Pharmacokinetic of Antibiotics in Preterms

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Antibiotics are widely prescribed and administered in preterm neonates. Almost 61.3% of neonates admitted into neonatal intensive care units receive an antibiotic course during hospitalization. Nevertheless, most antibiotics were not investigated in neonatal pharmacokinetic (PK) studies before licensing and, therefore, are used off label. Both population pharmacokinetic (popPK) and pharmacokinetic (PBPK) models have been developed so far to predict PK behavior and to tailor the dosing regimens of several antibiotics in neonates including preterms.

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1. Aminoglycosides

Aminoglycosides are the antibiotics of first choice for the treatment of neonatal infections due to Gram-negative bacteria. Gestational age, postnatal age, birth weight, maturation of renal function, and the percentage of body water are factors that have a strong influence on the pharmacokinetic (PK)/pharmacodynamic (PD) behavior of these drugs [1]. Aminoglycosides exert their antibacterial action by interfering with bacterial protein synthesis. Since this class of antibiotics is characterized by renal elimination (until >90%), it must be considered that full nephrogenesis is completed in the third trimester of pregnancy [2]. Considering this aspect, previous studies performed on aminoglycoside antibiotics have shown that a dosing regimen based on a single higher daily dose and longer intervals should be preferred in order to guarantee the same therapeutic efficacy with reduced side effects [3][4]. Recently, Lee SY et al. (2021) conducted a study on 30 preterm neonates, demonstrating that acute kidney injury during aminoglycosides treatment is more severe at both lower gestational ages and birth weights [5]. The bactericidal activity of aminoglycosides against Gram-negative infections, together with their synergism with beta-lactam antibiotics, the limited bacterial resistance, and the convenient costs, has justified the wide use of these antibacterials in neonates [6]. The most used aminoglycosides in preterm infants are netilmicin, gentamicin, and amikacin.

Netilmicin is generally the first aminoglycoside used in neonates, both as a prophylaxis and as a treatment of infections. The kidney is the main site of metabolism and elimination of the drug [7][8]. Investigators suggest a loading dose of 5 mg/kg, followed by a maintenance dose between 2.5 mg/kg and 5 mg/kg after 18, 24, or 36 h depending on gestational age (>27 weeks or <27 weeks). Authors recommend early monitoring of serum drug concentration to avoid renal toxicity [1][9].

Gentamicin is an aminoglycoside antibiotic characterized by a narrow therapeutic index (risk of nephrotoxicity and ototoxicity). As for other antibiotics of this class, its PK behavior is strongly affected by the patient's age, body weight, and renal functionality [10]. Different PK studies have suggested, for preterm neonates, a daily dose of 3.5–5 mg based on body weight with longer intervals of 36–48 h [1][11]. Gentamicin is often used in NICUs to treat Gram-negative infections and suspected sepsis [12]. However, in order to limit the risks of trough-associated nephrotoxicity, the use of high doses of gentamicin administered at prolonged dosing intervals has been widely adopted in NICUs in clinical practice [13]. A target trough concentration associated with reduced risks of toxicity for gentamicin is <1 µg/mL, which also minimizes bacterial adaptive resistance thanks to the post-antibiotic effect [14]. However, in vitro studies have suggested, for gentamicin, a PK/PD target of peak concentration (Cmax) over minimum inhibitory concentration (MIC) ratio ranging between 8 and 10 [15]. Recently, Neeli H. and colleagues realized a gentamicin pharmacokinetic (PBPK) model developed for preterm and extremely preterm neonates that was evaluated against data collected during clinical practice in a local NICU [2]. Based on their findings, the authors suggest that a higher dose (5 mg/kg), intravenously administered every 36 h, in neonates with a PMA of 30 to 34 and ≥35 weeks is able to minimize the risk of elevated trough concentrations and to provide effective antibacterial activity [2]. A similar conclusion was reached by Valitalo PA and colleagues (2015), who proposed dosing intervals of up to 72 h for both gentamicin and tobramycin, but with a different dose for gentamicin versus tobramycin (4.5 versus 5.5 mg/kg, respectively) [16]. In particular, the authors performed Monte Carlo simulations using validated neonatal pharmacokinetic models of gentamicin and tobramycin in order to evaluate target peak and trough concentration attainment and cumulative AUC over 1 week of treatment [16]. Moreover, they compared the performance of commonly used gentamicin and tobramycin dosing guidelines [17][18][19][20] with the simulated results. In detail, peak concentrations of 5–12 mg/L and trough concentrations <0.5 mg/L were chosen as targets for the proposed dosing guidelines, and the proportion of patients that reached trough concentrations <1 mg/L was calculated. Based on the performed simulations, the proposed dosing guidelines (4.5 mg/kg gentamicin or 5.5 mg/kg tobramycin) with a dosing interval based on birth weight and post-natal age have led to adequate peak concentrations with only 33–38% of the trough concentrations' target. These novel model-based dosing guidelines have been compared with the simulated performance of the existing neonatal dosing regimens [17][18][19][20]. Simulations based on the existing guidelines revealed adequate peaks but elevated trough concentrations (63%–90% above target) compared to the proposed ones. Therefore, the authors conclude that the proposed neonatal dosing strategies for gentamicin and tobramycin show an improved attainment of target concentrations and should be prospectively evaluated in clinical studies to assess the efficacy and safety of this treatment [16]. The suggested PK/PD target for gentamicin (Cmax/MIC ratio at least 8–10) has been further verified in a cross-sectional observational study with pharmacokinetic analysis performed on both preterm and full-term neonates (totally n = 113) [21]. In this research, a weight-based dosing interval (5 mg/kg, q24–48 h) achieved the target gentamicin concentrations for both peak and trough levels in the majority of neonates (n = 93/113) [21]. The same dosing interval, but with a slightly higher gentamicin dose (6 mg/kg), was used by Fjalstad JW and colleagues (2013). This high-dose gentamicin (6 mg/kg) regimen has been associated with a low elevated trough plasma concentration (>2 mg/L) and no evidence of ototoxicity [22].

A population pharmacokinetic (popPK) study on gentamicin in a large cohort of premature and term neonates has confirmed that, compared with term neonates, preterms require longer dosing intervals (up to 48 h), and extremely preterm neonates (below 28 weeks of GA) will also require higher doses of gentamicin (5 mg/kg) to achieve therapeutic concentrations [23]. In particular, these model-based simulations confirmed the high variability of gentamicin kinetics in newborns and that, although PMA was found to be a good predictor of gentamicin CL, the use of covariates such as growth (represented by BW) and maturation (represented by GA and PNA) represents the best approach to describe the gentamicin disposition in preterm neonates [23].

