MANUSCRIPT INFORMATION

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

Authors: Tamara van Donge,[a] Marc Pfister,[a,b] Julia Bielicki,[a,c] Chantal Csajka,[d,e] Frederique Rodieux,[f] John van den Anker,[a,g,h], Aline Fuchs[a]

Affiliation: Paediatric Pharmacology and Pharmacometrics Research, University of Basel Children's Hospital, Basel, Switzerland[a] ; Quantitative Solutions, a Certara Company, United Kingdom[b] ; Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's, University of London, London, United Kingdom[c] ; Service of Clinical Pharmacology, Department of Laboratory, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland[d] ; School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland[e]; Service of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland[f] ; Intensive Care and Department of Surgery, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands[g] ; Division of Clinical Pharmacology, Children's National Health System, Washington, DC, USA[h] ;

Mailing addresses:

Address correspondence to Aline Fuchs: aline.fuchs@ukbb.ch

Tamara van Donge: tamaravandonge@gmail.com

Marc Pfister: marc.pfister@ukbb.ch

Julia Bielicki: Julia.bielicki@ukbb.ch

Chantal Csajka: chantal.csajka@chuv.ch

Frederique Rodieux: frederique.rodieux@hcuge.ch

John van den Anker: johannes.vandenanker@ukbb.ch

Author's disclosure: Other authors declare no conflict of interest that could appear to have influenced the submitted work.

Key words: Aminoglycosides, pediatrics, pharmacokinetics, minimum inhibitory concentration

Running Title: Gentamicin drug exposure in neonates

Abstract word count (max 250): 240

ABSTRACT

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

INTRODUCTION

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

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

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

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

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

RESULTS

Variability in National and International Guidelines

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

Achievement of Efficacious and Safe Gentamicin Exposure

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

Dosing Optimization

Efficacy target attainment

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

Safety target attainment

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

MATERIALS & METHODS

Data Collection Dosing Regimens

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

Simulation of Gentamicin Exposure

Demographic data

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

Model selection

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

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

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

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

Evaluation Steps

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

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

Pharmacodynamic surrogates

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

Gentamicin Dosing Optimization

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

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

ACKNOWLEDGMENTS

This project is part of the national SwissPedDose project for harmonizing dosing in neonates, infants, and children supported by the Swiss Federal Public Health Office (BAG) which supports the research group of Paediatric Pharmacology and Pharmacometrics at UKBB.

We thank all physicians, nurses and medical personnel from the 7 hospitals that helped us and allowed us the data acquisition about drug dosing regimens. We like to thank the members of

the expert committee of the SwissPedDose project in addition to those listed as authors: Eric Giannoni, (Clinic of Neonatology, Department Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland), Thomas M. Berger (Board Member, Swiss Society of Neonatology, Luzern, Switzerland), René Glanzmann (Division of Neonatology, University of Basel Children's Hospital, Basel, Switzerland). We thank Prof. Herman Goossens and Ms Ann Versporten from the University of Antwerp and the ARPEC project group for provision of the ARPEC dataset.

