Systematic Review

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Evaluation of evidence for pharmacokinetics-pharmacodynamics-based dose optimization of antimicrobials for treating Gram-negative infections in neonates

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***Background & objectives*: Neonates present a special subgroup of population in whom optimization of antimicrobial dosing can be particularly challenging. Gram-negative infections are common in neonates, and inpatient treatment along with critical care is needed for the management of these infections. Dosing recommendations are often extrapolated from evidence generated in older patient populations. This systematic review was done to identify the knowledge gaps in the pharmacokinetics-pharmacodynamics (PK-PD)-based optimized dosing schedule for parenteral antimicrobials for Gram-negative neonatal infections.**

***Methods*: Relevant research questions were identified. An extensive electronic and manual search methodology was used. Potentially eligible articles were screened for eligibility. The relevant data were extracted independently in a pre-specified data extraction form. Pooling of data was planned.**

***Results*: Of the 340 records screened, 24 studies were included for data extraction and incorporation in the review [carbapenems - imipenem and meropenem (n=7); aminoglycosides - amikacin and gentamicin (n=9); piperacillin-tazobactam (n=2); quinolones (n=2); third- and fourth-generation cephalosporins (n=4) and colistin nil]. For each of the drug categories, the information for all the questions that the review sought to answer was incomplete. There was a wide variability in the covariates assessed, and pooling of results could not be undertaken.**

***Interpretation & conclusions*: There is a wide knowledge gap for determining the doses of antimicrobials used for Gram-negative infections in neonates. A different profile of newborns in the developing countries could affect the disposition of antimicrobials for Gram negative infections, necessitating the generation of PK-PD data of antimicrobials in neonates from developing countries. Further, guidelines for treatment of neonatal conditions may incorporate the evidence-based PK-PD-guided dosing regimens.**

Key words Antimicrobials - dose optimization - Gram-negative infections - neonates - pharmacokinetics-pharmacodynamics

Parenteral antimicrobials are administered largely in inpatient settings, and their optimized use is critical in determining clinical outcomes. Individualization of drug doses based on pharmacokinetic (PK) determinants has proven to be a clinically useful approach[1]. Parenteral antimicrobials constitute a group of therapeutic agents where the knowledge of covariates affecting PK and pharmacodynamics (PD) is of immense importance in optimizing drug dosage.

The PD outcome such as clinical response to antimicrobial treatment takes time to appear. Hence, other correlates of efficacy and safety outcomes such as time above minimum inhibitory concentration (T>MIC) or peak concentration (C_{max}) to MIC ratio or area under the curve (AUC) to MIC ratio (AUC/MIC) and trough levels have been developed.

Neonates with serious infections pose a difficult situation for clinicians for not only making correct decision regarding choice of antimicrobials but also deciding their correct doses. The complex situation arises because of several considerations. The age that needs to be taken into consideration for determination of an important covariate has to be decided from a variety of options such as post-natal age (PNA), post-menstrual age (PMA), gestational age (GA) and/or post-conceptional age (PCA); the weight ranges from a few hundred grams to kilograms; status of drug metabolizing enzymes is changing[2]; creatine clearance (CLcr) is changing both due to the development process itself and often due to the infective state[3]. There is high variability in the serum albumin affecting the drug-protein binding. Neonates requiring parenteral antimicrobials are on other medications which may alter PK and/or PD of the administered antimicrobial. In the studies evaluating the effect of these factors as covariates, it becomes difficult to delineate the role of each of these factors. Further, issues such as existence of patent ductus arteriosus (PDA)[4], high-frequency oscillatory ventilation (HFOV)[5], extracorporeal membrane oxygenation (ECMO)[6] and therapeutic hypothermia[7] may also contribute to altered PK. Assessment of PD parameters is also difficult in neonates and particularly so in premature neonates.

Conventionally, neonatal sepsis, the condition in which parenteral antimicrobials are lifesaving, has been divided into early- and late-onset sepsis. Both Gram-positive and Gram-negative organisms are responsible for sepsis in neonates. In a study conducted in six countries, it was shown that Gram-negative bacilli accounted for 46.9 per cent of isolates[8]. An alarming level (>50%) of resistance was seen with second- and third- generation cephalosporins while over 40 per cent of Gram-negative isolates demonstrated resistance to gentamicin[8]. An important contributor to the development of antimicrobial resistance is inappropriate dosing of antibiotics. Therefore, the current review was aimed at evaluating available literature for PK-PD data of antimicrobials used for Gram-negative infections requiring hospitalization in neonates with the purpose of optimization of dosage.

Material & Methods

A systematic literature search of PubMed (till February 2015), Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present), Embase, Clinical trials, ProQuest dissertations thesis (PQDT) database and the Cochrane Database of Systematic Reviews (Till February, 2015) was performed for all studies evaluating the efficacy, safety, PD and PK of antimicrobials in neonates. The keywords (medical subject headings and free text) newborn, neonate, infant, preterm, imipenem, meropenem, cefotaxime, ceftriaxone, cefoperazone, ceftazidime, cefepime, quinolones-ciprofloxacin, levofloxacin, moxifloxacin, colistin, polymyxin B, aminoglycosides and third- and fourth-generation cephalosporins, pharmacokinetics and pharmacokinetics-pharmacodynamics, clinical trial, meta-analysis, randomized controlled trial, and review were combined. The search limits included studies published in English and conducted in humans. Reference lists of identified articles were also manually screened for additional relevant studies.

Only those studies were included which (*i*) were undertaken in neonates; (*ii*) included at least assessment of covariates for determining PK parameters; (*iii*) evaluation of PD parameters was either a part of study design or at least evaluated while interpreting the results; and (*iv*) in addition to neonates, studies conducted on infants up to four months were also considered.

Key questions

The key questions included (*i*) Which were the key PK-PD determinants of treatment outcomes in neonates on parenteral antimicrobials for Gram-negative infections?, (*ii*) Within the neonatal population, were there any specific considerations for preterm, very low birth weight, small for GA (SGA)?, (*iii*) How did coexisting PDA, ECMO, parenteral nutrition, therapeutic hypothermia and fluid administration alter

the PK-PD of the administered antimicrobial?, (*iv*) Was there a justification for using a loading dose?, (*v*) Was there a justification for prolonged infusion? and (*vi*) How appropriate was the choice of the antimicrobial, its dose and route for administration for CNS infection?

Data extraction

The following data were extracted independently from the included studies: aim of the study, study population, PK-PD parameters, outcomes and important conclusions. The drugs considered were carbapenems (meropenem and imipenem), piperacillin-tazobactam, aminoglycosides (gentamicin and amikacin), quinolones, third- and fourth-generation cephalosporins and polymyxins (colistin and polymyxin B) all used for Gram-negative infections and parenterally for neonates. Within a class, emphasis was laid on antimicrobials found to be more commonly used. A total of 24 studies were found to satisfy the inclusion criteria (Figure). The salient features of these studies are summarised in Table I[9-31].