In another study, a PBPK model was developed using the Simcyp Simulator V17 to predict the PK of several drugs, including gentamicin and vancomycin, in preterm neonates [24]. For both gentamicin and vancomycin, the PBPK model prediction for plasma concentration–time profiles after single and multiple intravenous doses has shown a good agreement with the observed data in the preterm population. In terms of physiological parameters, since gentamicin and vancomycin are subjected to kidney elimination, the maturation of the renal function was able to predict the exposure of these two compounds after intravenous administration. Therefore, the authors conclude that, although not substitutive of clinical trials, the prediction of PK behavior in preterm patients using PBPK modeling could be useful to decide on first-time dosing in this population in the absence of clinical data [24].

2. Beta-Lactams

Beta-lactams are the most used antibiotics in newborns. Due to their structural similarity with the enzyme transpeptidase, which is involved in the crosslinking of peptidoglycan chains, beta-lactams act to block the ex novo formation of bacterial cell walls. These antibiotics are time-dependent agents. Therefore, their efficacy is linked to the time spent using the free drug fraction above the MIC value for the pathogen (%fTime>MIC). The optimal PD target should be at least 40–50% of the time, but, in severe infections, 100% of the time is recommended. Beta-lactams have a good safety profile; therefore, TDM is rarely applied to these agents. However, in cases of severe infections, the distribution volume and filtration glomerular rate are significantly increased over time in newborns. These pathological changes dramatically affect the PK of different drugs, including antibiotics. Therefore, in special situations, the monitoring of antibiotics' concentrations could be particularly advisable. The most used beta-lactams in neonates include penicillins, carbapenems, and cephalosporins.

2.1. Penicillins

Among penicillins, ampicillin is the most widely used antibiotic in the neonatal period. It is generally used in association with other antibiotics, mainly aminoglycosides, for both prophylaxis and the therapy of early and late onset infections. As for other antibiotics, ampicillin is almost completely (90%) eliminated by the kidney; therefore, its circulating levels are primarily dependent on renal functionality. Penetration into the cerebrospinal fluid is limited. However, in the case of inflamed meninges, its penetration rises to 39%. Ampicillin is the most used drug in the case of a suspected or confirmed *Listeria meningitis* infection, especially if it occurs in the first week of life [25].

Although ampicillin is one of the most administered antibiotics in NICUs, its PK behavior and safety in neonates are poorly described. Actual dosing regimens take into account the GA- and PMA-related variations in renal drug clearance and recommend lower and less frequent dosing in the most premature neonates [19]. However, the knowledge of ampicillin dosing in the most extremely premature neonates (GA of ≤32 weeks at birth) is still limited. A popPK model developed by Tremoulet A and collaborators (2014) included neonates stratified by GA (<34 or >34 weeks) and PNA (<7 or >7 days). Drug concentrations were used to construct a nonlinear mixed-effects modeling in NONMEM, followed by Monte Carlo simulations, aiming to determine the probability of target attainment for the time in which the total steady-state ampicillin concentrations remained above the MIC (%T>MIC) for 50%, 75%, and 100% of the dosing interval. Results have shown that PMA and serum creatinine are important covariates for ampicillin clearance. Finally, the authors suggest a simplified dosing regimen of 50 mg/kg every 12 h for GA of <34 weeks and PNA of <7 days, 75 mg/kg every 12 h for GA of <34 weeks and PNA of >8 and <28 days, and 50 mg/kg every 8 h for GA of >34 weeks and PNA of <28. They conclude that the revised dosing regimen, based on GA and PNA, is able to achieve the desired therapeutic target in 90% of subjects [26].

Similarly, in a prospective study by Padari H et al. (2021), the authors performed a non-compartmental analysis (NCA) and a popPK modeling on 14 neonates (GA of 32–42 wks) who were receiving ampicillin for suspected or proven early onset sepsis and pneumonia. A visual predictive check for the final PK model was performed to assess the probability of the target attainment of various dosing schemes against MIC of 0.5, 1, 2, 4, and 8 mg/L. As PD targets were evaluated, 40% fT > MIC and 100% fT > MIC, and the safety margin of Cmax > 140 mg/L, assuming 100% and 80% of unbound ampicillin fractions in serum. Based on the simulations' results, the authors suggest that, during the first week of life in neonates with GA ≥32 weeks, empiric ampicillin dose of 50 mg/kg q12h (iv, intravenous) will achieve plasma concentrations above the group B streptococcal (GBS) breakpoint of 0.25 mg/L susceptibility throughout the dosing interval. In the case of pathogens with a higher susceptibility breakpoint, the dose of 50 mg/kg q8h is sufficient to achieve a target of fT100% > MIC = 2 mg/L. These dosing regimens exceed the safety margin values of Cmax above 140 mg/L in less than a third of patients and, therefore, can be considered sufficiently safe [27].

A retrospective evaluation of previously published popPK models has been performed for both ampicillin and gentamicin on preterm neonates with GA <28 weeks [28]. In particular, Monte Carlo simulations were used to generate concentration–time profiles for the most commonly used dosing regimens of ampicillin 50−100 mg/kg/dose every 8−12 h for 24−48 h courses (i.e., 2–6 doses) and 1 dose of 5 mg/kg gentamicin. The post-discontinuation antibiotic exposure (PDAE), defined as the time from the last dose to the time when the concentration decreased below MIC, was evaluated for both antibiotics. Simulation results show that all ampicillin dosing regimens (50–100 mg/kg every 8–12 h for 2–6 doses) achieved therapeutic exposures > MIC range. After the last dose, the PDAE mean ranged from 34 to 50 h for *E. coli* (MIC = 8) and 82 to 104 h for GBS (MIC = 0.25); the longer PDAE values occurred with higher doses, shorter intervals, and longer courses. Short-course ampicillin (2 doses, 50 mg/kg every 12 h) provided a PDAE of 34 h for *E. coli* and 82 h for GBS. Single-dose 5 mg/kg gentamicin provided PDAE > MIC = 2 for 26 h. The authors conclude that PDAE could be an innovative metric designed to identify opportunities to reevaluate dose–exposure relationships, although prospective studies are necessary to confirm the relationship between PDAE and clinical outcomes [28].

