Understanding pharmacokinetics/pharmacodynamics in managing neonatal sepsis

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Purpose of review

This review describes recent pharmacokinetic and/or pharmacodynamic studies of antimicrobial agents used for treatment of neonatal sepsis.

Recent findings

Pharmacodynamic targets in adults and neonates with sepsis are likely similar; thus, extrapolations are possible. When using β-lactams, the free-drug concentration should be maintained above the minimum inhibitory concentration (MIC) level for the entire dosing interval, but thus far clinical studies have failed to demonstrate that continuous infusion should be preferred over bolus administration. In aminoglycosides, peak concentration (C_{max})/MIC ratio of 8 or even higher, if possible, should be targeted. For vancomycin, the pharmacokinetic/pharmacodynamic target area under the serum concentration curve (AUC)/MIC ratio of more than 400 is advocated for clinical effectiveness in adults, but with current dosing this will be achieved only if MIC is less than 2 mg/l. In other situations alternative agents are recommended. Neonatal dosing regimens of echinocandins have not been established; preliminary data indicate a dose of 25 mg/m^2 for caspofungin and 7 mg/kg q24h (patients with birth weight $\geq$1000 g) or 10 mg/kg q24 h (patients with birth weight $<$1000 g) for micafungin ensure exposure similar to currently recommended adult doses.

Summary

The targets proposed, mainly for adults with sepsis, are likely applicable also to neonates, but prior to recommending them for clinical application more studies in septic neonates are required.

Keywords

aminoglycosides, echinocandins, fluconazole, meropenem, vancomycin

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Introduction

Several recent reviews have characterized pharmacokinetics/pharmacodynamics of antimicrobial agents in critically ill adults with sepsis, but there are almost no data in neonates [1,2]. Although it is appreciated that differences between these populations exist, there are several common features, such as perfusion failure, capillary leakage and modification of volume of distribution (V_d), changes in hepatic metabolism and renal excretion, impairment of the gastrointestinal system and lung injury, all of which have influence on the pharmacokinetic/pharmacodynamic characteristics of a drug. Pharmacodynamic studies in septic neonates are difficult to conduct; thus, much of the data in this review are obtained from studies in adults or older children as in general the pharmacodynamic properties of an antibiotic appear to be similar. Our main focus is to review recent pharmacokinetic and/or pharmacodynamic studies on antimicrobial agents potentially used for the treatment of neonatal sepsis.

Pharmacokinetic/pharmacodynamic measures of antimicrobial effects

The three main pharmacodynamic parameters linking the measures of drug exposure to microbiological and clinical effects are: the area under the serum concentration curve to minimum inhibitory concentration ratio (AUC/MIC), being a pharmacokinetic/pharmacodynamic target for fluoroquinolones, glycopeptides and linezolid; peak concentration to MIC ratio (C_{max}/MIC), characterizing aminoglycosides; and the time that free, nonprotein bound, drug concentration remains above MIC of the microorganisms (f%T $>$ MIC) – a target for β-lactam antibiotics (Table 1).

It is appreciated that neonates are immunocompromised with host response shifted towards immune tolerance

Table 1 Pharmacokinetic–pharmacodynamic targets correlating with efficacy [1,3•,4••,5••,6•,7•]

Antibiotic	Pharmacodynamic parameter	Pharmacokinetic/pharmacodynamic magnitude required for efficacy: Mild-to-moderate infection, normal host	Severe infection, immunocompromised host	Predictors of clearance in neonates
Penicillins	f%T > MIC	50	70–100	Creatinine, PCA
Cephalosporins	f%T > MIC	50	70–100	Creatinine, PCA
Meropenem	f%T > MIC	40–60	70	Creatinine, PCA
Vancomycin	AUC_{0-24}/MIC	≥400	850[a]	CBW, PMA, creatinine
Aminoglycosides	C_{max}/MIC	8–12	>10	CBW, PMA
Fluconazole				
Therapeutic use	AUC_{0-24}	400 mg × h/ml	800 mg × h/ml	
Prophylactic use	T > MIC	40%	NA	

