MIC of 1.0 mg/L in 90% of neonates. To ensure trough concentration
319 associated with less toxicity during the first 60 days of life, dosing intervals of 36 to 48 hours
320 are recommended, depending on PNA and GA. Therapeutic drug monitoring should be
321 considered for treatment longer than three days to adjust and individualize dosing intervals
322 and avoid potentially harming trough concentrations of gentamicin. This study also highlights
323 the lack of consensus on magnitude of the targeted PK/PD index, desirable PTA to achieve
324 and need for models to address the immaturity of the immune system of neonates. Our
325 findings stress the urgent need for prospective clinical evaluations of efficacy and safety
326 outcomes with gentamicin.

327

328 **MATERIALS & METHODS**

329 **Data Collection Dosing Regimens**

330 Gentamicin dosing regimens were collected from eight international guidelines (Frank Shann,
331 British National Formulary for Children, Nelson Textbook of Pediatrics, Neonatal Formulary
332 7th edition, The Blue Book, Lexicomp Pediatric & Neonatal Dosage Handbook, The Red
333 Book and Neofax) (17, 29, 64-69) and seven Swiss NICUs (Aarau, Bern, Chur, Geneva,
334 Lausanne, St Gallen and Zurich). Variables used for the selection of *a priori* dosing regimens
335 were compared i.e. dose per administration, dosing interval, total daily dose and demographic
336 characteristics.

337

338 **Simulation of Gentamicin Exposure**

339 **Demographic data**

340 Simulation of individual gentamicin exposure used real demographic data from the Antibiotic
341 Resistance and Prescribing in European Children (ARPEC) (70, 71) point prevalence study,
342 and including only European neonates with the complete set of the following characteristics:
343 gestational age, birth weight, current weight and postnatal age. As all data were on neonates
344 and infants treated for suspected infection, the skewed distribution of demographic
345 characteristics in this population likely reflects the epidemiology of suspected sepsis at birth
346 (Table 4). Postmenstrual age was computed as the sum of gestational age and postnatal age.
347 The final dataset included 1071 patients with real-life demographic data and their correlation.

348

349 **Model selection**

350 Multiple population PK models for gentamicin in neonates have been published and were
351 recently reviewed (28). The search strategy provided by Wilbaux *et al.* was applied and
352 extended until February 2017. Criteria for model selection consisted of: (i) data on which the
353 model was developed includes the population of interest i.e. term and preterm neonates aged

354 up to at least 60 days, (ii) robustness of data used for model development (number of centers,
355 prospective collection, number of subjects and concentrations measurements), (iii) relevance
356 of covariate effects included in the model with respect to developmental and maturational
357 changes in neonates and (iv) assessment and documentation of the predictive performance of
358 the model.

359
360 The population PK model of Germovsek *et al.* (19) was preferred over others (45-53, 58, 61,
361 72-78) for the following reasons: (i) this model was developed with rich data collected
362 prospectively in three large previously conducted studies (45, 75), (ii) the analysis dataset
363 consisted of data from 205 neonates providing 1325 gentamicin serum concentrations, (iii)
364 appropriate representation of the target population with gestational age, postnatal age and
365 weight ranging from 23.3 - 42.3 weeks, 1 – 78 days and 2.03 – 5.05 kg, respectively. In this
366 analysis, data were best described by a 3-compartmental model with linear elimination.
367 Clearance and volume of distribution were scaled allometrically to body weight. A maturation
368 function incorporating PMA (79) in addition to PNA and serum creatinine concentration
369 (SCr) influenced drug clearance.