Finally, general recommendations suggest using dosages between 50 and 75 mg/kg every 12 h. In cases where higher dosages (50–100 mg/kg every 8 h) are needed, a close neurological monitoring for the risk of convulsions is advisable, especially for Cmax values above 140 mg/L [26][27][29].

Amoxicillin is a penicillinase-susceptible semi-synthetic amino-penicillin and is a structural and pharmacological relative of ampicillin [30]. Amoxicillin is a time-dependent antibiotic, and the PK/PD index is the fraction of time during which the antibiotic concentration remains above the MIC minimal of the targeted pathogen (%fT > MIC) [31]. The clinical PK of amoxicillin in neonates has been clearly reviewed by Pacifici GM and Allegaert K., (2017) [30]. However, despite the longstanding use of amoxicillin for the treatment of neonatal sepsis, there is a lack of data supporting a tailored dosing strategy. In this context, van Donge T and colleagues (2020) assessed individual intravenous amoxicillin exposures based on six international guidelines, namely, the Swiss Agency for Therapeutic Products 2015 (Swissmedic), the British National Formulary for Children 2015, the Neonatal Formulary 7th edition (NNF7), Frank Shann's Drug 2014 (Shann), The Harriet Lane 2014, and Lexicomp 2016, by applying a previously developed popPK model [32]. The aim of the study performed by van Donge et al. was to evaluate efficacious and safe exposure for current neonatal amoxicillin dosing regimens using the %fT > MIC as the end points of interest and the potential neurotoxicity with Cmax > 140 mg/L value as the threshold. Exposure was simulated by attributing each dosing regimen to a cohort of neonates with a median (IQR) GA of 34 (29–39) weeks, derived from the clinical data for neonates in the Antibiotic Resistance and Prescribing in European Children (ARPEC) study [33]. Six international guidelines and all surveyed Swiss NICUs provided recommendations for intravenous amoxicillin dosing, ranging from 10 mg/kg every 12 h to 50 mg/kg every 4 h. Total daily doses of amoxicillin in use in Swiss NICUs (50–200 mg/kg/day) were higher than those recommended in the international guidelines (20–200 mg/kg/day) with one exception (Shann; suggesting a maximum total daily dose of 300 mg/kg). Simulation results revealed that none of the dosing regimens achieved targets of ≥100%fT > MIC at any of the relevant MICs for a desired probability of target attainment (PTA) of ≥90%. All dosing regimens achieved a PTA ≥90% for *Streptococcus agalactiae* (MIC 0.25 mg/L) and *Listeria monocytogenes* (MIC 1 mg/L) when targeting ≤ 70%fT > MIC. In contrast, none of the regimens resulted in a PTA ≥ 90% targeting ≥ 70%fT > MIC for *enterococci* (MIC 4 mg/L). In terms of neurotoxicity, the Cmax associated with potential neurotoxicity was exceeded using four dosing regimens (100 mg/kg q12, 60/30 mg/kg q12/8, 50 mg/kg q12/8/6, and 50 mg/kg q12/8/4) for ≥10% of neonates. Therefore, the authors conclude that new randomized trial designs combining both pharmacometric modeling and simulation could be used to select the optimal dosing regimens in preterm neonates [34].

One issue in conducing PK studies in neonates is determined by the limited sampling and the low blood volumes available. A valid approach could be represented using scavenged samples, left over from the routine clinical care of infants without obtaining additional blood. In fact, these samples can be collected in the clinical laboratory from discarded blood (heparinized or EDTA tubes) obtained during routine clinical practice. Therefore, if combined with the collection of timed PK samples (collected ad hoc for study protocols), scavenged samples could be used for PK characterization in preterms [35]. An example of this application was reported by Cohen-Wolkowiez M and colleagues (2012) [36]. These authors developed a popPK model of piperacillin using targeted sparse sampling and scavenged samples obtained from preterm infants ≤32 weeks of gestational age at birth and < 120 postnatal days. This model was developed using nonlinear mixed-effect modeling. Thereafter, Monte Carlo simulations based on

the final popPK model were used to explore dose–exposure relationships, adopting the current piperacillin dosing recommendations. From the evaluation of a population's mean clearance, an augmented CL was observed with the increase of gestational age at birth; newborns with serum creatinine ≥ 1.2 mg/dL show a 60% reduction in piperacillin CL. Therefore, after allometric scaling, serum creatinine was included in CL model, resulting in an increased model fit. The authors conclude that piperacillin dose adjustments will likely be performed considering this parameter. Finally, this research confirms the utility of scavenged sampling in performing PK studies and providing dosing recommendations in preterm neonates. However, this approach is not feasible for unstable drugs, and a compound's stability is an important covariate that should be considered when using the leftover samples [36].

In another study by the same author, piperacillin-tazobactam PK was evaluated in premature and term neonates of ages <61 days with suspected systemic infections [37]. In particular, neonates were administered intravenous piperacillin-tazobactam (80 to 100 mg/kg of body weight every 8 h) based on GA and PNA. Interestingly, the drugs' levels were measured in both plasma and dried blood spot collected samples. PK data were analyzed using population nonlinear mixed-effect modeling. The final model was used to generate 1000 Monte Carlo simulation replicates per time point of piperacillin-tazobactam exposure, and the simulated results were compared with those observed in the research. The time unbound piperacillin concentrations remained above the MIC for 50% and 75% of the dosing interval at steady state was evaluated as a target attainment rate. The results obtained for piperacillin and tazobactam PK models show that body weight and PMA are covariates for clearance, whilst body weight is a covariate for the volume of distribution. These covariates were used to optimize dosing in newborns. Moreover, DBS drug concentrations resulted in a 50 to 60% lower amount compared to those in plasma; however, when combined with plasma concentrations, the generated PK model parameters were similar to those for plasma alone. Finally, the authors conclude that, following a PMA-based dosing regimen (100 mg/kg q8h, 80 mg/kg q6h, and 80 mg/kg q4h for PMA of <30, 30 to 35, and 35 to 49 weeks, respectively), 90% of simulated infants were able to achieve the surrogate therapeutic target time above the MIC (<32 mg/L) for 75% of the dosing interval [37].