REFERENCES

1. **Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, Lawn JE, Cousens S, Mathers C, Black RE.** 2016. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet (London, England) **388:**3027-3035.
2. **Kent A, Kortsalioudaki C, Monahan IM, Bielicki J, Planche TD, Heath PT, Sharland M.** 2016. Neonatal gram-negative infections, antibiotic susceptibility and clinical outcome: an observational study. Archives of Disease in Childhood - Fetal and Neonatal Edition **101:**F507.
3. **Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD.** 2014. Early-Onset Neonatal Sepsis. Clinical Microbiology Reviews **27:**21-47.
4. **Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, Laforgia N, Ciccone MM.** 2016. Early and Late Infections in Newborns: Where Do We Stand? A Review. Pediatrics & Neonatology **57:**265-273.
5. **Cantey JB, Wozniak PS, Sanchez PJ.** 2015. Prospective surveillance of antibiotic use in the neonatal intensive care unit: results from the SCOUT study. Pediatr Infect Dis J **34:**267-272.
6. **World Health Organization.** 2013. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. World Health Organization.
7. **Chattopadhyay B.** 2002. Newborns and gentamicin—how much and how often? Journal of Antimicrobial Chemotherapy **49:**13-16.
8. **Allegaert K, Veerle C, van den Anker JN.** 2015. Dosing Guidelines of Aminoglycosides in Neonates: A Balance Between Physiology and Feasibility. Current Pharmaceutical Design **21:**5699-5704.
9. **Kirby WMM, Standiford HC.** 1969. Gentamicin: in vitro studies. The Journal of infectious diseases**:**361-363.
10. **Lacy MK, Nicolau DP, Nightingale CH, Quintiliani R.** 1998. The pharmacodynamics of aminoglycosides. Clinical infectious diseases **27:**23-27.
11. **Nielsen EI, Cars O, Friberg LE.** 2011. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: a step toward model-based dose optimization. Antimicrobial agents and chemotherapy **55:**4619-4630.
12. **Samiee-Zafarghandy S, van den Anker JN.** 2013. Nephrotoxic effects of aminoglycosides on the developing kidney. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM) **2:**e020227.
13. **Germovsek E, Barker CI, Sharland M.** 2017. What do I need to know about aminoglycoside antibiotics? Archives of Disease in Childhood - Education and Practice **102**:89-93.
14. **Etienne I, Joannides R, Dhib M, Fillastre JP.** 1992. Drug-induced nephropathies. La Revue du praticien **42:**2210-2216.
15. **Young TE.** 2002. Aminoglycoside Therapy in Neonates. With Particular Reference to Gentamicin **3:**e243-e248.
16. **Rao SC, Srinivasjois R, Hagan R, Ahmed M.** 2011. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database of Systematic Reviews **11** Art. No.: CD005091.
17. **Joint Formulary Committee.** 2015. Infection; Blood infection, bacterial. In: British National Formulary for Children. London: BMJ Group and Pharmaceutical Press, pp 274.
18. **Kent A, Turner MA, Sharland M, Heath PT.** 2014. Aminoglycoside toxicity in neonates: something to worry about? Expert Review of Anti-infective Therapy **12:**319-331.
19. **Germovsek E, Kent A, Metsvaht T, Lutsar I, Klein N, Turner MA, Sharland M, Nielsen EI, Heath PT, Standing JF.** 2016. Development and Evaluation of a Gentamicin Pharmacokinetic Model That Facilitates Opportunistic Gentamicin Therapeutic Drug Monitoring in Neonates and Infants. Antimicrob Agents Chemother **60:**4869-4877.
20. **Abitbol CL, DeFreitas MJ, Strauss J.** 2016. Assessment of kidney function in preterm infants: lifelong implications. Pediatric Nephrology **31:**2213-2222.