CBW, current body weight; PCA, postconceptional age; PMA, postmenstrual age.
[a] The value required for microbiological eradication in patients with *S. aureus* ventilaor-associated pneumonia [4••].

rather than defence from infection [8]. Critically ill adults and neonates develop variations in extracellular fluid content, renal and liver function, all affecting drug exposure and thus requiring different dosing regimens compared with patients with mild-to-moderate disease [1,9]. For example, blood concentrations of hydrophilic agents, such as β-lactams, aminoglycosides and glycopeptides, may dramatically drop due to substantial fluid extravasation into the interstitial space. Therefore, higher doses of hydrophilic agents should be considered. An increase in the extravascular compartment leading to a significant increase in V_d may also result from abundant intravenous fluid therapies, total parenteral nutrition, pleural effusion, peritoneal exudate and ascites. Hypoalbuminaemia, a common condition in critically ill patients, on the one hand may increase fluid extravasation and lower antibiotic levels in blood, but on the other hand it will increase the free fraction of drug.

Causative agents of neonatal sepsis and their antibiotic susceptibility

The incidence of neonatal sepsis is inversely proportional to gestational age and birth weight [10•].

Although Gram-positive microorganisms like group B streptococci (GBS) and other Gram-positive cocci still prevail in early onset sepsis (EOS) among term and late preterm neonates [11,12], in very low birth weight (VLBW) infants Gram-negative pathogens have emerged as the predominant cause [10•,13]. Improved survival, especially among those with extreme prematurity, has increased the incidence of late onset sepsis (LOS), with coagulase negative staphylococci (CoNS), Enterobacteriaceae and *Candida* spp. prevailing in all age categories [10•,12]. Escalating antibiotic resistance observed in large international databases has also involved common neonatal pathogens with extremely high rates reported in the developing world. Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a recognized cause of neonatal sepsis. Gram-negative infection and antimicrobial resistance have both been associated with higher mortality, with all-cause mortality reaching approximately 25% in EOS and 18% in LOS in VLBW neonates [10•].

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical Laboratory Standards Institute (CLSI) continue to refine the MIC breakpoints. It should be noted though that the information on neonatal sepsis-causing microorganisms is almost entirely missing. Frei *et al.* [3•] recently conducted Monte Carlo simulation (MCS) of 10 000 participants to develop pharmacokinetic/pharmacodynamic breakpoints for numerous antimicrobial classes against key Gram-negative aerobic bacteria. With regard to agents used in the treatment of neonatal sepsis (e.g. piperacillin/tazobactam, meropenem, gentamicin and tobramycin) breakpoint discrepancies between pharmacokinetic/pharmacodynamic based CLSI and EUCAST criteria were within one dilution. In contrast, the pharmacokinetic/pharmacodynamic and EUCAST breakpoints against Enterobacteriaceae were lower than those of CLSI for cefepime (1 vs. 8 mg/l) and ciprofloxacin (0.125 vs. 0.5 mg/l) [3•]. Application of different breakpoints may lead to different dosing recommendations in various regions.

Pharmacokinetic/pharmacodynamic characteristics of specific antibiotics

The pharmacokinetic/pharmacodynamic characteristics of antimicrobial agents used in the treatment of neonatal sepsis are discussed in the following sections.

β-Lactam antibiotics

A β-lactam combination with an aminoglycoside has remained the cornerstone of empiric antibiotic treatment in neonatal sepsis. Traditionally, the pharmacodynamics of β-lactams is determined by the f%T > MIC with different targets suggested for immunocompetent and immunocompromised hosts (Table 1). The additional

value of AUC_{0-24}/MIC has been recently confirmed by McKinnon *et al.* [6•], who found improved clinical cure and bacteriological eradication rates with cefepime and ceftazidime in adults with sepsis, when AUC_{0-24}/MIC was at least 250 and f%T > MIC about 100%. While f%T > MIC best predicted clinical failure, AUC_{0-24}/MIC was the only one predicting bacteriological failure.