Piperacillin-tazobactam PK was also evaluated in a popPK model developed by Li Z and colleagues (2013) in moderate preterm newborns (median GA 36.04 weeks). In particular, a total of 207 piperacillin and 204 tazobactam concentration–time datasets from 71 patients were analyzed using a nonlinear mixed-effect modeling approach. Thereafter, the final models were evaluated using both bootstrap and visual predictive checks by simulating one thousand datasets based on the final model. This PK analysis revealed that PMA is the most significant covariate of the central clearance of piperacillin and tazobactam, although the combination of the current body weight and PNA seems to be superior to PMA alone. Moreover, body weight is the most important covariate for the apparent central volume of distribution. Based on these results, the authors conclude that a dosing strategy of piperacillin/tazobactam 44.44/5.56 mg/kg/dose every 8 or 12 h allows researchers to achieve the PD target (free piperacillin concentrations >4 mg/L for more than 50 % of the dosing interval) in about 67% of infants. Finally, the authors suggest that higher doses or more frequent dosing regimens could be necessary for controlling infection in this population in NICU [38].

2.2. Carbapenems

Among carbapenems, meropenem is the most used in newborns, especially to treat late-onset sepsis (LOS) and complicated intra-abdominal infections. Its safety profile is good, with rare cases of cytopenia [39][40]. Meropenem is a broad-spectrum antibiotic approved by the US Food and Drug Administration for use in pediatric patients, including treating complicated intra-abdominal infections in infants <3 months of age (MERREM(R) IV (meropenem for injection, summary of the product characteristics) [41]. In neonates, meropenem is currently only approved for treating complicated intra-abdominal infections (cIAIs) sustained by both Gram-positive and Gram-negative bacteria. Whereas meropenem's pharmacokinetics in adults are well defined, there is a lack of knowledge about PK properties in preterms.

In a recent article by Ganguly S. and colleagues (2021), the authors applied a PBPK modeling to characterize the disposition of meropenem in preterm and term neonates [42]. This model was developed using 645 plasma concentrations from 181 infants (GA 23–40 weeks; PNA 1–95 days). The PBPK-model-based simulations were performed to evaluate suggested meropenem dosing for infants <3 months of age with cIAIs, as reported on the product label. The PBPK-model-predicted clearance in a virtual infant population was successfully able to capture the post hoc estimated clearance of meropenem in this population, as suggested by a previously published popPK model [43]. Similarly, almost 90% of virtual infants showed a 4 mg/L target plasma concentration for >50% of the dosing interval following the product-label-recommended dosing. The authors conclude that the PBPK model supports the meropenem dosing regimens recommended on the product label for infants <3 months of age and that both the PBPK and popPK modeling approaches suggest similar meropenem dosing recommendations for this specific age range [42].

In a study performed by Padari H and colleagues (2012), the authors compared the steady-state PK and safety of meropenem administered at a dose of 20 mg/kg every 12 h via short (30 min) or prolonged (4 h) infusion to neonates with a GA of <32 weeks (birth weight < 1200 g), aiming to define the appropriate dosing regimen for a phase 3 efficacy study of neonatal LOS [44]. Meropenem concentrations were measured immediately before and 0.5, 1.5, 4, 8, and 12 h after the 4th to 7th dose. The results show, for a short infusion, a higher mean drug concentration in serum (Cmax) compared to prolonged infusion (89 vs. 54 mg/L). For intermediate or resistant microorganisms (with meropenem MICs of >2 mg/L), such as *Acinetobacter spp. and Pseudomonas aeruginosa*, previous PK/PD simulation studies involving neonates suggested better PK/PD target attainment with 4 h infusions [45]. In a study by Padari H and colleagues, PK analysis revealed that all the patients in the short-infusion group and 8/10 in the long-infusion group achieved the PD target %fT>MIC of 100% for a MIC of 2 mg/L. Moreover, the meropenem clearance was not influenced by postnatal or postmenstrual age, and the one-compartment popPK model demonstrated that covariates serum creatinine, PNA and GA, were not able to improve the best model fit. Based on these results, the authors conclude that the final parameters estimated are the steady-state distribution volume (Vss) of 0.301 L/kg and the CL of 0.061 L/h/kg. Moreover, at a MIC cut-off of 8 mg/L with a short infusion, no neonate is expected to have a %fT>MIC of 40%, with target values of >95%. Therefore, they conclude that, in very-low-birth-weight neonates, meropenem infusions of 30 min are optimal, since they guarantee a reasonable balance between high Cmax and %fT>MIC for susceptible organisms with no dosing adjustments over the first month of life. Additionally, they suggest that a dose of 20 mg/kg given as a 30 min infusion could be used in a larger study of efficacy in patients with LOS [46]. Conversely, a prospective, randomized clinical trial compared the

intravenous infusion of meropenem over 4 h (infusion group) or 30 min (conventional group) at a dosing regimen of 20 mg/kg/dose every 8 h and 40 mg/kg/ dose every 8 h in neonates (GA 33–34 weeks) with Gram-negative late-onset sepsis (GN-LOS) admitted to NICU [47]. The results of this research revealed that the prolonged infusion of meropenem is better associated with clinical improvement, microbiologic eradication, and less neonatal mortality compared to the conventional strategy [47].

Doripenem is a parenteral carbapenem with broad-spectrum activity against aerobic Gram-negative and Gram-positive pathogens and anaerobic pathogens. The PK behavior, safety, and tolerability of doripenem were evaluated in a phase I study that also included neonates with chronological ages (CA) less than 4 weeks (<32 weeks and ≥32 to ≤44 weeks in GA) [48]. The results show that a single dose of doripenem (5 mg/kg of body weight for <8 weeks and 8 mg/kg for >8 weeks in chronological age) administered as a 1 h infusion in term and preterm newborns <12 weeks CA was similar to what was observed in neonates and very young infants with other carbapenems (PK/PD target attainment %T >MIC between 70–99%) [48].

Imipenem is a broad-spectrum antibacterial agent used in critically ill neonates after failure of first-line treatments [49]. A recent popPK analysis developed by Dao K and colleagues (2021) including preterm neonates with a median GA of 27 weeks (range: 24–41). PK data were analyzed using a one-compartment non-linear mixed-effect modeling and revealed that GA and PNA exhibited the greatest impact on the PK parameters, followed by serum creatinine. Moreover, simulations using a dosing regimen of 20–25 mg/kg every 6–12 h according to PNA led to the highest percentage of target attainment (T>MIC over 100% of time). Therefore, the authors conclude that a dosing adjustment according to body weight, GA and PNA is the best strategy to optimize imipenem exposure in neonates [50].