21. **Fjalstad JW, Laukli E, van den Anker JN, Klingenberg C.** 2013. High-dose gentamicin in newborn infants: is it safe? Eur J Pediatr **173**:489-495.
22. **Allegaert K, van den Anker J.** 2015. Neonatal drug therapy: The first frontier of therapeutics for children. Clin Pharmacol Ther **98:**288-297.
23. **Hillman N, Kallapur SG, Jobe A.** 2012. Physiology of Transition from intrauterine to Extrauterine Life. Clinics in perinatology **39:**769-783.
24. **Ford S, Calvert J.** 2008. Adaptation for life: a review of neonatal physiology. Anaesthesia & Intensive Care Medicine **9:**93-98.
25. **Hartnoll G, Betremieux P, Modi N.** 2000. Body water content of extremely preterm infants at birth. Archives of Disease in Childhood Fetal and Neonatal Edition **83:**F56-F59.
26. **Metsvaht T, Nellis G, Varendi H, Nunn AJ, Graham S, Rieutord A, Storme T, McElnay J, Mulla H, Turner MA, Lutsar I.** 2015. High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination. BMC Pediatr **15:**41.
27. **Samardzic J, Allegaert K, Wilbaux M, Pfister M, van den Anker JN.** 2016. Quantitative clinical pharmacology practice for optimal use of antibiotics during the neonatal period. Expert Opinion on Drug Metabolism & Toxicology **12:**367-375.
28. **Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K, van den Anker JN, Pfister M.** 2016. Pharmacometric Approaches to Personalize Use of Primarily Renally Eliminated Antibiotics in Preterm and Term Neonates. J Clin Pharmacol **56:**909-935.
29. **2015 Nelson's Pediatric Antimicrobial Therapy, 21st Edition.** Edited by Bradley JS, Kimberlin DW.
30. **Spyridis N, Syridou G, Goossens H, Versporten A, Kopsidas J, Kourlaba G, Bielicki J, Drapier N, Zaoutis T, Tsolia M, Sharland M, Members APG.** 2016. Variation in paediatric hospital antibiotic guidelines in Europe. Arch Dis Child **101:**72-76.
31. **Pawluk S, Jaam M, Hazi F, Al Hail MS, El Kassem W, Khalifa H, Thomas B, Abdul Rouf P.** 2017. A description of medication errors reported by pharmacists in a neonatal intensive care unit. Int J Clin Pharm **39:**88-94.
32. **Koumpagioti D, Varounis C, Kletsiou E, Nteli C, Matziou V.** 2014. Evaluation of the medication process in pediatric patients: a meta-analysis. Jornal de Pediatria **90:**344-355.
33. **The European Committee on Antimicrobial Susceptibility Testing.** 2017. Breakpoint tables for interpretation of MICs and zone diameters, version 7.1. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf. Accessed 02-06-2017.
34. **Wayne PA.** 2009. Clinical and Laboratory Standards Institute (CLSI) performance standards for antimicrobial disk diffusion susceptibility tests 19th ed. approved standard. CLSI document M100-S19 **29**.
35. **Woksepp H, Hällgren A, Borgström S, Kullberg F, Wimmerstedt A, Oscarsson A, Nordlund P, Lindholm ML, Bonnedahl J, Brudin L, Carlsson B, Schön T.** 2017. High target attainment for β-lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied. European Journal of Clinical Microbiology & Infectious Diseases **36:**553-563.
36. **Kent A, Kortsalioudaki C, Monahan IM, Bielicki J, Planche TD, Heath PT, Sharland M.** 2016. Neonatal gram-negative infections, antibiotic susceptibility and clinical outcome: an observational study. Arch Dis Child Fetal Neonatal Ed **101**:F507-F512.
37. **Federal Office of Public Health and Federal Food Safety and Veterinary Office.** 2016. Swiss Antibiotic Resistance Report 2016. Usage of Antibiotics and Occurrence of Antibiotic Resistance in Bacteria from Humans and Animals in Switzerland. Publication number: 2016-OEG-30.
38. **Moore RD, Lietman PS, Smith CR.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. Journal of Infectious Diseases **155:**93-99.