370 Since there were no SCr values available in the ARPEC dataset used for simulations, SCr was
371 set to typical values in this neonatal population as proposed by Germovsek *et al.* (19) i.e. the
372 measured SCr concentration/typical value of SCr concentration ratio was set to 1. A deviation
373 of SCr concentration to 60 $\mu\text{mol/L}$ from a typical SCr concentration 70 $\mu\text{mol/L}$ has only a
374 marginal effect on drug clearance in the applied model (clearance 2% lower). Linear PK was
375 assumed for the total range of doses tested and the weight remained constant during the first
376 week of treatment. Gentamicin exposures associated with dosing regimens of interest were
377 simulated in all neonatal patients in the available dataset ($n = 1071$). Each patient was
378 simulated once and peak concentrations were retrieved at 1 hour post dose, i.e. 0.5 hour
379 following the end of infusion.

380

381 **Evaluation Steps**

382 Germovsek *et al.* evaluated their model by bootstrap and visual predictive checks as well as
383 against an external dataset (163 neonates, prospective collection from five hospitals). Model
384 trough concentrations predicted from their model and from literature (45, 46, 49, 50, 58, 72-
385 76) were compared using their external evaluation dataset. The predicted trough
386 concentrations were the least biased for their model (19). We also compared predicted
387 gentamicin exposure with the applied model to two other published models (45, 63) using our
388 final dosing recommendation.

389

390 Model-based simulations for gentamicin dosing up to 7 days were performed with the
391 software package NONMEM® (version 7.3.0; ICON Development Solutions, Ellicott City,
392 MD), data evaluation and visual representations were performed with R (version 3.1.2; R
393 Development Core Team, Vienna, Austria, <http://www.r-project.org>).

394

395 **Pharmacodynamic surrogates**

396 $C_{\max}/MIC > 10$ ratio was chosen as the PD surrogate. Gentamicin concentrations ≥ 5 mg/L
397 and ≥ 10 mg/L, corresponding to MIC breakpoints of 0.5 mg/l and 1.0 mg/L respectively,
398 were set as peak targets. A trough concentration ≤ 2 mg/L was set as an appropriate target
399 minimizing toxic effects. The proportion of patients reaching the targets for efficacy and
400 safety surrogates were computed after the first dose (first dose study on day 1) and after one
401 week of treatment (last dose on study day 7), and defined as the probability of target
402 achievement (PTA). The aim was to select a dosing regimen leading to a $PTA \geq 90\%$ within
403 the predefined targets for efficacy and safety (44).

404

405 **Gentamicin Dosing Optimization**

406 A stepwise approach was applied to identify an optimal dosing regimen. As a first step, the
407 minimal dose per administration (mg/kg) that achieved target peak concentrations was
408 selected (target attainment with respect to efficacy). The following escalating single doses per
409 body weight were simulated: 4, 5, 6, 7, 7.5, 8, 10, 12, 14 and 16 mg/kg. As a second step,
410 adequate dosing intervals were evaluated for the selected dose to avoid accumulation and
411 maintain target trough concentrations ≤ 2 mg/L (target attainment with respect to safety). The
412 following dosing intervals were evaluated in the simulation study: 24 hours, 36 hours, 48
413 hours and 72 hours. As a third step, neonatal patients were categorized into subgroups to test
414 whether dosing could be further optimized and personalized in neonates with dose
415 adjustments based on patient characteristics (e.g. various doses based on PNA categories). A
416 sensitivity analysis was performed for a trough concentration ≤ 1 mg/L.

417

418 The results were retrieved after the first dose and one week of treatment but priority was
419 given to achieving efficacious and safe exposure after the first dose, considering that (i)
420 accurate treatment within the first hours of infection is crucial (54), (ii) treatment will be
421 discontinued within 72 hours in a majority of neonatal patients for non-confirmed infection or
422 switched to a more targeted therapy for confirmed infection, (iii) a large proportion of treated
423 neonatal patients are expected to undergo therapeutic drug monitoring to ensure efficacious
424 and safe exposures beyond the first 2-3 days of treatment in high income countries.