2.3. Cephalosporins

Along with a large total-body water volume and immature renal function, neonates are also characterized by low albumin levels [51]. This last aspect should be considered when administering drugs with a high percentage of protein-bond. Cefazolin is highly bound to human serum albumin, and its indications in neonates are mainly prophylactic (72%) and, to a lesser extent, therapeutic (17%) (e.g., coagulase-negative staphylococcal sepsis) [52]. Since exclusively unbound cefazolin distributes to the extravascular compartments and is subjected to renal elimination, low albumin levels could affect cefazolin disposition. In this context, a popPK model was realized using both total and unbound cefazolin plasma concentrations as a guide for dosing in preterm and term neonates [53]. In this research, the popPK analysis was performed on 119 total and unbound plasma concentrations of cefazolin obtained from 36 (pre)term neonates with PNA 1–30 days. Monte Carlo simulations were applied, aiming for unbound concentrations above a MIC value of 8 mg/L (60% of the time) in all patients. The results of this one-compartment PK model show that the current BW is the main covariate for Vd, whereas birth BW and PNA are the main covariates for clearance and albumin plasma concentrations for maximum protein binding (Bmax). Moreover, based on simulations, the authors proposed a body-weight- and PNA-adapted dosing regimen that resulted in similar exposure across different weight and age groups. Finally, the authors conclude that both the total and unbound cefazolin concentrations in neonates can be described in a one-compartment popPK model that includes

saturable protein binding. Moreover, birth BW and PNA are considered the main covariates affecting the variability in cefazolin CL. Therefore, they propose a new model-based neonatal cefazolin dosing regimen suggesting, however, a future prospective validation of their model [53].

Cefotaxime is another antibiotic widely prescribed to treat Gram-negative bacterial sepsis in neonates [54]. However, dosing regimens are often characterized by high variability rates [55]. A popPK model was developed by Leroux et al. (2016) by elaborating data from 100 neonates (GA range 23–42 weeks) with an allometric two-compartment model. This PK analysis indicated the current weight, GA, and PNA as significant covariates. Monte Carlo simulations have been used as visual prediction validation of the PK model aiming to assess a target attainment of fT>MIC of 75% of the dosing interval at steady state for each dosing regimens. Based on this model validation, the authors proposed a dosing regimen of 50 mg/kg between and four times a day, according to GA and PNA, in order to improve dosing in older newborns (PNA > 1 week and/or GA > 32 weeks, time > MIC 75%) [56].

Ceftolozane/tazobactam is a combination of the β-lactam/β-lactamase inhibitors that has a broad-spectrum activity against the most common Gram-negative bacteria, including MDR strains. The PK and safety profile of this combination was evaluated in a phase I, noncomparative, open-label, multicenter study on pediatric patients with proven/suspected Gram-negative infections or perioperative prophylaxis receiving a single intravenous (iv) dose of ceftolozane/tazobactam [57]. In particular, patients were divided into two groups: Group A (GA > 32 weeks) and Group B (GA ≤ 32 weeks). The results show that PK profiles in neonates and young infants were generally comparable to those of older children receiving a single iv dose of ceftolozane/tazobactam. Therefore, the authors conclude that, among term and premature neonates and young infants, PK was comparable to older children, and that ceftolozane/tazobactam was generally well tolerated. However, they highlight the necessity of proper neonatal PK trials [57].

Ceftazidime (CAZ) belongs to third-generation cephalosporins. It is approved for children > 1 month. Its use in neonatal age is limited to severe infections, especially with cerebro-spinal fluid (CSF) involvement. Old studies in preterm demonstrated that the clearance of CAZ increases with gestational age and higher GFR [58]; in the first 10 days of life, the GFR is increased, and the CAZ clearance is consequently accelerated, whereas the distribution volume and elimination half-life are significantly reduced between day 3 and day 10 after birth. The dosage of CAZ is 25–50 mg/kg bw twice daily, but attention must be paid to concomitant medications that reduce GFR, such as indomethacin [59][60]. The emergence of extensively drug-resistant (XDR) or pan drug-resistant (PDR) Gram-negative bacteria is also a major concern in NICU. Treatment options are limited, and mortality is high. Complicated abdominal infections and severe sepsis are the most frequent manifestations. Ceftazidime/avibactam (CAZAVI) is a novel combination of ceftazidime with a new beta-lactamase inhibitor, avibactam, a non-beta-lactam/beta-lactamase inhibitor with good activity against XDR *Enterobacteriaceae* (including *Klebsiella pneumoniae* carbapenemase producer), *Pseudomonas aeruginosa and Acinetobacter baumanii*. CAZAVI is licensed for use in infants > 3 months [61]. PK behavior in children was already evaluated in a phase I study and two phase II studies [62][63]. A dose of 10–40 mg/kg q8h for those ≥ 3 to 6 months old with creatinine clearance > 50 mL/min/1.73 m^2 was suggested. The safety results were similar to ceftazidime alone, and treatment appeared effective in pediatric patients with complicated abdominal infections [62]. In terms of CAZAVI use in preterms, a

report was published showing similar results related to the efficacy and safety profile [64]. However, future prospective trials on this population are needed.

3. Glycopeptides

Glycopeptides inhibit the synthesis of cell-well peptidoglycan and affect bacterial cell membrane permeability [65] Oritavancin, a newer lipoglycopeptide derivative, may also have an effect on the inhibition of RNA synthesis, but a direct involvement is still debated [66]. They are used to treat severe infections sustained by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and coagulase negative staphylococci (CoNS), which are often the cause of late-onset sepsis in newborns [66].

3.1. Vancomycin

Preterms or neonates born with very low birth weights are particularly susceptible to serious Gram-positive infections during their NICU stay. In fact, the use of central venous catheters and total parenteral nutrition is often a source of infections. This augmented susceptibility is also due to an immature immune system that is not able to guarantee an adequate anti-microbial response. *Staphylococcus aureus* and coagulase-pathonegative staphylococci are responsible for almost 55% of late-onset nosocomial infections in newborns [67]. The glycopeptide antibiotic, vancomycin, is widely used to treat methicillin-resistant *S. aureus* infections in premature and full-term neonates [68]. Vancomycin is water-soluble, has a limited plasma protein binding capacity (i.e., IgA and albumin), and is mainly eliminated by the kidneys via glomerular filtration and renal tubular transport. Compared to adults, neonates have a higher extracellular fluid volume and a limited renal elimination rate. Most premature neonates present with a higher distribution volume and low renal clearance; therefore, vancomycin clearance may vary 2-to 3-fold according to the neonatal age range and co-morbidity [69][70][71]. Consequently, vancomycin dosing is different based on either PMA or serum creatinine levels. In this context, TDM and individualized treatments should be warranted in neonates treated with vancomycin [72][73].