39. **Turnidge J.** 2003. Pharmacodynamics and dosing of aminoglycosides. Infectious disease clinics of North America **17:**503-528.
40. **Scheetz MH, Hurt KM, Noskin GA, Oliphant CM.** 2006. Applying antimicrobial pharmacodynamics to resistant gram-negative pathogens. American Journal of Health-System Pharmacy **63:**1346-1360.
41. **Eliopoulos GM, Drusano GL, Ambrose PG, Bhavnani SM, Bertino JS, Nafziger AN, Louie A.** 2007. Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally. Clinical Infectious Diseases **45:**753-760.
42. **Kashuba AD, Nafziger AN, Drusano GL, Bertino JS, Jr.** 1999. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother **43:**623-629.
43. **Strunk T, Richmond P, Simmer K, Currie A, Levy O, Burgner D.** 2007. Neonatal immune responses to coagulase-negative staphylococci. Current Opinion in Infectious Diseases **20:**370-375.
44. **Mouton JW, Brown DFJ, Apfalter P, Cantón R, Giske CG, Ivanova M, MacGowan AP, Rodloff A, Soussy CJ, Steinbakk M, Kahlmeter G.** 2012. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clinical Microbiology and Infection **18:**E37-E45.
45. **Nielsen EI, Sandström M, Honoré PH, Ewald U, Friberg LE.** 2009. Developmental Pharmacokinetics of Gentamicin in Preterm and Term Neonates. Clinical Pharmacokinetics **48:**253-263.
46. **Fuchs A, Guidi M, Giannoni E, Werner D, Buclin T, Widmer N, Csajka C.** 2014. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates. Br J Clin Pharmacol **78:**1090-1101.
47. **DiCenzo R, Forrest A, Slish JC, Cole C, Guillet R.** 2003. A Gentamicin Pharmacokinetic Population Model and Once-Daily Dosing Algorithm for Neonates. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy **23:**585-591.
48. **Frymoyer A, Meng L, Bonifacio SL, Verotta D, Guglielmo BJ.** 2013. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. Pharmacotherapy **33:**718-726.
49. **Kelman AW, Thomson AH, Whiting B, Bryson SM, Steedman DA, Mawer GE, Samba-Donga LA.** 1984. Estimation of gentamicin clearance and volume of distribution in neonates and young children. British journal of clinical pharmacology **18:**685-692.
50. **Lanao JM, Calvo MV, Mesa JA, Martin-Suarez A, Carbajosa MT, Miguelez F, Dominguez-Gil A.** 2004. Pharmacokinetic basis for the use of extended interval dosage regimens of gentamicin in neonates. J Antimicrob Chemother **54:**193-198.
51. **Stolk LML, Degraeuwe PLJ, Nieman FHM, de Wolf MC, de Boer A.** 2002. Population Pharmacokinetics and Relationship Between Demographic and Clinical Variables and Pharmacokinetics of Gentamicin in Neonates. Therapeutic Drug Monitoring **24:**527-531.
52. **García B, Barcia E, Pérez F, Molina IT.** 2006. Population pharmacokinetics of gentamicin in premature newborns. Journal of Antimicrobial Chemotherapy **58:**372-379.
53. **Bijleveld YA, de Haan TR, van der Lee HJH, Groenendaal F, Dijk PH, van Heijst A, de Jonge RCJ, Dijkman KP, van Straaten HLM, Rijken M, Zonnenberg IA, Cools F, Zecic A, Nuytemans DHGM, van Kaam AH, Mathot RAA, for the PharmaCool study g.** 2016. Altered gentamicin pharmacokinetics in term neonates undergoing controlled hypothermia. British Journal of Clinical Pharmacology **81:**1067-1077.
54. **Kumar A.** 2014. An alternate pathophysiologic paradigm of sepsis and septic shock: Implications for optimizing antimicrobial therapy. Virulence **5:**80-97.
55. **Yoshizawa K, Ikawa K, Ikeda K, Ohge H, Morikawa N.** 2013. Population Pharmacokinetic–Pharmacodynamic Target Attainment Analysis of Imipenem Plasma and Urine Data in Neonates and Children. The Pediatric Infectious Disease Journal **32:**1208-1216.