Results

Carbapenems

Imipenem: Three studies were included for the analysis[9-11]. Based on an ascending dose study in three neonates, the disposition characteristics of both imipenem and cilastatin were found to be highly variable in premature neonates (GA <37 wk)[9]. The authors recommended a dose of 20 mg/kg every 12 h in premature infants. On the basis of information obtained from a dataset of 60 participants, it has been shown that 30 min infusions of 15 mg/kg every eight hours and 25 mg/kg every 12 h were sufficient against common bacterial isolates in neonates[10]. The probability of target attainment (PTA) was described as a fraction that achieved at least 40 per cent T>MIC of free drug (fT>MIC). The PTA for a 0.5 h infusion increased both with the increase in dose (15-25 mg/kg) and the dosing frequency (q12h to 8 h). With an increase in duration of infusion at each of 15 and 25 mg/kg q8h, there was an increase in PK-PD breakpoints. A shift to a higher value of PK-PD breakpoint was noted for a longer duration of infusion at each dose level. These values, respectively, for a 0.5 h infusion and a 1.5 h infusion were 2-4 µg/ml for a 15 mg/kg dose q8h and 4-8 µg/ml for a 25 mg/kg dose q8h. Further, 1.5 h infusions of 25 mg/kg every eight hours (75 mg/kg/day) were required in neonates to be effective against *Pseudomonas aeruginosa* (MIC for 90% of the isolates was equal to 16 µg/ml)[10]. Gionani *et al*[11], in their analysis of samples of 19 critically ill children, of whom three were neonates found that administration of a dose of 100 mg/kg/day in three or four divided doses was able to achieve an fT>MIC of 70-100 per cent for all recovered Gram-negative pathogen. No evidence was found for PK-PD evaluation in various subgroups of neonates such as SGA, those receiving ECMO or therapeutic hypothermia or those with PDA.

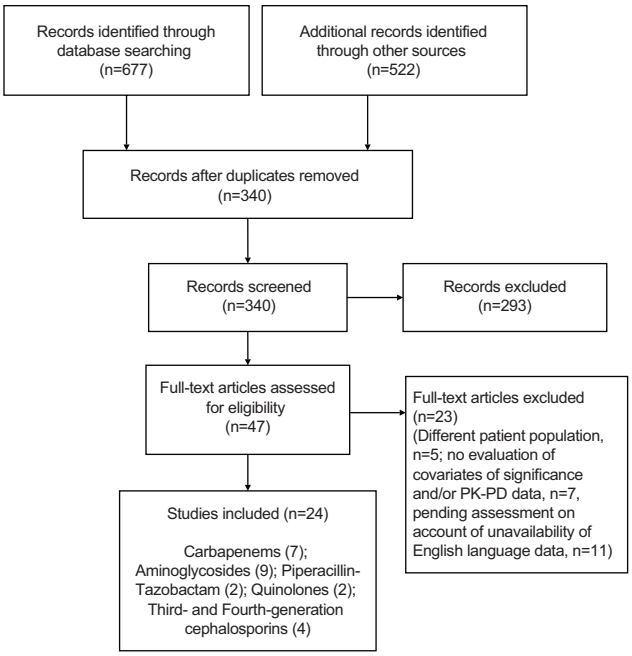

Figure. Flow chart showing the design and inclusion of studies. PK-PD, pharmacokinetics-pharmacodynamics.

Meropenem: Four studies satisfied our inclusion criteria[12-15]. Smith *et al*[12] have undertaken a PK-PD evaluation of dosage schedule which is commonly used in neonatal units. Dosing was done largely based on GA and PNA. They divided the patients into four groups: group 1 (GA <32 wk, PNA <14 days) - 20 mg/kg body weight (BW) every 12 h; group 2 (GA <32 wk, PNA ≥14 days), and group 3 (GA ≥32 wk, PNA <14 days) - 20 mg/kg BW every eight hours and group 4 (GA ≥32 wk, PNA ≥2 wk) - 30 mg/kg BW every eight hours. The PD target exposure level for each infant was defined as plasma meropenem concentrations above >4 µg/ml for 50 per cent of the dose interval and >2 µg/ml for at least 75 per cent of the dosing interval. Trough meropenem concentrations exceeded the therapeutic target of 2 µg/ml in >80 per cent of infants. The PD targets of exposure were achieved in over 90 per cent of patients for both PD target exposure levels.

Table I. Characteristics of included studies

Study	Participants	Aim of the study	Pharmacodynamic outcome evaluated	Main conclusion
		Imipenem		
Reed *et al*, 1990[9]	41 preterm infants	To characterize single and multiple dose PK study of imipenem and cilastatin	No PD parameter was assessed	PCA or infant BW were noted to be important covariates A dose of 20 mg/kg administered every 12 h in infants of 36 wk of PCA was recommended
Yoshizawa *et al*, 2013[10]	Neonates (n=60) (data presented separately for neonates)	PK-PD target attainment analysis of imipenem; to elucidate the PK properties in neonates and children and to rationalize and optimize dosing regimens	Assessment of PTA of T>MIC of 40 per cent was considered	V_d was double while CLcr was half in neonates as compared to that of children While 0.5 h infusions of 15 mg/kg every eight hours was shown to be sufficient against common bacterial isolates, 1.5 h infusions of 25 mg/kg every 8 h were required to be effective against *Pseudomonas aeruginosa*
Giannoni *et al*, 2006[11]	Critically ill children and neonates, neonates (n=3)	Assessment of 100 mg/kg/day in three to four divided doses	PTA of T>MIC of 40% was considered	The high dose regimen (100 mg/kg/day) used by the physicians in charge ensured an fT>MIC of 70-100% for all except MRSA
		Meropenem		
Smith *et al*, 2011[12]	Premature and term infants <91 days (n=200)	Comparison of PK-PD for 4 treatment groups based on GA, PNA and the dose given	Plasma meropenem concentrations above: >4 µg/ml for 50% of the dose interval and >2 µg/ml for at least 75% of the dosing interval	CL was associated with SCR and PMA. For both the outcomes, target PD levels were attained in >90% of cases. Estimated CSF penetration was >70%
Padari *et al*, 2012[15]	GA of <32 wk and a birth weight of <1500 g and PNA <56 days (n=19)	Comparison of a short (30-min) or prolonged (4 h) infusion in VLBW	C_{max} and fT>MIC of 100% for a MIC of 2 mg/l	Meropenem infusions of 30 min may be acceptable as they strike a balance between desired C_{max} with convenience of dosing
van den Anker *et al*, 2009[14]	23 preterm and 15 full term neonates	Comparison of three different doses of meropenem	Simulated target attainment of fT>MIC of 40%	A dose of 40 mg/kg at 8 h interval and prolonged infusion was able to achieve the target in simulated experiments
Bradley *et al*, 2008[13]	37 neonates; 22 were <36 wk	Evaluation of PK of two different doses of meropenem in neonates	Description of PK of 10 and 20 mg/kg dose and assessment of percentage of patients achieving a PD target of 60% T>MIC	Both PCA and SCR were independent predictors of meropenem CL. PD target of 60% T>MIC was achieved in >99% of infants when treated with 10 mg/kg every 12 h for all considered organisms