Similar to adults, continuous vancomycin infusion has been used in newborns. The advantages are represented by better target attainment and an easier interpretation of drug levels. However, the ideal dosing regimen for the administration of vancomycin in neonates is still debated [74][75]. However, continuous infusion does not exclude the influence that fluid status and comorbidities exert on vancomycin clearance, especially in critically ill patients [76].

So far, several dosing algorithms have been proposed and used during routine clinical practice [77]. These algorithms include a fixed dose based on body weight for all neonates, PMA-based dosing, PMA- and weight-based dosing, PMA- and PNA-based dosing, and serum-creatinine-based dosing [78]. These four common dosing regimens for vancomycin in preterm and term neonates were compared using a popPK model followed by Monte Carlo simulations in order to assess the probability that each regimen would achieve the widely used therapeutic target serum trough concentrations of 5–15 mg/L and the newly suggested target for methicillin-resistant *S. aureus*, of 15–20 mg/L [77][79]. In a study by Mehrotra N. et al. (2012) [78], TDM data for vancomycin were collected from 134 preterm (66%) and term (34%) neonates, with a PNA of 1–121 days and PMA of 24.6–44 weeks. These data were

used to develop a popPK model in this target population followed by Monte Carlo simulations for four recommended dosing regimens: a standard dose for all neonates, PMA-based dosing, PMA and PNA-based dosing, and serum-creatinine-based dosing. The results obtained from these comparisons demonstrated that serum-creatinine-based dosing shows the highest chance of reaching the target trough concentration range of 5–15 mg/L. Therefore, the authors conclude that, although this may sometimes be challenging in the neonatal setting, measuring the serum creatinine concentration before dosing vancomycin in preterms could be useful to reach therapeutic drug concentrations [78].

The most recognized PK/PD target for vancomycin is the 24 h area under the concentration–time curve (AUC 0–24)-to-MIC ratio (AUC 0–24/MIC) of >400 for microorganisms with a MIC value up to 1 mg/L [79][80][81][82], although some authors have supposed that a lower target may be effective in neonates [83]. However, this PK/PD target was originally defined in adult methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia [81] and was never validated in neonatal Staphylococci septicemia [84].

Conversely, the above PK/PD target was further validated in a popPK "meta-model" performed by Jacqz-Aigrain E and colleagues (2019) [85]. In this research, a "meta-model" was built using NONMEM with vancomycin concentrations from 1631 neonates (median GA ranging from 22.3–42.1), and Monte Carlo simulations were performed to design an optimal intermittent infusion, aiming to reach a target AUC 0–24 of 400 mg*h/L at steady-state in at least 80% of neonates [85]. The results of this PK analysis indicated current body weight, PMA and serum creatinine to be significant covariates for vancomycin CL. After model validation, simulations show that a loading dose (25 mg/kg) and a maintenance dose (15 mg/kg q12h or 15 mg/kg q8h based on PMA) were able to reach the AUC 0–24 target earlier than the suggested "Blue Book" dosage regimen [86] in >89% of the treated patients. Therefore, the authors suggest that this dosing regimen could be used for neonates and to assist in the design of a model-based, multinational, European trial, named NeoVanc [85]. It is also worth noting that the AUC 0–24/MIC target level of 400 is based on the total vancomycin concentration, whilst Smits et al. recently demonstrated that the fraction unbound (FU) of vancomycin is much higher in neonates (median 0.9) compared with adults (median 0.6) [87]. In this research, the authors claimed that the traditional "total drug target approach" is aimed at achieving similar total vancomycin exposure in neonates as in adults without considering the differences in protein binding and thus targeting a common PK/PD index of AUC 0–24/ MIC ≥ 400 for optimal dosing in neonates. Therefore, these authors proposed a novel "unbound drug target approach" aimed at achieving similar unbound vancomycin exposure in neonates as in adults and thus considering an AUC 0–24/MIC ≥ 267 for optimal dosing in neonates to be a target [87]. Based on this finding, Leroux S and colleagues (2019) [84] evaluated the impact of this "unbound drug target approach" on vancomycin dosing by using a PK/PD simulation of 249 preterm neonates that were enrolled in a previous pharmacokinetic study [88]. Specifically, in this neonatal population, the overall medians (ranges) GA, PNA, and BW were 29 weeks (23–34), 11 days (1–27), and 1200 g (415–2630), respectively. These neonates received vancomycin in a 60 min infusion at a dose of 15 mg/kg once or twice a day according to their postnatal age and serum creatinine value [88]. The vancomycin PK parameters and exposure profiles of these 249 neonates were analyzed using a PK model previously developed during a popPK meta-analysis of vancomycin in neonates [85]. In the selected cohort of neonates, the population PK parameters obtained with this PK model [85] produced a vancomycin AUC 0–24 values (mean ± SD) of 446.4 ± 161.3 mg·h/L at a steady state. Based on the