Continuous vs. bolus infusion of β-lactams

The time-dependent pharmacodynamics of β-lactam antibiotics has prompted a search for strategies to improve exposure. Van Zanten [14] has listed several possibilities to extend f%T > MIC of an antibiotic, which include interference with elimination (e.g. probenecid), frequent dosing, increasing the dose, changing to antibiotics of longer serum half-life and administration by extended or continuous infusion. For the latter, the concentration at which maximal bactericidal effect is achieved is an important determinant of efficacy, as a continuous infusion results in a much lower C_{max} compared with bolus administration. Potential drawbacks are associated with the stability of administered antibiotics and lower serum concentrations that may not exceed the MIC of more resistant pathogens throughout the infusion period.

The data on whether continuous infusion should be preferred over bolus administration of β-lactam antibiotics are controversial. A recent meta-analysis suggested similar clinical results with intermittent boluses and continuous infusion in adults [15], contrasting the results of an earlier analysis showing lower clinical failure rates in the continuous infusion group [16]. However, in the more recent meta-analysis [15] higher antibiotic doses were used in the intermittent compared with continuous infusion dosing. Increased drug clearance in paediatric populations is likely to increase the benefit of prolonged infusions. In a pharmacokinetic/pharmacodynamic optimization study, simulation of different infusion times showed significantly improved likelihood of obtaining bactericidal targets with 3 and 24 h compared with 0.5 h infusion for cefepime, ceftazidime, imipenem/cilastatin, meropenem and piperacillin/tazobactam in a population aged from 2 to 12 years [17].

Cefotaxime

Cefotaxime is an antibiotic well suited for administration as continuous infusion due to its time-dependent pharmacodynamics, slow bactericidal effect and maximal bacterial killing at relatively low concentration. In a paediatric trial involving 222 participants, including neonates, Bertels *et al.* [18•] found a wide variation in cefotaxime serum concentration (from 0.6 to 182.6 mg/l) with continuous cefotaxime infusion in a dose of 100 mg/kg/day. As could be expected from the predominantly renal elimination route of cefotaxime, the largest variations and highest concentrations were seen within the first week of life, of note the low end (0.6 mg/l) remaining below the recognized MIC breakpoints for common neonatal pathogens. The need for therapeutic drug monitoring (TDM) once or twice in continuous infusion of β-lactams has been suggested when more resistant pathogens are encountered [14].

Meropenem

Meropenem, a carbapenem with wide range of antibacterial activity and favourable side-effect profile, has been increasingly used in neonates. Two recent pharmacokinetic studies have attempted to identify an optimal dosing regimen in neonates. Bradley *et al.* [19•] studied 10 and 20 mg/kg of meropenem given as a single 30-min infusion in 37 neonates with gestational age of 23–41 weeks and postnatal age (PNA) of 1–61 days. Serum creatinine and postconceptional age (PCA) appeared the best predictors of meropenem clearance. MCS showed that the pharmacokinetic/pharmacodynamic target of 60% f%T > MIC for GBS and Gram-negative bacilli, based on the MIC distributions reported by the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) antibiotic surveillance programme, could be achieved in more than 99% of infants in all gestational age and PNA groups with the dose of 10 mg/kg/q12 h. For *Pseudomonas aeruginosa*, a dose of 20 mg/kg/q8 h achieved pharmacokinetic/pharmacodynamic target in 95% of preterm and 91% of term neonates. Another study by van den Anker *et al.* [20••], including 38 term and preterm neonates, confirmed the crucial role of PCA in meropenem clearance. Using MCS, the authors showed enhanced pharmacokinetic/pharmacodynamic target attainment with 4 h compared with 0.5 h infusion of 20 or 40 mg/kg q8 h or q12 h. Although all dosing regimens appeared adequate for microorganisms with MIC less than 4 mg/l, only 4 h infusion of 40 mg/kg/q8 h produced therapeutic target (f%T > MIC of 40%) attainment in excess of 90% out to an MIC of 8 mg/l in both term and preterm neonates.