425

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439

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664

665

666 **Figure 1:** Percentage of neonates with target peak concentrations for various gentamicin
667 doses per kg of body weight after first dose for entire neonatal population. Tested target peak
668 concentrations ≥ 5 , ≥ 10 , ≥ 20 , ≥ 40 mg/L corresponding to MICs of 0.5, 1.0, 2.0 or 4.0 mg/L
669 respectively.

670

671 **Figure 2:** Distribution of peak and trough concentration after single 7.5 mg/kg gentamicin
672 dose for four subgroups over 48h interval (PNA < 7 days or PNA ≥ 7 days & GA ≤ 28 weeks)
673 or 36h interval (PNA ≥ 7 days & GA > 28 weeks). PNA; post-natal age, GA; gestational age.
674 Boxes represent the interquartile range (IQR), solid lines are the median, 25th and 75th
675 quantile and whiskers equal 25th quantile -1.5 IQR and 75th quantile + 1.5 IQR.

676

Guideline	Demographic characteristics	Dose (mg/kg)	Interval (hours)	No. of subgroups*	Targets (mg/L)		
					Peak (%)		Trough (%)
					≥ 5	≥ 10	
No demographic variable							
Center 5	-	4	24	1	96	26	4
Center 7 (1) †	-	5	24	1	99	54	12
Center 7 (2) †	-	5	36	1	99	54	< 0.5
Center 7 (3) †	-	5	48	1	99	54	< 0.5
One demographic variable							
BNFc	PNA	5	24 / 36	2	99	54	3
Blue Book (min)	GA	4	24 / 36	2	96	26	1
Blue Book (max)	GA	5	24 / 36	2	99	54	4
Two demographic variables							
Center 1	PNA & WT	4 / 5	24 – 48	5	97	39	2
Center 2	PNA & WT	5 / 6	24 – 48	7	99	58	4
Center 3 (min)	PNA & GA	4 / 5	24 – 48	6	96	28	1
Center 3 (max)	PNA & GA	5	24 – 48	6	99	54	4
Center 4	PNA & PMA	4 / 4.5 / 5	24 – 48	6	96	30	2
Center 6	PNA & GA	4 / 4.5 / 5	24 – 48	6	96	30	1
Nelson	PNA & GA	4 / 4.5 / 5	24 – 48	7	97	37	1
NNF7	PNA & GA	5	24 – 48	4	99	55	5
Lexicomp	PNA & GA	4 / 4.5 / 5	24 – 48	6	98	43	1
Red Book (min)	PNA & WT	4 / 5	24 – 48	6	97	39	2
Red Book (max)	PNA & WT	4 / 5	24 – 48	6	98	44	2
Neofax	PNA & PMA	4 / 4.5 / 5	24 – 48	5	96	30	1
Shann	PNA & WT	5 / 6	24 – 48	7	99	58	4

Table 1: Probability of target attainment for guidelines and Swiss centers for effective peak concentration (≥ 5 or ≥ 10 mg/L) and trough concentration > 2 mg/L.

* Subgroups are based on demographic characteristics as indicated in guidelines.

† Guidelines suggested a dosing interval range of 24 – 48 hours and therapeutic drug monitoring was recommended after first dose.

BNFc; British National Formulary for Children, Blue Book; Manual of childhood infections Blue Book, Nelson; Nelson Textbook of Pediatrics, NNF7; Neonatal Formulary 7th edition, Lexicomp; Lexicomp Pediatric & Neonatal Dosage Handbook, Red Book; Red Book report of the Committee on Infectious Diseases, Shann; Frank Shann Drug Doses, PNA; postnatal age, GA; gestational age, WT; weight, PMA; postmenstrual age.