traditional “total drug target approach,” the AUC 0–24/MIC ≥ 400 target was achieved by only 54.2% of the neonates (for a MIC of 1 mg/L). Meanwhile, with the “unbound drug target approach,” the AUC 0–24/MIC ≥ 267 target was reached by 91.2% of the neonates (for a MIC of 1 mg/L) [84]. Thereafter, in order to assess how this new finding based on the “unbound drug target approach” will guide the optimal use of vancomycin as an intermittent infusion in preterm neonates, the authors performed Monte Carlo simulations (*n* = 100) for different dosing regimens. Considering the “unbound drug target approach,” a dosing regimen of 10 mg/kg BID for neonates with a PMA of less than 30 weeks and 10 mg/kg TID for neonates with a PMA of 30 weeks or more was sufficient to achieve a 90% probability of target attainment (AUC 0–24/MIC ≥ 267) at a steady state. Moreover, the vancomycin trough concentrations associated with this dosing regimen were 12.7 mg/L (5th to 95th percentile: 5.1–26.5) at a steady state. Therefore, the authors conclude that, considering the maturational changes in vancomycin protein binding, it should not be feasible to consider a similar AUC 0–24/MIC target level for vancomycin in both neonates and adults. Consequently, they suggest also considering the impact of a higher unbound fraction in neonates when administering vancomycin to these patients [84]. However, considering the well-known limitations in calculating the AUC 0–24 in neonates, the trough concentration is more routinely applied in clinical practice for drug monitoring. In this context, a one-compartment popPK model was developed by Frymoyer A and colleagues (2014) [89] to examine the relationships between troughs and AUC 0–24 in neonates. In terms of covariates, the clearance (CL) was predicted by BW (an indicator of size), PMA (an indicator of maturation), and serum creatinine (Cr; an indicator of renal function). Monte Carlo simulations were performed to assess the effect of dose, PMA, and serum creatinine level on troughs and AUC 0–24 achievements. Based on their results, the authors conclude that a target vancomycin trough concentration between 7 and 11 mg/L is highly predictive of an AUC 0–24 of >400 across simulated neonates for various PMAs, serum creatinine (Cr) levels, and dosing strategies. Moreover, they suggest that higher trough concentrations of 15 to 20 mg/L, as usually recommended in adults, are unnecessary in neonates based on AUC 0–24/MIC when treating neonates for invasive MRSA infections with an MIC of ≤1 mg/L [89]. This model, developed by Frymoyer A and colleagues (2014), was retrospectively validated on a cohort of 243 neonates with a median GA of 30 weeks (range: 22–41) and a median weight of 1.6 Kg (range: 0.4–6.8) [90]. The aim of this research was to conduct an external evaluation of the published pharmacokinetic model and to confirm the relationship between the vancomycin trough concentration and AUC 0–24 in neonates. The results of this research show that the model was able to predict the observed vancomycin concentrations with reasonable precision. Moreover, these data further confirm that in neonates a vancomycin trough concentration of 15–20 mg/L is unnecessary to achieve an AUC 0–24/MIC ≥400 with a MIC ≤1 mg/L and that lower trough concentrations (approximately 10 mg/L) are likely adequate to provide adequate exposure for invasive MRSA while also appropriately covering for coagulase negative staphylococcal infections [90].

The clinical utility and safety of model-based dosing regimens for vancomycin were evaluated in a study performed by Leroux S et al. (2016) [91]. In particular, the authors applied a model-based vancomycin dosing calculator, developed from a previously published popPK model [92], to the routine clinical care in three neonatal intensive care units. This model-based application of vancomycin dosing was demonstrated in 190 neonates with a mean GA and a mean PNA of 31.1 weeks and 16.7 days, respectively. The percentage of patients with a first-serum vancomycin concentration achieving the target window of 15 to 25 mg/L was selected as the endpoint for

evaluating the clinical utility. The model-based dosing regimen (determined by birth weight, current body weight, PNA, and serum creatinine) was based on a loading dose of 11.1 mg/kg/day infused over 60 min and followed by the maintenance dose of 28.3 mg/kg/day administered as a continuous infusion over 24 h. The safety evaluation was focused on nephrotoxicity, which was evaluated based on changes in serum creatinine concentrations from the baseline obtained within 48 h of starting the vancomycin administration. The results obtained from this PK model application to clinical practice reveal that the target attainment rate increased from 41% to 72% of neonates without any case of vancomycin-related nephrotoxicity. However, the authors conclude that a prospective controlled trial is needed to further confirm their data [91].

An external validation of a previously published popPK model for vancomycin was performed by Janssen E et al. (2016) [93]. In particular, the aim of this research was to evaluate the predictive performance of the previously published neonatal and pediatric pharmacokinetic models [94][95] against an external vancomycin dataset containing TDM data from both preterm (median GA of 32 weeks) and term neonates and infants [96]. The model used for this research was previously developed by De Cock RFW and colleagues (2014), who proposed a semi-physiological function for the GFR-mediated clearance used to establish evidence-based dosing regimens of renally excreted antibiotics, including gentamicin, tobramycin, and vancomycin [94][95]. For its external validation, the previously published popPK models were used to simulate each of the observations of the datasets 1000 times. Concentration–time profiles were simulated in neonates and children for different dosing regimens reported in the Dutch Children's Formulary [17], British National Formulary for Children (BNFc) [20], the regimen proposed by the Infectious Diseases Society of America (IDSA) [80], and the meningitis regimen of the NeoFax manual [19], using the parameter estimates from the original models. These simulations were performed in order to evaluate current dosing regimens and to propose a model-based dosing algorithm. A PK/PD target AUC 0–24/MIC > 400 without any concentration exceeding 40 mg/L was evaluated for each simulated dosing regimen. The results show that both the neonatal and pediatric models were able to describe the observed data in the external dataset well. However, with the currently used dosing regimens, the target AUC 0–24/MIC and trough concentrations were hardly reached in neonates and young infants. Therefore, the authors proposed a dosing algorithm based on body weight at birth and PNA for neonates, with daily doses divided over three to four doses. In particular, for infants aged <1 year, doses between 32 and 60 mg/kg/day over four doses are proposed, while above 1 year of age, 60 mg/kg/day seems appropriate. Moreover, in order to reach an AUC 0–24/MIC of 400 on the first day of treatment, a loading dose should be administered. Finally, the authors conclude that a prospective clinical study should be performed to validate this model-based dosing algorithm [93].

Similarly, a model-based dosing approach designed to individualize empiric vancomycin dosing in neonates was retrospectively applied to data from 492 neonates (median GA 32 weeks, range 24–42) treated with vancomycin in two healthcare systems, and empiric dose recommendations from the following four sources were examined: Neo-Vanco, Neofax [97], Red Book [98], and Lexicomp [99][100]. Predicted AUC 0–24 and troughs concentrations were also calculated and compared. Neo-Vanco was developed based on a published, externally validated population pharmacokinetic model that incorporates predictors of PMA, weight, and serum creatinine level [90][101]. Using a simulation-based methodology, an individualized dose aimed at attaining an AUC 0–24/MIC ratio of >400, while reducing trough concentrations of >20 mg/L (toxicity target), was calculated. The final aim of the study conducted

by Frymoyer A and colleagues was to compare expected vancomycin exposure levels in neonates on the basis of a Neo-Vanco-derived dosing strategy to those from three commonly used recommendations, Neofax [97], Red Book [98], and Lexicomp [99]. The results show that the percentage of neonates predicted to achieve an AUC 0–24/MIC of >400 was 94% with Neo-Vanco, 18% with Neofax, 23% with Red Book, and 55% with Lexicomp (all $p < 0.0001$ vs. Neo-Vanco). Meanwhile, the predicted troughs of >20 mg/L were inconstant and similar across the dosing approaches. Therefore, the authors conclude that this model-based approach to individualizing empiric vancomycin doses in neonates was able to improve the achievement of target exposure levels and can be easily adopted in clinical practice based on easily available clinical characteristics (weight, PMA, and serum creatinine level). However, a future prospective validation is required [100].