With increasing resistance cutting down the list of available antibiotics in the physician's armamentarium, suppression of resistance has become increasingly important. Compared with bactericidal effect, significantly higher pharmacodynamic targets ensure meeting this aim – for meropenem, C_{min} 1.7 times the MIC is needed to minimize resistant mutant amplification in *P. aeruginosa* when administered along with an aminoglycoside and 6.2 times the MIC when administered alone [20••]. In the study by van den Anker *et al.*, this target was met more than 80% of the time out to an MIC of 2 mg/l only, with the 4 h infusion of meropenem in a dose of 40 mg/kg q8 h when combined with aminoglycoside.

Aminoglycosides

Aminoglycoside pharmacodynamics is determined by the C_{max} > MIC (Table 1), with susceptibility generally well

preserved among neonatal pathogens. However, the presently suggested C_{max} targets are somewhat arbitrary and should be subject to evidence-based alteration [21••]. In a recent pharmacokinetic/pharmacodynamic study in neonates, Sherwin *et al.* [7•] identified the C_{max}/MIC ratio of amikacin as the only independent predictor of treatment failure, with C_{max} /MIC ratio less than 8 associated with increased relative risk of failure and suggested amikacin C_{max} of 24–35 mg/l as an acceptable maximum.

Population pharmacokinetic studies have confirmed the role of current body weight (CBW) and PCA as explanatory factors for the variability in aminoglycoside pharmacokinetics in neonates, with CBW as the principal determinant of V_d [21••,22]. A TDM database analysis of 116 neonates (87 nonseptic and 29 with confirmed sepsis) by Sherwin *et al.* [23] supports the earlier finding of a higher V_d of aminoglycosides in septic neonates [9]. Lingvall *et al.* [9] have pointed to the duration of infusion as an important determinant of aminoglycoside pharmacokinetics/pharmacodynamics. In a series of simulation experiments Sherwin *et al.* [24•] have shown that due to the small volumes and low infusion rates used in neonates, the dose delivered within the estimated infusion period is generally lower than intended, varies significantly with the weight of the neonate and may be as low as 60% in ELBW neonates.

Extended interval vs. once daily vs. multiple administration of aminoglycosides

Once daily dosing of aminoglycosides combined with TDM has become a generally accepted practice with safety and clinical efficacy at least equivalent to multiple daily dosing. Still, data have shown that even with once daily dosing regimens, the C_{max} and C_{min} are outside the therapeutic range in a substantial proportion of preterm neonates [25,26]. More recently, individualized dosing with TDM 24–48 (60) h after the first dose has been explored for improved therapeutic target attainment [7•,21••,22]. Begg *et al.* [21••] have modelled various dose adjustment algorithms of gentamicin based on an 8-year TDM database of standard Stickland extended-interval dosing protocol. They demonstrated that further extending dosing interval to at least five half-lives (i.e. 60 h in neonates with CBW < 1.5 kg, 48 h with CBW 1.5–3.0 kg and 36 h with CBW 3–5 kg) resulted in a substantial improvement in achieving target C_{max} (>10 mg/l) and C_{min} (<1 mg/l) values. Prolonging dose interval requires larger first dose administration and higher C_{max} to attain mean AUC_{24}. On the contrary, targeting C_{max} as high as possible provides the best chance of efficacy and should decrease the likelihood of true bacterial as well as adaptive resistance [21••]. Sherwin *et al.* [7•,22] have suggested individualized extended interval amikacin and netilmicin dosing regimens for neonates with dose adjustment by body weight (as the single determinant of V_d) and dosing interval adjustment by both PMA and CBW. The safety of these dosing recommendations, though supported by favourable pharmacokinetic/pharmacodynamic profile, remains to be confirmed in clinical trials.