	GA = 30 weeks		GA = 38 weeks	
	PNA: 2 days WT: 1.3 kg	PNA: 15 days WT: 1.5 kg	PNA: 2 days WT: 3.0 kg	PNA: 15 days WT: 3.3 kg
Nelson	5 mg/kg * 48h	4 mg/kg * 24h	4 mg/kg * 24h	4 mg/kg * 24h
BNFc	5 mg/kg * 36h	5 mg/kg * 24h	5 mg/kg * 36h	5 mg/kg * 24h
Shann	5 mg/kg * 36h	5 mg/kg * 24h	5 mg/kg * 24h	6 mg/kg * 24h
Lexicomp	4.5 mg/kg * 36h	5 mg/kg * 36h	4 mg/kg * 24h	5 mg/kg * 24h
Center 1	5 m/kg * 48h	5 mg/kg * 36h	4 mg/kg * 24h	4 mg/kg * 24h
Center 3	4-5 mg/kg * 36h	4-5 mg/kg * 24h	4-5 mg/kg * 24h	4-5 mg/kg * 24h
Center 6	4.5 mg/kg * 36h	4 mg/kg * 24h	4 mg/kg * 24h	4 mg/kg * 24h
Center 7	5 mg/kg * 24-48h	5 mg/kg * 24-48h	5 mg/kg * 24-48h	5 mg/kg * 24-48h

Table 2: Variability in gentamicin dosing recommendations for two typical patients. GA; gestational age, PNA; postnatal age, WT; body weight, h; hours, *; every, Nelson; Nelson's Pediatric Antimicrobial Therapy handbook, Shann; Frank Shann, Lexicomp; Lexicomp Pediatric & Neonatal Dosage Handbook, Center; Swiss neonatal and pediatric centers.

Dosing Regimen	Demographic Characteristics	First dose			After 1 Week of Treatment		
		% Neonates with ratio Peak/MIC > 10	% Neonates with Trough		% Neonates with ratio Peak/MIC > 10	% Neonates with Trough	
			< 1 mg/L	< 2 mg/L		< 1 mg/L	< 2 mg/L
MIC 0.5 mg/L							
4 mg/kg * 36h	PNA < 7 & GA ≤ 28	98	62	100	98	43	94
4 mg/kg * 36h	PNA < 7 & GA > 28	97	91	100	97	86	99
4 mg/kg * 36h	PNA ≥ 7 & GA ≤ 28	96	88	100	97	70	96
4 mg/kg * 24h	PNA ≥ 7 & GA > 28	94	80	99	95	65	93
MIC 1.0 mg/L							
7.5 mg/kg * 48h	PNA < 7 & GA ≤ 28	98	40	98	98	38	87†
7.5 mg/kg * 48h	PNA < 7 & GA > 28	91	85	99	92	84	97
7.5 mg/kg * 48h	PNA ≥ 7 & GA ≤ 28	95	81	99	95	67	92
7.5 mg/kg * 36h	PNA ≥ 7 & GA > 28	90	83	99	91	74	95

Table 3: Probability of target attainment for pre-defined peak and trough concentration targets following optimal dosing regimen (administration of 7.5 mg/kg over different dosing interval according to patients characteristics). MIC; Minimum Inhibition Concentration, PNA; Post-natal age (days). GA; Gestational age (weeks). † To achieve a PTA of 90% would require a dosing interval of 60h (PTA = 97%). After second dose with a dosing interval of 48h (96 hours after the start of treatment), PTA would still be of 93%.

Number of Neonates	N (%)
Total population	1071 (100 %)
Preterm (GA < 37 weeks)	654 (58 %)
Preterm (GA < 28 weeks)	201 (18 %)
Demographic Characteristics	Median (min – max)
Gestational age (weeks)	34 (22 – 44)
Birth weight (kg)	2.1 (0.4 – 4.8)
Post-natal age (days)	7 (0 – 60)
≤ 7 days (%)	54 %
Current weight (kg)	2.2 (0.48 – 4.86)
Post menstrual age (weeks)	35.7 (23.7 – 47.6)

Table 4: Demographic characteristics from the Antibiotic Resistance and Prescribing in European Children data subset used for exposure simulation. GA; gestational age, kg; kilograms.