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Study	Participants	Aim of the study	Pharmacodynamic outcome evaluated	Main conclusion
		Aminoglycosides		
Sherwin *et al*, 2009[16]	80 neonates from GA from 24 to 41 wk	To optimize the ongoing dosing regimen of amikacin as per PK-PD assessment	Percentage of neonates achieving a peak/MIC <8	A peak/MIC ratio of <8 was considered likely to predict treatment failures correctly
Allegaert *et al*, 2007[17]	282 preterm infants <31 wk of GA on respiratory support	Assessment of role of prenatal renal development on CL of amikacin	-	Neonates born SGA were found to have a 16.2% reduction in drug CL. This effect was present from birth up to the PNA of 4 wk
Allegaert *et al*, 2005[18]	205 extreme preterm neonates	Assessment of impact of dosing changes made in neonatal intensive care unit with increase in dosing interval	Assessment of covariates accounting for CL variability	PCA, weight and ibuprofen use were shown to be associated with variability in CL. This regimen was able to attain target C_{max} and trough concentrations, >20 mg/l and <5 mg/l in 77-87% of cases, respectively
Labaune *et al*, 2001[19]	Neonates in the first two days of life, 63 for model building and 57 for prospective validation	Validation of an individualized dosing regimen for neonates in first two days of life	Target attainment of C_{max}/MIC ratio >10 of amikacin by the simplified regimen of once a day administration	Target peak serum levels of amikacin were obtained in 62-80% of patients after the first dose and in 80-100% after the second dose, and trough concentrations were obtained in 100%
Thingvoll *et al*, 2008[20]	Preterm neonates <28 wk of gestation, n=30	Comparison of 48 h versus 24 h dosing interval for gentamicin	Percentage of patients achieving target C_{max} and trough concentrations of gentamicin	The 48 h dosing interval showed a significantly better attainment of target concentrations as compared to 24 h dosing interval
Rastogi *et al*, 2002[21]	58 neonates weighing between 600 and 1500 g	Comparison of 48 h versus 24 h dosing interval for gentamicin	Percentage of patients within the therapeutic range	90% of all peak serum gentamicin concentrations in the 48 h group were in a higher therapeutic range of 6-12 µg/ml as compared with 55% of 24 h group
Williams *et al*, 1997[4]	106 neonates with PDA	Assessment of PDA on PK of gentamicin	Gentamicin CL was decreased and volume of distribution was greater for patients with PDA	Gentamicin dosing should be altered in neonates with PDA
Touw *et al*, 2001[23]	12 neonates with PDA and 12 with closed ductus	Assessment of PDA on PK of gentamicin	Pharmacokinetic parameters	No significant difference between both populations for gentamicin total body CL and volume of distribution
Watterberg *et al*, 1987[22]	24 neonates with PDA	Evaluation of pharmacokinetics of gentamicin in extremely low birth weights with PDA	Pharmacokinetic parameters	An alteration in volume of distribution without effect on half-life and CL was noted

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Study	Participants	Aim of the study	Pharmacodynamic outcome evaluated	Main conclusion
		Piperacillin-tazobactam		
Li *et al*, 2013[24]	71 neonates	To develop population PK models for piperacillin/ tazobactam in neonates and infants of less than two months of age	Determination of significant covariates for PK parameters Assessment of probability of target attainment	Combination of current BW and PNA proved to be superior to PMA alone. The dosing strategy 44.44/5.56 mg/kg/ dose piperacillin/tazobactam every 8 or 12 h achieved the PD target (fT>MIC 50% of the dosing interval) in 67% of infants
Cohen-Wolkowiez *et al*, 2012[25]	Premature and term infants <61 days	Determination of covariates and probability of target attainment	Target attainment rates for the time unbound piperacillin concentrations remained above MIC for 50 and 70% of the dosing interval at steady state	BW and PMA were included in the final model. With PMA based dosing 100 mg/kg q8h, 80 mg/kg q6h, and 80 mg/kg q4h for PMA of <30, 30-35 and 35-49 wk, respectively, 90% of simulated concentrations achieved therapeutic concentration
		Quinolones		
Zhao *et al*, 2014[26]	64 neonates and young infants less than three months of age	To assess the population and to use these data to calculate an optimal dosing regimen	To establish important covariates for describing population PK and assess probability of target: attainment (AUC/MIC of 125)	Important covariates obtained were gestational age, PNA, current weight, SCR and use of inotropes PD target was reached in more than 70% of cases
Aggarwal *et al*, 2004[27]	24 preterm neonates	Determination of multiple dose PK of intravenous ciprofloxacin in preterm neonates	PK parameters	A dose of 10 mg/kg bd was able to achieve trough levels above the MIC for most of the pathogens
		Third- and fourth-generation cephalosporins		
Jacobs & Kearns, 1989[28]	18 VLBW newborns between 500 and 1500 g, GA 28.4 (2.4) wk	To assess cefotaxime PK	-	Administration of 50 mg/kg daily dose of cefotaxime may be adequate in VLBW neonates
van den Anker *et al*, 1995[29]	28 preterm infants	To assess the PK of once and twice day regimens of ceftazidime	PK parameters	Once a day administration was as good as twice a day administration of ceftazidime
Capparelli *et al*, 2005[30]	55 premature and term infants less than four months of age	To assess the important population PK of cefepime in neonates and suggest a dosing schedule for achieving desired PD	-	While CLcr was an important covariate for pharmacokinetics, a reduction in dose and dosing frequency (to 30 mg/kg every 12 h) was suggested

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Study	Participants	Aim of the study	Pharmacodynamic outcome evaluated	Main conclusion
Lima-Rogel *et al*, 2008[31]	31 newborns less than two months of age, 10 additional newborns for validation	To determine population PK model for cefepime	Factors for the final model	BSA and CLcr were included in the final analysis. Based on their PK analysis, the authors predicted that 250 mg/m^2 dose administered every 12 h (for most Gram negative organisms) or 550 mg/m^2 every 12 h for *P. aeruginosa*

Supercript numerals denote reference numbers. PCA, post-conceptional age; PD, pharmacodynamics; PK, pharmacokinetics; CLcr, creatinine clearance; PTA, probability of target attainment; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; GA, gestational age; PNA, post-natal age; PMA, post-menstrual age; SCR, serum creatinine; CL, clearance; CSF, cerebrospinal fluid; VLBW, very-low birth weight; BW, body weight; SGA, small for gestational age; PDA, patent ductus arteriosus; AUC, area under the curve; BSA, body surface area; fT>MIC, time above minimum inhibitory concentration of free drug

Although the meropenem CSF concentration was variable, nearly 70 per cent of the administered dose penetrated into the CSF samples in the study.