56. **Bradley JS, Sauberan JB, Ambrose PG, Bhavnani SM, Rasmussen MR, Capparelli EV.** 2008. Meropenem Pharmacokinetics, Pharmacodynamics, and Monte Carlo Simulation in the Neonate. The Pediatric Infectious Disease Journal **27:**794-799.
57. **Tremoulet A, Le J, Poindexter B, Sullivan JE, Laughon M, Delmore P, Salgado A, Ian-U Chong S, Melloni C, Gao J, Benjamin DK, Capparelli EV, Cohen-Wolkowiez M.** 2014. Characterization of the Population Pharmacokinetics of Ampicillin in Neonates Using an Opportunistic Study Design. Antimicrobial Agents and Chemotherapy **58:**3013-3020.
58. **Lopez SA, Mulla H, Durward A, Tibby SM.** 2010. Extended-interval gentamicin: population pharmacokinetics in pediatric critical illness. Pediatr Crit Care Med **11:**267-274.
59. **Quiros Y, Vicente-Vicente L, Morales AI, López-Novoa JM, López-Hernández FJ.** 2011. An Integrative Overview on the Mechanisms Underlying the Renal Tubular Cytotoxicity of Gentamicin. Toxicological Sciences **119:**245-256.
60. **Kent A, Turner MA, Sharland M, Heath PT.** 2014. Aminoglycoside toxicity in neonates: something to worry about? Expert Rev Anti Infect Ther **12:**319-331.
61. **Thomson AH, Kokwaro GO, Muchohi SN, English M, Mohammed S, Edwards G.** 2003. Population pharmacokinetics of intramuscular gentamicin administered to young infants with suspected severe sepsis in Kenya. British Journal of Clinical Pharmacology **56:**25-31.
62. **Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME.** 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive care medicine **43:**304-377.
63. **Fuchs A, Zimmermann L, Bickle Graz M, Cherpillod J, Tolsa J-F, Buclin T, Giannoni E.** 2016. Gentamicin Exposure and Sensorineural Hearing Loss in Preterm Infants. PLOS ONE **11:**e0158806.
64. **Shann F.** 2008. Drug doses. Collective Pty Limited.
65. **Ainsworth SB.** 2014. Neonatal formulary: drug use in pregnancy and the first year of life. John Wiley & Sons.
66. **Sharland M, Butler K, Cant A, Dagan R, Davies G, de Groot R, Elliman D, Esposito S, Finn A, Galanakis M.** 2016. Manual of childhood infections: the blue book. Oxford University Press.
67. **Taketomo CK, Hodding JH, Kraus DM.** 2013. Pediatric & neonatal dosage handbook: a comprehensive resource for all clinicians treating pediatric and neonatal patients. Lexi-comp.
68. **Report of the Committee on Infectious Diseases, 30th ed.** In: Kimberlin DW, Bradley MT, Jackson MA, et al., eds. Red Book. Elk Grove Village, IL: American Academy of Pediatrics, 2015.
69. **Thomas EY, Mangum B.** 2010. Neofax 2010. Thomson Reuters.
70. **Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, Calle GM, Garrahan JP, Clark J, Cooper C, Blyth CC, Francis JR, Alsalman J, Jansens H, Mahieu L, Van Rossom P, Vandewal W, Lepage P, Blumental S, Briquet C, de Louvain C, Robbrecht D, Maton P, Gabriels P, Rubic Z, Kovacevic T, Nielsen JP, Petersen JR, Poorisrisak P, Jensen LH, Laan M, Tamm E, Matsinen M, Rummukainen M-L, Gajdos V, Olivier R, Le Maréchal F, Martinot A, Prot-Labarthe S, Lorrot M, Orbach D, Pagava K, Hufnagel M, Knuf M, Schlag SAA, Liese J, Renner L, Enimil A, Awunyo M, Syridou G, Spyridis N, et al.** 2016. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. Journal of Antimicrobial Chemotherapy **71:**1106-1117.
71. **Versporten A, Sharland M, Bielicki J, Drapier N, Vankerckhoven V, Goossens H.** 2013. The Antibiotic Resistance and Prescribing in European Children Project: A Neonatal and Pediatric Antimicrobial Web-based Point Prevalence Survey in 73 Hospitals Worldwide. The Pediatric Infectious Disease Journal **32:**e242-e253.
72. **Lingvall M, Reith D, Broadbent R.** 2005. The effect of sepsis upon gentamicin pharmacokinetics in neonates. British journal of clinical pharmacology **59:**54-61.
73. **Botha JH, du Preez MJ, Adhikari M.** 2003. Population pharmacokinetics of gentamicin in South African newborns. Eur J Clin Pharmacol **59:**755-759.

74. **Weber W, Kewitz G, Rost KL, Looby M, Nitz M, Harnisch L.** 1993. Population kinetics of gentamicin in neonates. European journal of clinical pharmacology **44:**S23-S25.
75. **Thomson AH, Way S, Bryson SM, McGovern EM, Kelman AW, Whiting B.** 1988. Population pharmacokinetics of gentamicin in neonates. Developmental pharmacology and therapeutics **11:**173-179.
76. **Jensen PD, Edgren BE, Brundage RC.** 1992. Population Pharmacokinetics of Gentamicin in Neonates Using a Nonlinear, Mixed-Effects Model. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy **12:**178-182.
77. **Sherwin CM, Kostan E, Broadbent RS, Medlicott NJ, Reith DM.** 2009. Evaluation of the effect of intravenous volume expanders upon the volume of distribution of gentamicin in septic neonates. Biopharm Drug Dispos **30:**276-280.
78. **Bijleveld YA, van den Heuvel ME, Hodiamont CJ, Mathôt RAA, de Haan TR.** 2017. Population Pharmacokinetics and Dosing Considerations for Gentamicin in Newborns with Suspected or Proven Sepsis Caused by Gram-Negative Bacteria. Antimicrobial Agents and Chemotherapy **61:**e01304-01316.
79. **Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NHG.** 2008. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatric Nephrology **24:**67.