Vancomycin

Vancomycin is almost exclusively cleared by renal elimination and is still the first-line antibiotic for treatment of staphylococcal infections. Earlier studies have shown that size, age (PNA, gestational age and PMA) and renal function are the predictors of vancomycin clearance but the contribution of each component has been poorly described. In a population pharmacokinetic analysis of TDM data from 214 neonates with a PMA of 30.4 weeks and weight of 1.30 kg (range 0.42–2.6 kg), Anderson *et al.* [27] demonstrated about two-fold increase of vancomycin clearance from 24 weeks of PMA to 34th week, and overall 82% of variability was predictable (size explained 49.8%, PMA 18.2% and renal function 14.1%). This suggests that TDM of vancomycin may be unnecessary provided that changes in weight, PMA and creatinine are monitored.

A variety of pharmacokinetic/pharmacodynamic parameters have been proposed for vancomycin, including T > MIC, C_{max}/MIC and AUC/MIC. Traditionally, peak and trough concentrations have been monitored, and the trough levels in all age categories, including neonates have been maintained between 5 and 10 mg/l [4••]. More recently, the nephrotoxicity and ototoxicity of vancomycin in adult patients with normal renal function not receiving concomitant nephrotoxic agents and consequently also the appropriateness of recommended trough levels has been questioned. Furthermore, the efficacy of vancomycin in cases with increased MIC values has been doubted. Soriano *et al.* [28•], in a prospective study of 414 adult with MRSA infections, demonstrated higher bacteraemia associated mortality with empirical vancomycin if the MIC of infecting strain was 2 mg/l, suggesting the need for alternative agents in such cases. Although the study did not include patients with CoNS, which account for about 50% cases of neonatal sepsis, these findings are likely applicable to CoNS as more than 80% of CoNS strains have MIC at least 2 mg/l [29].

Recently vancomycin treatment guidelines for adult patients were revised, and a consensus statement by the American Society of Health System Pharmacists, Infectious Diseases Society of America and Society of Infectious Diseases Pharmacists was published [4••]. For vancomycin use in adults, the following recommendations are given: an AUC/MIC ratio of more than 400 is advocated as a target for clinical effectiveness; trough serum concentrations are the most accurate and practical

method of monitoring effectiveness and avoiding resistance development and should be maintained above 10 mg/l. In complicated infections (e.g. bacteraemia, endocarditis, osteomyelitis, meningitis, hospital acquired pneumonia), concentrations of 15–20 mg/l are recommended; there is no evidence to support monitoring of peak serum vancomycin concentrations to decrease nephrotoxicity or prevent ototoxicity. It is likely that these recommendations apply also to neonates, but this needs to be confirmed in future trials.

Only one recent paediatric and no neonatal studies have looked at vancomycin dosing in the light of the newly published guidelines. Frymoyer *et al.* [30•] developed a model to predict vancomycin AUC_{0-24}/MIC for children aged between 2 and 12 years for doses of 40 and 60 mg/kg/daily. For MRSA MIC of 1.0 mg/l, the target AUC_{0-24}/MIC ratio of more than 400 was achieved only with the dose of 60 mg/kg/day. When, however, the MIC was 2 mg/l, the AUC_{0-24} was consistently less than 400 in each model, suggesting that similar to adults alternative therapies might be needed in cases of *S. aureus* infection with MIC values of at least 2 mg/l.

Pharmacokinetic and pharmacodynamic characteristics of antifungal agents

Recently several new antifungals including echinocandins and new azoles have been introduced into adult practice, but studies in neonates are still ongoing.

Caspofungin

In a pharmacokinetic study Saez-Llorens *et al.* [31] determined peak and trough concentrations of caspofungin given once daily at a dose 25 mg/m^2 as a 1-h infusion on Day 1 ($n = 6$) and Day 4 ($n = 12$) to patients with PNA of 1–11 weeks and birth weight of 0.68–3.8 kg. Caspofungin peak levels were similar to those in adults after a loading dose of 70 mg/day followed by a maintenance dose of 50 mg/day but lower than in infants and children exposed to the dose of 50 mg/m^2 daily. Trough levels, on the contrary, were slightly elevated compared with those in adults and paediatric patients. The sample size, however, was too small to give any definite recommendations about caspofungin dosing in neonates.