In a preterm pilot study, the authors used data from eight preterm infants with neonatal ventriculitis (median GA 25.3 weeks; range 23.9–27.7) treated with intraventricular vancomycin at a standard starting dose of 15 mg/kg, in order to develop a popPK model on the use of intraventricular vancomycin in the preterm population [102]. Three covariates (serum creatinine, ventricular index (VI), and CSF protein) were tested on the model, whilst the AUC and average CSF concentration predictions were generated from the final model. Time to sterilization, defined as the length of time taken for CSF WCC (white cell count) to fall to <20/mm^3 and simultaneously achieve sterile CSF, was considered to be a PD target. The results show that covariates of VI and the CSF protein did not demonstrate any influence on CSF vancomycin and that time to sterilization with higher CSF AUC (0–24) and average concentration tends to be shorter. The authors conclude that further study with a larger data pool will be necessary to investigate the influence of VI on CSF vancomycin and to optimize the best dosing strategy [102].

3.2. Teicoplanin

Among glycopeptides, teicoplanin has bactericidal activity and efficacy against Gram-positive bacteria, such as methicillin-resistant staphylococci, including coagulase-negative staphylococci (CoNS), which is comparable to that of vancomycin [103]. Although they share a similar mechanism of action, the teicoplanin PK properties are different from vancomycin. In fact, whilst protein bonds are between 30 and 55 % for vancomycin, teicoplanin is highly bound to serum albumin (90%), resulting in a half-life that ranges from 100 to 170 h compared to 6–12 h for vancomycin [104][105]. Therefore, it can be administered once daily either intravenously or intramuscularly. Moreover, it is worth noting that a lower incidence of adverse events, including that of nephrotoxicity, has been reported for teicoplanin compared to vancomycin [106][107]. Therefore, teicoplanin has become one of the most prescribed antibiotics by neonatologists in NICUs [108].

A loading dose of 16 mg/kg at day 1, followed by a maintenance dose of 8 mg/kg daily is considered the gold standard to achieve the optimal efficacy with a targeted trough concentrations (Ctrough) > 10–30 mg/L depending on the severity of infection. Nevertheless, limited data exist in terms of teicoplanin PK/PD properties in neonates, and there is growing evidence that teicoplanin PK displays considerable variability in children in comparison to adults, suggesting the application of TDM in routine clinical practice [109][110][111]. Moreover, the PK/PD target that better correlates with teicoplanin in vitro activity is the Ctrough with an ideal value ≥ 10 mg/L [112]. However, this value could be variable according to the site of infection (Targocid®, summary of product characteristics) [113].

In order to assess the optimal dosing regimen, especially in preterm newborns, a popPK model was developed by Kontou A and colleagues (2020) [114]. In particular, the authors analyzed plasma teicoplanin concentrations from 60 neonates with PMAs of 26 to 43 weeks using a nonlinear mixed-effects modeling approach to develop a popPK model with NONMEM software. Monte Carlo simulations were performed to evaluate currently recommended dosing (a loading dose of 16 mg/kg and a maintenance dose of 8 mg/kg/day) using a PK/PD index and the AUC/MIC ratio of ≥400 based on vancomycin experience. The results of this research show that teicoplanin PK is variable in neonates and that body weight is the most significant covariate affecting PK parameters, while the estimated creatinine clearance is also an important covariate on teicoplanin CL. Moreover, the Monte Carlo simulation demonstrated that, with the current dosing regimen, an AUC/MIC ratio of ≥400 was reached by only 68.5% of neonates with a current body weight of < 1 kg when the MIC was equal to 1 mg/kg, versus 82.2%, 89.7%, and 92.7% of neonates with body weight of 1 to <2, 2 to <3, or ≥3 kg, respectively. Therefore, the authors conclude that the current teicoplanin dosing regimen is not suitable for preterm neonates with extremely low birth weights (ELBW) and those with body weight < 2 kg. Additionally, based on their simulations, a stratification of doses according to body weight minimizes the number of patients with suboptimal teicoplanin exposures. In fact, neonates with a body weight < 2 kg may need a higher maintenance dose than the 8 mg/kg currently recommended for pathogens with MIC values of ≤ 1 mg/L, while, for neonates with a body weight ≥ 2 kg, the recommended doses seem to be adequate. An increase of the maintenance dose up to 10 mg/kg and 11 mg/kg for preterm neonates with a BW of 1 to <2 kg and <1 kg, respectively, can help to reach the therapeutic targets early in therapy and reduce the risk of therapeutic failures [114].

4. Fluoroquinolones

An application of TDM for studying the PK of antibiotics in preterm neonates was reported in three interesting case reports of preterm newborns affected by *Mycoplasma hominis* meningitis and treated with moxifloxacin [115][116][117]. In particular, in the case report described by Yeung T and colleagues, an extremely preterm male (GA = 25 weeks) was treated with doxycycline (4 mg/kg IV every 24 h) and moxifloxacin (5 mg/kg IV every 24 h). TDM was applied to measure the serum concentrations of moxifloxacin and to estimate the pharmacokinetic and pharmacodynamic parameters. These parameters were compared to the targets described in other case reports of *M. hominis* meningitis. In particular, Cmax was 2.5 mg/L whilst the AUC was 28.1 mg·h/L. Considering the MIC values reported in the literature, the estimated Cmax/MIC for this patient was 21 to 158 (target Cmax/MIC: >10), and the AUC/MIC was 234 to 1757 (target AUC/MIC: ≥100). This report describes the successful treatment of *M. hominis* neonatal meningitis and provides important information on the PK/PD parameters of moxifloxacin in preterm neonates. Moreover, it highlights the importance of performing TDM in order to monitor the target attainment rate [117].

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