Recommendations from two paediatric studies using Monte Carlo simulation have also emphasized that a different regimen may be used for more resistant organisms such as *P. aeruginosa*[13,14]. In one of these studies[13], two doses of 10 and 20 mg/kg were administered to neonates less than two months of age. Meropenem serum concentrations were measured at specified times during the 24 h post-infusion. Monte Carlo simulations were used for assessing PTA. Thirty seven neonates were enrolled, of whom, 22 were preterm (<36 wk of gestation). Meropenem clearance was related to chronological age and GA, being higher for older chronological age and GA. Serum creatinine and PCA were the best predictors of meropenem elimination. Simulation studies demonstrated that at the dosage levels used, the desired PD targets were attained in over 90 per cent of term and preterm neonates against *P. aeruginosa*.

In another study[14], meropenem was administered in different doses (10, 20 and 40 mg/kg) as short (30 min) or prolonged infusion (four hours) to 23 preterm and 15 full-term neonates. In their study, 40 per cent fT>MIC was taken as PD target for running the simulations. For both the doses of 20 and 40 mg/kg, PTA was better achieved with the prolonged infusion (four hours). The authors showed that a dose of 40 mg/kg administered as a prolonged infusion produced target attainments in excess of 90 per cent to a MIC of 8 mg/l, irrespective of GA.

In a special population of neonates (preterm and weighing <1.2 kg), Padari *et al*[15] compared the steady-state PK of meropenem when given as a short (30 min) or prolonged (4 h) infusion given in a dose of 20 mg/kg q12. A short infusion resulted in a higher mean drug concentration in serum than a prolonged infusion (89 vs. 54 mg/l). Neither PNA nor PMA influenced the clearance of meropenem. For an MIC of 2 mg/l, both short and prolonged infusions were able to achieve fT>MIC in more than 80 per cent of cases. A value of fT × 6.2 × MIC was designated as a cut-off for prevention of resistance to *P. aeruginosa*. This target was again achieved in over 80 per cent of patients in both infusion groups (Table I).

No study could be found addressing PK-PD of meropenem in special sub-groups of neonates.

Aminoglycosides

Nine studies[4,16-23] satisfied the inclusion criteria. Sherwin *et al*[16], conducted a study in 80 neonates with a sizeable population of preterm neonates with extremely low birth weight, and demonstrated that PMA and current weight were important determinants of clearance of amikacin. Based on their PK-PD data, the authors showed that the main predictor of treatment failure was an amikacin peak to MIC ratio of less than eight. This led to redefining of dose schedule as follows - 15 mg/kg at 36 h interval, 14 mg/kg at 24 h interval and 15 mg/kg at 24 h intervals for neonates with PMA of ≤28 wk, 29-36 wk and ≥37 wk, respectively.

The importance of weight at the time of birth as an important determinant of renal clearance of amikacin has been demonstrated. It has been shown that for SGA, the renal clearance may be decreased by 16 per cent as compared to appropriate for GA neonates[17].

In view of sepsis occurring within the first two days of life, it may be required to start

aminoglycosides within the first two days. Extended-interval dosing for amikacin has ranged from 24 to 42 h, *viz*. PCA<28 wk, 20 mg/kg per 42 h; PCA 28-30 wk, 20 mg/kg per 36 h; PCA 31-33 wk, 18.5 mg/kg per 30 h; PCA 34-37 wk, 17 mg/kg per 24 h; PCA>37 wk, 15.5 mg/kg per 24 h with additional six hours of increase if the neonate had received ibuprofen or had suffered hypoxia. This regimen was able to attain target C_{max} and trough concentration >20 and <5 mg/l in 77-87 per cent of cases, respectively[18]. The variation in clearance was accounted for largely by PCA and current weight of the neonates. Taking these two factors into account the authors predicted a dosing regimen for extreme preterm neonates. The recommended doses ranged from 6 mg/kg at a dosing interval of 44 h for a neonate of 24 wk PCA and weight of 0.5 kg to a dose of 15.7 mg/kg at a dosing interval of 29 h for a neonate weighing 1.3 kg and PCA of 30 wk[18].

Once a day individualized amikacin dosing in neonates was proposed based on population PK model[19]. A dosing chart was made following the data obtained from PK parameter values of the reference population. These were previously estimated using a non-parametric algorithm on 63 newborns treated with amikacin for two days and divided into three groups of 30, 30-34 and >34 wk. The authors generated a detailed table for dosing based on GA and birth weight, and recommended the following daily dosage regimen (mg/kg/day) for the first injection: GA <30 wk, 4.09; GA=30-34 wk, 9.31 and GA 134 wk, 12.84. The findings of this study were validated in 57 individuals who were administered the drug in the recommended dosage. More than two-thirds and nearly all patients achieved target peak serum levels of amikacin after first and second doses, respectively, and trough concentrations were achieved universally. It has been shown that for preterm neonates <28 wk of gestation, a 48 h dosing interval for gentamicin may be superior to 24 h interval[20]. The 48 h dosing group had a higher mean gentamicin peak (9.43 vs. 6.0 µg/ml) and lower mean gentamicin trough (1.08 vs. 1.54 µg/ml), compared with the 24 h dosing group. Compared to the 24-h group, a peak level <6 µg/ml was seen in a small percentage (43 vs. 7%) in the 48 h group. The same fact was earlier evaluated for extremely low birth weight neonates (600-1500 g)[21].

Effect of simultaneous existence of PDA on the PK parameters of aminoglycosides has been evaluated in three studies[4,22,23]. While two of these studies[22,23] indicated a need for alteration of dosing in neonates with gentamicin, one study[4] did not show any alteration in PK variables.

Piperacillin-tazobactam

Two studies were included in the analysis[24,25]. In a population PK study conducted in children less than two months of age, it was shown that a dose of 44.44/5.56 mg/kg every 8 or 12 h may not be enough for controlling infection in neonates and infants less than two months of age in the Neonatal Intensive Care Unit. The authors suggested a higher dose or more frequent regimens in this group of patients[24]. Further, considering the probability of target attainment (PTA) for extended spectrum beta lactamase (ESBL), the same group conducted simulation studies. Considering a PK-PD correlate best associated with favourable outcome (fT>MIC% >50%), a wide variation was noted in the dose requirement for infants. While those with a BW of 1 kg and PNA of three days, a dose of 10 mg/kg every eight hours was found to be adequate; it was suggested that the dose needed to be increased to 100 mg/kg given every six hours in an infant with a BW of 4.5 kg and a PNA of seven days[24].