Micafungin

In contrast to caspofungin, which in neonates requires lower doses compared with infants and older children, the weight-adjusted doses of micafungin for neonates exceed those of any other age group by more than four-fold. Two pharmacokinetic studies have recently been published. The first one bridged pharmacokinetic/pharmacodynamic data collected in a rabbit model of hematogenous *Candida* meningoencephalitis (HCME) to neonates by using population pharmacokinetics and MCS [32••]. In animals, micafungin penetrated into the central nervous system (CNS) only after administration of doses exceeding 2 mg/kg; near-maximal effect was achieved following a dose of approximately 8 mg/kg. In premature neonates ($n = 22$), the doses of 0.75, 1.5 and 3 mg/kg, infused over 30 min were studied. The steady state AUC_{0-24} (pharmacokinetic/pharmacodynamic parameter of echinocandins), reached after administration of 9 mg/kg in 9999 simulated neonates, was comparable with 2 mg/kg in children ages 2–17 years and 150 mg in adults. The near-maximal effect in HCME was observed with neonatal doses of 12–15 mg/kg. In the second study, micafungin doses of 7 mg/kg q24 h (patients with birth weight $\geq$1000 g) or 10 mg/kg q24 h (patients with birth weight $<$1000 g) were given for 4–5 days to 13 infants aged less than 120 days [33]. The median AUC_{0-24} was similar to that shown to be adequate for CNS candidiasis in animal models. Both dosing regimens were well tolerated, and the authors recommend these doses to be taken forward to larger clinical studies.

Fluconazole

The fluconazole pharmacokinetic/pharmacodynamic indices for adults with *Candida* infections are AUC of 400 mg $\times$ h/l for clinically stable and 800 mg $\times$ h/l for critically ill patients. The pharmacokinetic/pharmacodynamic parameters for prophylactic use are less clear, but an in-vitro model has indicated that T $>$ MIC of at least 40% may be required to prevent the emergence of resistant *Candida*. Wade *et al.* [5••] analysed fluconazole pharmacokinetic properties with a pop-pharmacokinetic model derived from 357 fluconazole plasma concentrations collected from 55 infants with the gestational age of 23–40 weeks and PNA of 1–90 days. By using MCS, they predicted that infants with invasive candidiasis require a minimum of 12 mg/kg of fluconazole to meet the pharmacokinetic/pharmacodynamic target of 400 mg $\times$ h/ml for *Candida* spp. with MIC of less than 8 μg/ml. For early prevention of candidiasis in 23–29-week infants dosages of 3 or 6 mg/kg given twice weekly will maintain the T $>$ MIC of 40% when MIC values are 2 and 4 μg/ml, respectively. For late prevention, the 6 mg/kg dose every 48–72 h based on gestational age and PNA is required to maintain similar T $>$ MIC.

Conclusion

Studies have shown that with current pharmacokinetic/pharmacodynamic targets many antibiotics used in the treatment of neonatal sepsis fail to cure the infection. Therefore, several new target values such as C_{max}/MIC as high as possible for aminoglycosides, %T $>$ MIC of 100% for β-lactams, AUC/MIC more than 400 for vancomycin and AUC_{0-24} of 800 mg $\times$ h/l for fluconazole have been proposed mostly for critically ill adult patients. Higher therapeutic targets hold higher potential for resistance suppression, an issue of great importance to ensure

ongoing efficacy of available antibiotics. As pharmacodynamic properties of antibiotics in different age groups are largely similar, it is likely that these targets also apply in management of neonatal sepsis. Still, more clinical studies and simulations, preferably in critically ill neonates, are required before these new targets could be recommended for routine practice.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 275–276).

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