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

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

Guideline	Demographic characteristics	Dose (mg/kg)	Interval (hours)	No. of subgroups*	Targets (mg/L)		
					Peak (%)		Trough (%)
					≥ 5	≥ 10	> 2
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

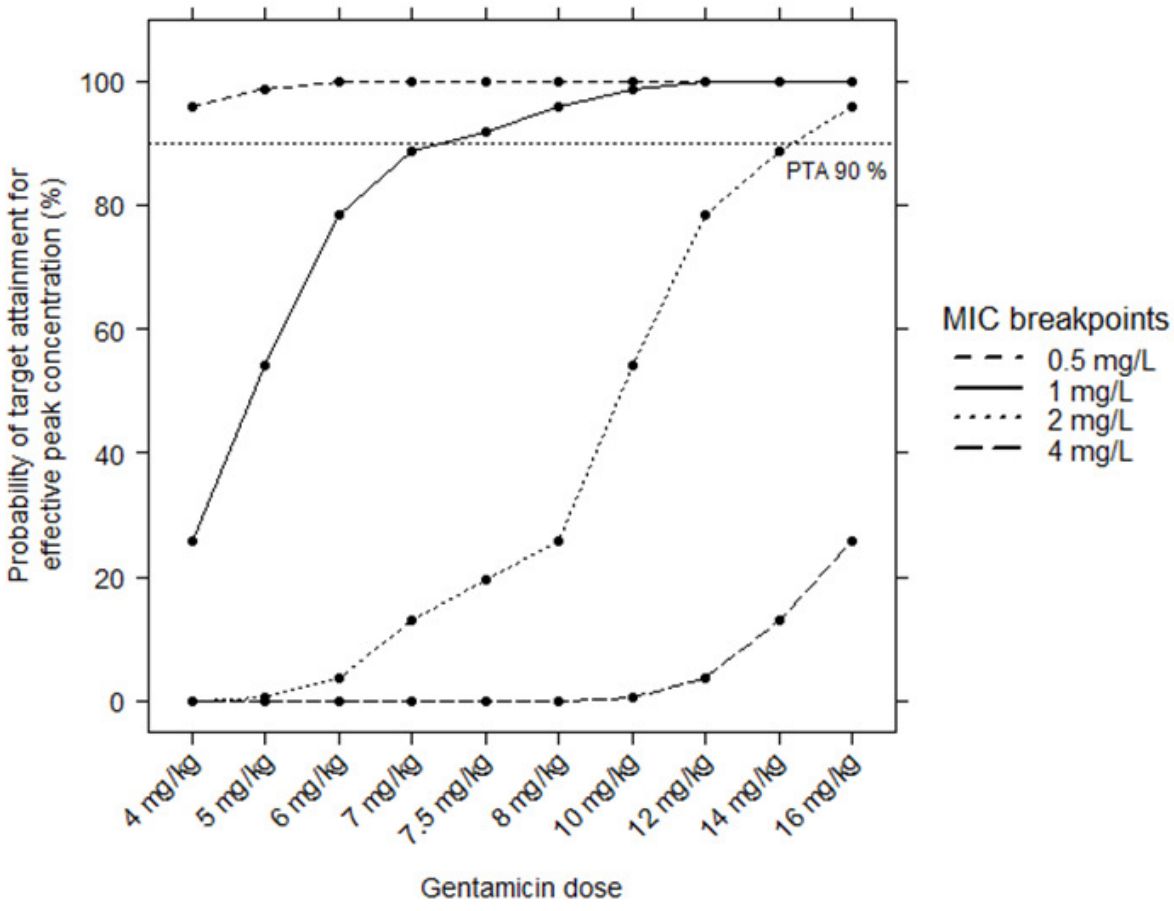
Table 2: Variability in gentamicin dosing recommendations for two typical patients. GA; gestational age, PNA; postnatal age, WT; body weight, h; hours, *; every, Nelson; Nelson's Pediatric Antimicrobial Therapy handbook, Shann; Frank Shann, Lexicomp; Lexicomp Pediatric & Neonatal Dosage Handbook, Center;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