Another study done in infants <32 wk GA who were <120 days old and who were receiving i.v. piperacillin or piperacillin-tazobactam for routine medical care were evaluated[25]. A PD target of T>MIC of 50 and 75 per cent of the dosing interval for 16 and 64 mg/l was evaluated. Only 60 per cent of all infants achieved piperacillin concentrations >16 mg/l for 50 per cent of the dosing interval. Piperacillin concentration of >64 mg/l was found to be inadequate for infants in the 30-32 wk age group. The percentage of patients achieving target PD concentration for >75 per cent of the dosing interval was even lesser.

Quinolones

Two studies[26,27] were included for evaluation. As a part of 'Treat Infection in Neonates', 60 infants <120 wk of age were enrolled in population PK analysis of ciprofloxacin[26]. The median PMA of participating neonates was 35.7 wk. For quinolones, a PD target, AUC/MIC of 125 was considered. A dosing regimen of 7.5 mg/kg twice daily for infants with PMA of <34 wk and a dose of 12.5 mg/kg for the rest were decided. The MIC susceptibility breakpoint of 0.5 mg/l was considered. Monte Carlo simulations showed that for the aforementioned dosing regimen and PD targets, more than 90 and 84 per cent of new-borns with PMA <34 and >34 wk, respectively, achieved the desired target. The associated risks of overdose for

the proposed dosing regimen were <8 per cent. The concentrations of ciprofloxacin in six CSF samples were highly variable (187-1650 ng/ml). The median value of CSF/serum concentration ratio was 0.32. CSF collection time correlated with CSF/serum concentration ratio in a manner, suggesting a slower elimination from the CSF as compared to that from systemic circulation. Ciprofloxacin clearance decreased with the co-administration of inotropic drugs.

In a study conducted in 24 preterm neonates, ciprofloxacin was administered in a dose of 10 mg/kg 12 hourly[27]. The mean peak concentrations ranged from 2.3 to 3.0 µg/ml and mean trough levels ranged from 0.7 to 1.0 µg/ml. The trough levels were above the MIC_{90} of most clinically important pathogens, except *Staphylococcus aureus* and *P. aeruginosa*. In case of the latter organism, the peak values were adequate, but the AUC above the MIC_{90} was estimated to be inadequate. Although the authors did not employ population PK-PD model for their analysis, the report may be considered first evidence for providing important data regarding determination of PK profile of ciprofloxacin in this subgroup of neonates.

No studies were identified for specific subgroups of neonates.

Third- and fourth-generation cephalosporins

Among the third-generation cephalosporins, cefotaxime is most commonly used in neonates. There is an increasing use of cefoperazone in this patient population; hence, a literature search for the same was also undertaken. Cefepime, a fourth-generation cephalosporin, is also used for Gram-negative infection in neonatal population and hence included in this review.

Third-generation cephalosporins: Four studies were included for evluation[28-31]. In a group of very low birth weight (VLBW) neonates[28], a single 50 mg/kg/day dose of cefotaxime was able to achieve concentrations of cefotaxime and its active metabolite desacetyl-cefotaxime was sufficient to achieve CSF sterilization within 24-48 h (Table I).

Twenty preterm infants received 25 mg/kg once or twice daily[29]. Twice-daily dosing with ceftazidime led to high serum trough concentrations (42.06 vs. 13.4 mg/l). Although once-daily dose resulted in significant reduction in mean trough concentrations, the smallest of these concentrations (8.1 mg/l) was above MIC for major neonatal pathogens such as *Streptococcus agalactiae* and *E. coli*.

Fourth-generation cephalosporins: In a landmark study, Capparelli *et al*[30] based on their population PK study, were able to suggest that cefepime clearance was closely associated with serum creatinine. The authors further suggested that cefepime, if administered at a dose of 30 mg/kg/dose every 12 h for infants <14 days, regardless of GA, should provide antibiotic exposure equivalent to or >50 mg/kg every eight hours in older infants and children.

In a population PK study of cefepime in neonates[31], it was administered at a dose of 50 mg/kg of BW as 30 min infusion at a dosing interval of 8 or 12 h. The authors identified two important correlates, BSA and CLcr, of plasma concentration.

No studies could be included for addressing the issues of special population of neonates.

Colistin

No study could be included for colistin in the current review.

Discussion

Carbapenems

Although within this group, meropenem, imipenem, doripenem and ertapenem are included, for the current review, only imipenem and meropenem have been evaluated as these are commonly used in neonates.

Imipenem: Imipenem is largely distributed in the extracellular fluid and is removed predominantly by glomerular filtration. Though for the current review, only three studies were included for PK-PD data, 12 studies in foreign language were categorized as 'pending assessment'. One study was reported in French[32] and 11 studies were reported in the Japanese language[33-43].The early works carried out in neonates formed the basis of dosing of imipenem in neonates[44,45]. The background work for describing the PK of imipenem-cilastatin was earlier undertaken in 30 neonates[44]. No accumulation of either imipenem and cilastatin, was noted. A marked inter-subject variability, particularly for cilastatin, was noted.

In view of the findings in this review, there is a need to revisit the dosing schedules described in standard references[46]. However, it is important to note that the direct evidence available so far for premature infants is from the study done by Reed *et al*[9], according to which a 20 mg/kg/dose at q12 h provides a desirable PK profile.

The PD response to treatment may vary with the condition of the neonate. The earlier study carried out in 104 premature and new-born infants belonging to high-risk group with extreme prematurity, perinatal asphyxia and amnion infection as well as various malformations, relied on retrospective data on peak and trough imipenem concentrations[47]. A dose of 50 mg/kg/day in two divided doses was used. The PK parameters were expressed in terms of peak and trough serum concentrations. With imipenem following time-dependent kinetics, relying on peak and trough serum concentrations for PD assessment may be inappropriate. Six deaths were reported, of which five were due to cause unrelated to sepsis[47]. Later on, a need for higher dose in children with more severe infections was highlighted. In case reports of two neonates who failed to respond to imipenem given in recommended doses of 60 or 75 mg/kg/day, the trough levels were found to be undetectable[48]. These findings were thought to be the cause of non-responsiveness of the patients despite the presence of imipenem susceptible strains of bacteria and administration of recommended doses. These findings were corroborated in the study done by Giannoni *et al*[11]. An important concern regarding the effect of a broad-spectrum antimicrobial on the faecal flora of children was addressed in a study[49]. It was noted that the faecal flora of treated neonates was largely unaffected. A possible explanation could be the fact that glomerular filtration accounted for the majority of drug elimination. Inclusion of outcomes which reflect upon alteration of microbiological flora and development of resistance could help in evaluation of results of PK-PD studies in a more comprehensive manner.

Keeping in view the evidence obtained from the literature search, a paucity of data to guide therapy was noted for imipenem. No evidence was found for PK-PD evaluation in various subgroups of neonates such as SGA, those receiving ECMO or therapeutic hypothermia or those with PDA.

Meropenem: Meropenem is largely distributed in extracellular water and is excreted by glomerular filtration. As, in a neonate, percentage of body water and renal functions changes rapidly, the disposition of meropenem is likely to get influenced by virtue of these changes. The half-life of meropenem in infants is substantially longer than that in adults[50]. In the study conducted by Smith *et al*[12] although patients with elevated creatinine were excluded, creatinine was still retained as a significant covariate in the final analysis. PNA was found to be best associated with changes in renal function, and as meropenem is excreted by glomerular filtration, PNA emerging as an important covariate for dosing was expected. Meropenem is often used for CNS infections, a slower elimination of meropenem was noted from the CSF as compared to systemic circulation. A potential role of meningeal inflammation in meropenem CSF concentrations was also noted, however, the conclusion was made from only nine CSF samples in the study.

Recommendations from two paediatric studies using Monte Carlo simulation have also emphasized that a different regimen may be used for more resistant organisms such as *P. aeruginosa*[13,14]. However, one needs to draw the conclusions with caution as the assessment of PTA was largely based on simulation study. Further, in practice, the use of PCA for guiding therapy may not be a practical option as PCA can be correctly measured only for the neonates in whom assisted fertilization is undertaken.

Although, it has been suggested that a longer duration of infusion of meropenem may be useful[14], an important concern with the use of meropenem is its potential to degrade following reconstitution[51]. Though meropenem infusions of 30 min are acceptable in very low birth weight neonates, this may not hold true for intermediate or resistant microorganisms (with meropenem MICs of >2 mg/l) such as *Acinetobacter* spp. and *P. aeruginosa*.

Meropenem has shown good CSF penetrability and offers a good option for use in neonatal meningitis. However, there is a dearth of data in these patients. The results of pharmacokinetic evaluations done in NEOMERO projects (undertaken by European multicenter network), done with the aim of evaluating pharmacokinetics, safety and efficacy of meropenem in infants below three years of age, once published will be able to throw a better light. The reports of this work may be able to answer some of the pending unanswered PK-PD queries. However, it seems unlikely that the issue of special subgroups of neonates would still be addressed.

Aminoglycosides

A remarkable change in aminoglycosides therapeutics has been seen based on PK-PD studies. From the earlier practice of two to three times dosing, a practice of once a day dosing has become a norm for adults. This was based on application of knowledge regarding the relevance of concentration-dependent

kinetics, post-antibiotic effect and the phenomenon of adaptive resistance demonstrated by aminoglycosides. Even in neonates, a greater probability of target C_{max} and trough level attainment with extended interval dosing of gentamicin[52]. A systematic review of gentamicin concluded in favour of extended interval dosing in neonates[52]. Eleven studies[52] were included in this review with a total sample size of 574. All infants in both 'once a day' as well as 'multiple doses a day' regimen showed adequate clearance of bacteraemia. 'Once a day' dosing of gentamicin was superior as compared to 'multiple doses a day' regimen for other PK parameters. On the lines of gentamicin, amikacin extended interval dosing was found to achieve a higher PTA and extended interval is now a routine practice.

Some key developments included the identification of PMA and current weight rather GA and birth weight as guides for dosing regimens. This was based on observation that treating GA and PNA as separate covariates did not give usable information about renal clearance in neonates more than 72 h of age. PMA was considered to be more closely related to the renal clearance[53].

SGA neonates are an important subgroup requiring antimicrobial therapy. Growth restriction by itself has a negative impact on the normalized weight of the kidney, on the number of nephrons, on glomerular filtration rate (GFR) and on tubular function[54]. The importance of weight at the time of birth as an important determinant of renal clearance of amikacin has been demonstrated[53]. It was shown that clearance of gentamicin was lesser for SGA as compared to AGA neonates if the drug was administered within seven days of birth or when the PMA was less than 32 wk[55]. This report has reemphasized the need for elucidating the PK parameters in SGA neonates.

Since, complicated dose regimens with dosing intervals ranging from 18 to 48 h, have been described for aminoglycosides, Labaune *et al*[19] took into consideration the fallouts of such strategy in practice setting and designed their study with once a day regimen and a shorter duration of infusion.

Aminoglycosides are one class of agents for which effect of simultaneous existence of PDA on the PK parameters has been evaluated in three studies[4,22,23]. It would make the information more useful if concomitantly administered drugs such as ibuprofen are taken into account.

Change in PK of gentamicin in neonates receiving high-frequency oscillatory ventilation (HFOV) was evaluated[5]. The evidence for this has not been considered in this review because the study was conducted with 12 hourly dosing interval, a practice which is not followed anymore. HFOV is often resorted to intensive care settings and in future it may be interesting to explore the evidence for this subgroup of patients as well.

Before the adoption of extended interval dosing, it was shown that loading doses might be needed for aminoglycosides. Subsequent to adoption of extended dosing, the need for loading dose, especially in preterm infants with birth weight <1500 g who required amikacin therapy, was evaluated[56]. Although, a loading dose of 10 mg/kg followed by 7.5 mg/kg/24 h administered in preterm neonates, was found to have more than 80 per cent PTA, the principle has not come into standard practice.

Although aminoglycosides have been evaluated most extensively for refining the dosage regimen based on PK-PD data in neonates, important points of consideration are the inclusion of resistance parameters in the PD outcomes, the effect of co-administration of potentially nephrotoxic drugs such as vancomycin and amphotericin-B, which is sometimes required in these patients. Further, with different studies having used algorithms based on PNA or PCA for evaluation of PD parameters, it becomes difficult to arrive at a conclusion based on results of good quality studies. Valitalo *et al*[57] used datasets from previously done studies to generate a dataset of 5000 virtual patients. Monte Carlo simulations on the basis of validated models were undertaken to evaluate the attainment of following targets for gentamicin and tobramycin - peak (5-12 mg/l) and trough (<0.5 mg/l) concentrations. They found a discrepancy in attainment of peak and trough concentrations when different guidelines were used. While the Dutch National Formulary for Children, the British National Formulary for Children and NeoFax resulted in adequate trough but inadequate peak concentrations; the case with Red Book was reverse with peak concentrations being less than 75 per cent below target. They proposed a dose of 4.5 mg/kg of gentamicin with dosing intervals determined by birth weight and PNA. The PNA considered were 5, 6-10, 11-20 and >20 days, while three categories of birth weight were considered <1, 1 and 2 and >2 kg. The dosing intervals ranged from 24 to 72 h. The authors predicted attainment of adequate peak concentrations with only 33-38 per cent of the trough concentrations above target[57]. This regimen

needs to be validated. Moreover, it did not take into consideration the covariates such as existence of PDA and use of concomitant antimicrobials.