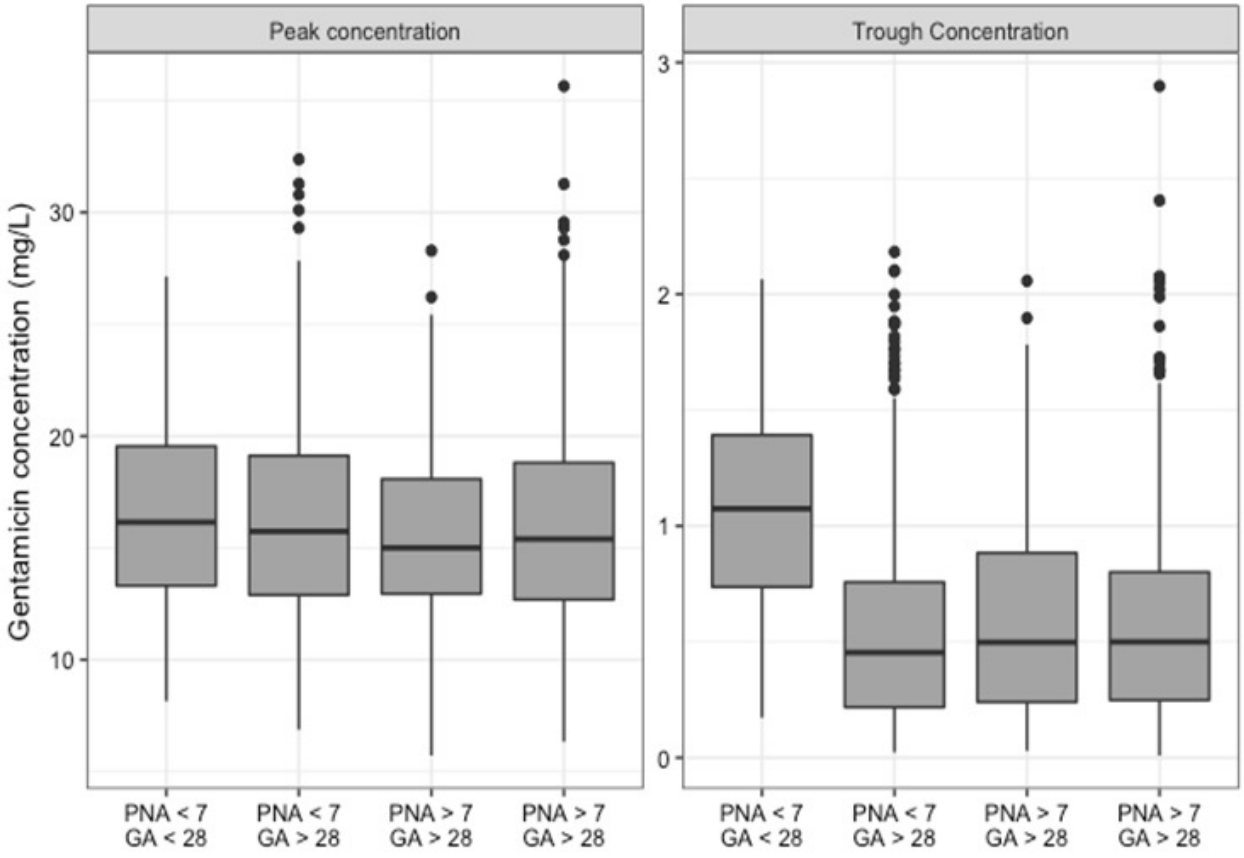
		First dose			After 1 Week of Treatment		
Dosing Regimen	**Demographic Characteristics**	**% Neonates with ratio Peak/MIC**	**% Neonates with Trough**		**% Neonates with ratio Peak/MIC**	**% Neonates with Trough**	
		> 10	< 1 mg/L	< 2 mg/L	> 10	< 1 mg/L	< 2 mg/L
MIC 0.5 mg/L							
4 mg/kg * 36h	PNA < 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.


Probability of target attainment for effective peak concentration (%)
100
80
60
40
20
0
PTA 90 %
4 mg/kg
5 mg/kg
6 mg/kg
7 mg/kg
7,5 mg/kg
8 mg/kg
10 mg/kg
12 mg/kg
14 mg/kg
16 mg/kg
Gentamicin dose
MIC breakpoints
0.5 mg/L
1 mg/L
2 mg/L
4 mg/L


Peak concentration
Trough Concentration
Gentamicin concentration (mg/L)
30
20
10
3
2
1
0
PNA < 7
GA < 28
PNA < 7
GA > 28
PNA > 7
GA > 28
PNA > 7
GA > 28
PNA < 7
GA < 28
PNA < 7
GA > 28
PNA > 7
GA > 28
PNA > 7
GA > 28