Issues related to inhaled route of tobramycin have not been covered since its use in intensive care setting is still restricted.

Piperacillin-tazobactam

Piperacillin-tazobactam is used for multiple infective conditions in inpatient settings. There is a paucity of PK data in neonatal age group. The PD correlate of piperacillin-tazobactam is f T>MIC of approximately 50 per cent of the dosing interval for Gram-negative bacteria[24].

In a study the patients received dosing as per NeoFax (100 mg/kg every 8-12 h) and The Harriet Lane Handbook (75 mg/kg every 8-12 h)[25]. The dosage schedule recommended in these handbooks is probably derived from a study conducted in infants and children, wherein the authors based on their study findings had noted that a dose of 100 mg of piperacillin and 12.5 mg of tazobactam per kg of BW administered as a fixed-dose combination every six to eight hours may be appropriate for attaining clinical efficacy in infants and children[58]. Piperacillin clearance increased with allometrically scaled BW, and it decreased proportionally with increasing serum creatinine. However, the results must be interpreted with caution as the results are based on scavenged samples. Since the enrolled participants ranged from two months to 12 yr, this study has not been included in the current review.

Quinolones

Among the quinolones, ciprofloxacin, norfloxacin and levofloxacin are frequently used in neonates. In the inpatient setting, parenteral ciprofloxacin is commonly used. A wide variability exists in the dose of ciprofloxacin used ranging from ≤10 to ≥21 mg/kg/day[59]. It was noted that ciprofloxacin clearance decreased with the co-administration of inotropic drugs[26]. A possible explanation is that inotropic agents are often given when there is decreased blood pressure, which will result in decreased GFR.

In a case series of six neonates a good penetration of ciprofloxacin in CSF was reported[60]. This information may be useful for CNS infections showing susceptibility to ciprofloxacin. A single case report of moxifloxacin use for a case of *Mycoplasma hominis* meningitis has been described[61]. Moxifloxacin was administered at a dose of 5 mg/kg q24h. Moxifloxacin was infused over one hour, and blood samples were collected around the seventh and fourteenth doses of moxifloxacin at 0.7, 1.9, 17.5 and 22.1 h after the end of infusion. The C_{max}/MIC ratio was approximated as 27. The levels of moxifloxacin metabolites were higher in infant than in adults. The implication of higher levels of inactive metabolites was not evaluated in this single patient report. As these metabolic processes may be compromised in neonates, it may be a prudent exercise to evaluate the same in a larger cohort of neonates.

Third- and fourth-generation cephalosporins

Among the third-generation cephalosporins, cefotaxime is most commonly used in neonates. Although the antimicrobial profile of ceftriaxone is similar to that of cefotaxime, the use of ceftriaxone is associated with concern in case of neonates with hyperbilirubinemia[62]. Further, administration of ceftriaxone and calcium-containing solutions or products may lead to fatal reactions with calcium-ceftriaxone precipitates in lung and kidney. There is an increasing use of cefoperazone in this patient population; hence, a literature search for the same was also undertaken. Cefepime, a fourth-generation cephalosporin, is also used for Gram-negative infection in neonatal population and hence included in this review.

The first PK study of cefotaxime in neonates concluded that a dose of 50 mg/kg administered every 12 and 8 h, respectively, in neonates less than seven days and those between 7 and 28 days would be appropriate[63]. There was no PD evaluation undertaken in this study. Further, in the study, the comparison between groups was made for the current weight of the neonate. However, the dosing recommendations were made based on PNA.

In a study on PK of ceftriaxone in neonates the authors concluded that the half-life of drugs was related to the current weight of neonates with it being longer (7.7-8.4 h) for neonates weighing <1500 g[64]. It was further observed, that accumulation of ceftriaxone might occur for those neonates who received the drug at a frequency greater than once a day. However, based on another PK study, a dose of 50 mg/kg given every 12 h was suggested for neonates less than seven days old[65]. Another PK study in very low birth weight neonates[66] showed a significant linear correlations between GA and weight and cefotaxime half-life and total body clearance. A dose of 50 mg/kg every 24 h was considered appropriate for this group.

Kearns *et al*[67] proposed in his review that either a cefotaxime dosage of 50-75 mg/kg every eight hours or 75 mg/kg every 12 h should provide adequate antimicrobial concentrations of desacetyl-cefotaxime in serum, especially if the combination of cefotaxime and desacetyl-cefotaxime is synergistic. None of the studies included in this review could be included for our analysis since a simulation for PD parameters was not undertaken.

An important use of these agents is in neonatal meningitis owing to reliable penetration of both the agents in CSF. It has been shown that for ceftriaxone, the CSF concentrations achieved with 50 and 75 mg/kg were usually 10-100 times greater than the MIC for recovered bacteria[68]. Based on the study results, a tentative dosage schedule of 100 mg/kg given as i.v. infusions over 24 h was proposed. Cefotaxime has shown a good CSF penetration with an ability to achieve sterilization as early as 36 h[69]. However, this study was carried out in children over one month of age and cefotaxime was administered in a dose of 200 mg/kg/day in four divided doses.

Cefoperazone offers the advantage of longer half-life than other third-generation cephalosporins and crossing the blood-brain barriers such as cefotaxime and ceftriaxone. A pharmacokinetic study of cefoperazone has shown that cefoperazone administered in doses of 12.5 mg/kg every 12 h by i.v. or intramuscular (i.m.) routes may have similar pharmacokinetics[70]. The levels achieved in blood during 15-30 min after the dose were 12-100 times the MIC for 90 per cent of the strains of pathogens such as *E. coli* and *Proteus mirabilis* and 17-30 times more than necessary to inhibit 90 per cent of the strains of *S. aureus*. However, the results would need to be interpreted with caution since these were based on blood levels obtained soon after drug administration. No standard methodology for determination of covariates was used in this study and no criteria were mentioned for PD target attainment. However, the study may be considered as foundation for further studies.

The activity of ceftazidime against *P. aerugionosa* makes it particularly useful in infections due to *Pseudomonas* which is not uncommon. It was conventionally administered as twice daily dose in neonates. The requirement of an antimicrobial to maintain a concentration above MIC for most of the dosing interval is met in adults by either intermittent administration or by continuous administration. However, lower clearance in preterm neonates leads to once-daily administration of a low dose resulting in concentrations of cefatzidime that are above the MICs for major neonatal pathogens during the complete 24-h dosing interval[71]. The authors based this study on their previous observation in which they noted that ceftazidime clearance increased significantly with increasing GFR[72]. Prenatal exposure to indomethacin resulted in significantly lower GFR values and ceftazidime clearances[72].

A fourth-generation cephalosporin, cefepime, has been shown to have broader antibacterial spectrum than third-generation cephalosporins, including activity against aerobic Gram-positive organism. Its stability to beta-lactamase hydrolysis provides an additional advantage[73]. While cefepime has been evaluated by an optimized dosing regimen based on PK-PD data, such studies are not available for other cephalosporins.

Colistin

Colistin is often used in extensively drug- or multidrug-resistant organisms in neonatal population. The near-absence of PK and PD data in the neonatal age group compels clinicians to depend on the data derived from other, often paediatric patients. The drug has poor CNS penetrability. However, intraventricular or intrathecal routes have been used successfully for CNS infections[74]. For pulmonary infections, administration via inhalational route may ensure more concentration of the drug in pulmonary parenchyma[75]. The PK-PD data on colistin in neonates are not available. The situation is complicated further by unavailability of cost-effective methods of analysis of plasma concentration of polymyxins in blood. Very similar to the situation of colistin is the case of polymyxin B.

The present systematic review highlights the paucity of literature on the subject reviewed. Furthermore, a lot of practices are based on studies done in the period where PK-PD correlates of antimicrobials were not properly established. Conventional reporting of PK data does not throw light on PD responses. The review has certain limitations. Full-text articles of literature available in foreign language could not be analyzed and only abstracts had to be relied upon. However, this was largely seen for only one drug (imipenem). Pooling of data could not be undertaken for want of more than one study for a particular outcome.

Conclusions

The armamentarium of antimicrobials available for treatment of Gram-negative infections is running out.

Table II. Summary of evidence-based pharmacokinetics-pharmacodynamics (PK-PD) dosing regimen and action items

Drug	Dosage schedule (as per the evidence)	Knowledge gap/need for action
Imipenem	Depending on GA >37 wk (25 mg/kg i.v. every eight hours as 1.5 h infusion, particularly for *P. aeruginosa* and perhaps other Gram-negative infections). For other isolates, 15 mg/kg every 8 h or 25 mg/kg every 12 h given as 30 min infusion may be sufficient for <37 wk, 20 mg/kg i.v. every 12 h	No evidence available for SGA neonates, neonates with PDA, undergoing ECMO, therapeutic hypothermia, receiving parenteral, nutitrition, assessment for need for loading dose, dose optimization for meningitis, more information regarding duration of infusion
Meropenem	GA (wk) / PNA (days) / Dose <32 / <14 / 20 mg/kg every 12 h <32 / >14 / 20 mg/kg every 8 h ≥32 / <14 / 20 mg/kg every 8 h ≥32 / ≥14 / 30 mg/kg every 8 h Three hours infusion may give a greater probability of target attainment. For neonates with GA <32 wk, BW <1200 g, 20 mg/kg every 12 h administered over 30 min are acceptable. However, for Gram-negative infections a three hours infusion may be needed	As above
Cefotaxime	PNA <7 days, 50 mg/kg every 12 h, 7-28 days-50 mg/kg every 8 h, VLBW: 50 mg/kg every 24 h	As above
Ceftriaxone	No good quality evidence for making PK-PD-based dosing recommendation	As above
Ceftazidime	No good evidence based on PK-PD information	As above
Cefepime	Dosing as per body surface area 150-250 mg/m^2 every 12 h; for organisms such as *P. aeruginosa* and perhaps other Gram-negative organisms a higher dose of 550 mg/m^2 may be needed	As above
Cefoperazone	No evidence of PK-PD optimized dose recommendation. However, some pharmacokinetic evidence to suggest a dose of 50 mg/kg every 12 h may be sufficient for preterm neonates	As above
Amikacin	Based on PMA ≤28 wk: 15 mg/kg at 36 h interval 29-36 wk: 14 mg/kg at 24 h interval ≥37 wk: 15 mg/kg at 24 h interval Based on PCA <28 wk: 20 mg/kg every 42 h 28-30 wk: 20 mg/kg every 36 h 31-33 wk: 18.5 mg/kg every 30 h 34-37 wk: 17 mg/kg every 24 h >37 wk:15.5 mg/kg every 24 h Dosing intervals to be increased by six hours if history of administration of ibuprofen Significance of loading dose noted for preterm neonates with birth weight <1500 g: 10 mg/kg followed by 7.5 mg/kg/24 h after PNA of greater than one week	Extension of dosing interval with co-administration of ibuprofen As above

Contd...

Drug	Dosage schedule (as per the evidence)			Knowledge gap/need for action
Piperacillin-tazobactam	No revision of available schedules may be suggested. However, the dosing recommendation of 100 mg/kg/dose given 6-12 hourly may not be able to attain the desired concentrations			As above
Ciprofloxacin	10 mg/kg i.v., 12 hourly			As above
Gentamicin	PNA (days)	BW (kg)	Intervals (h)	Evidence for change of dose in patients with PDA is equivocal
	<5	<1	72	
		1-2>2	60	
			48	
	6-10	<1	60	
		1-2>2	48	
			36	
	11-20	<1	48	
		1-2>2	36	
			24	
	>20	<1	36	
		1-2>2	24	
			24	
	A peak concentration of 5-12 mg/l and a trough concentration of <0.5 mg/l are desired			

GA, gestational age; i.v., intravenous; *P. aeruginosa*, *Pseudomonas aeruginosa*; SGA, small for gestational age; PDA, patent ductus arteriosus; ECMO, extracorporeal membrane oxygenation; PNA, post-natal age; BW, bodyweight; VLBW, very-low-birth-weight; i.m., intramuscular; PD, PMA, post-menstrual age; PCA, post-conceptional age; BW, body weight
Source: Refs 9-23

The available agents have to be used judiciously and every measure aimed at improving efficacy and reducing toxicity with the use of antimicrobials for Gram-negative infections should be undertaken. An optimized dose based on PK-PD studies is one of the tools available to address this situation. Like in many centres world over, it is important to develop a collaborative effort to identify knowledge gaps for guiding antimicrobial therapy in neonatal infections caused by Gram-negative organisms. A good model for such collaborative exercise is being set by the Prato polymyxin consensus[76]. Determination of important covariates for PK and development of models based on the same, validation of these models in prospective studies, assessment of PK-PD parameters in various subgroup of neonates, particularly SGA, assessment of PK-PD parameters in case of different comorbidities and therapeutic modalities, validation of PD parameters of efficacy in neonatal population, incorporation of PD parameters of resistance development are some of the areas for research. While these activities are initiated, it may be suggested at this point that guidelines for the management of infective conditions of neonates, such as protocol for management of neonatal sepsis[77] as developed by Neonatology Forum of India, could consider incorporating evidence-based dosing regimens for antibiotics. Table II summarizes the findings comparing the dosing schedules based on PK-PD data available.

***Conflicts of Interest*:** None.

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