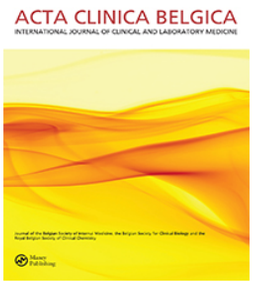

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ORIGINAL PAPER

Neonates are not just little children and need more finesse in dosing of antibiotics

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ABSTRACT

Objectives: Neonates are not just little children. They need more finesse in decisions on when to treat, which antibiotics to use and how to dose these antibiotics.

Methods: Representative compounds of three major classes of antibiotics (beta-lactams, aminoglycosides, glycopeptides) are discussed in a narrative review to illustrate the recent progress in the knowledge on PK and its covariates (how to dose).

Results: This knowledge can subsequently be converted to targeted exposure dosing regimens. This is because it is reasonable to postulate that pharmacodynamics (PD) of antibiotics are similar in neonates to that in other populations if a similar concentration–time profile and targeted exposure are attained. However, this approach has its limitations, since the clinical response may be different in neonates because of maturational differences in innate immunity or toxicity. These dosing regimens should at least be validated.

Conclusion: Relevant information on the PK of antibiotics and its covariates have been generated, but the next steps are to validate the dosing regimens suggested, and consider more sophisticated dosing regimens. This approach should subsequently pave the way to conduct comparative studies to assess the efficacy and safety of these commonly used drugs in neonates.

KEYWORDS
Pharmacokinetics; pharmacodynamics; newborn; antibiotics; PK-PD studies; clinical pharmacology

Introduction: setting the scene

In a recent analysis of a prospectively collected administrative database (2005–2010), it was shown that three of the top five most frequently prescribed drugs in neonatal intensive care units (NICU) were antibiotics (ampicillin, gentamicin, vancomycin), administered to 68, 67, and 9% of admitted neonates, respectively. This top five was further completed by caffeine (16%) and surfactant (8%) [1]. The extensive use of antibiotics in neonates is clearly related to the high incidence of *suspected* serious infections. Ten to 12% of all newborns are screened at birth for early-onset sepsis, while only about 3% of these cases showed evidence for a serious bacterial infection. In retrospect, >95 % of these neonates were exposed to antibacterial agents without a clear indication. On the other hand, late onset sepsis is much more common (0.8% of all neonates, 7% of admitted newborns, the majority in cases < 32 weeks gestational age). Coagulase negative staphylococci are the most common group of pathogens (54%) [2]. This overtreatment with antibiotics in the early-onset sepsis group can in part be explained by population specific outcomes with relevant high mortality (10–12%), while late onset sepsis is associated with neurocognitive impairment [2]. Furthermore, the between unit variability in antibiotic use rate can in part be explained by the volume of surgical cases, the incidence of necrotizing enterocolitis or documented infections, and the level of care [3].

Pathogens to aim for in early-onset sepsis in preterm and term neonates are either Gram-negative organisms, with *Escherichia coli* as the most common Gram-negative pathogen isolated, with *Haemophilus influenzae*, *Citrobacter* spp, or *Enterobacter* spp as less common isolates. Gram-positive organisms are *Group B Streptococcus*, with *Streptococcus viridans*, *Listeria monocytogenes* and coagulase-negative Staphylococci as less common [2]. This explains the choice of antibiotics such as penicillin or ampicillin, gentamicin, or vancomycin [1]. Moreover, the prevalence of multi-resistant pathogens-related infections in neonates has increased and dosing regimens applied within a given unit may affect this prevalence [2]. When comparing two routinely used empiric antibiotic policies (penicillin G + tobramycin *versus* amoxicillin + cefotaxime) for early-onset sepsis, a 18-fold higher risk for colonization with resistant strains was observed in the amoxicillin–cefotaxime regimen [8].

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Clinical care algorithms using an early-onset sepsis risk prediction model reduced the proportion of newborns undergoing laboratory testing (−66%) and receiving empirical antibiotic treatment (−48%) without apparent adverse effects [4]. Intriguingly, the latest NICE (National Institute for health and Care Excellence) guideline on neonatal early-onset sepsis resulted in greater consistency in diagnosis and management, but also in more investigations (repeated C-reactive protein measurements [CRP], increase in lumbar punctures), prolonged length of stay and antibiotic exposure [5]. This is likely because clinical evaluation alone is unreliable to identify infants in the early stages of neonatal infections, while CRP values are time-dependent and only increase after 12–24 h [6]. Decision-making guided by procalcitonin was superior to standard care to reduce the duration of antibiotic administration (52 h instead of 64 h) in neonates with suspected early-onset sepsis [7]. Despite these efforts, the prescription of antibiotics still remains very common.

The setting as described in the introduction necessitates the use of more finesse in decisions on *when* to treat, *which* antibiotics to use, but also *how* to dose antibiotics in neonates. How new data on PK can improve dosing regimens of antibiotics (beta-lactam antibiotics, aminoglycosides, vancomycin) will be the focus of the current narrative review. This will be preceded by an introduction on the specific aspects of clinical pharmacology in neonates. This is because pharmacokinetics (PK) and related maturational and non-maturational covariates are the main drivers of population specific dosing of antibiotics in neonates [9]. Obviously, the challenges to assure safe and effective use and evaluation of antibiotics in neonates are much broader (*when*, *which*, and *how*) and these challenges have been suggested by Jacqz-Aigrain et al. These key issues have been summarized and commented in Table 1 [10].

Table 1. Challenges to ensure safe and effective use and evaluation of antibiotics in neonates [10].

Understand neonatal pharmacology: maturational and non-maturational factors mainly affect the distribution (body water composition, protein binding) and clearance (renal maturation, ibuprofen co-administration, renal impairment)
Understand the specific characteristics of neonatal sepsis: Only 3% of the suspected infections had evidence for a bacterial infection and >95% were in retrospect exposed without need. Late onset sepsis is common, with coagulase negative staphylococci as the most common pathogens. Overtreatment can be explained by population-specific outcome with relevant mortality (10-12%) during early-onset sepsis group and morbidity related to late onset sepsis
Understand the PD of antibiotics: as the isolation of the pathogen is infrequent, the PK-PD relationship is commonly based on the MIC patterns of wild-type pathogens in epidemiologic studies
Get the dose right: Accurate prediction of the similar exposure of antibiotics can be guided by modeling and simulation. Subsequent prospective validation to proof that these exposure targets are reached is a subsequent crucial step
Choose the right empiric treatment and dosage: these decisions should be driven by the epidemiology of neonatal infections, and adapted to susceptibility patterns
Promote adapted monitoring: using validated analytical techniques based on low volume samples, and interpreting results based on valid target exposure and Bayesian models could allow TDM to be performed at the time of routine blood tests
Promote drug evaluation in neonates: it is accepted that antibiotics with proven efficacy in adults and older children do not always need to be tested extensively in neonates. This is described as bridging and extrapolation, and is summarized in the EMA Pediatric Study Decision Tree, and applies to antibiotics
Predict developmental toxicity: randomized controlled trial types of studies on antibiotics in neonates are too limited in number and size to draw robust conclusions on developmental toxicity. Large epidemiological studies and juvenile animal toxicity studies may serve as alternatives
Develop adapted formulations: dosing accuracy relates to the number of manipulations needed, fluid overload may be an issue, and excipient toxicity should be considered

Off label practices and extensive variability in dosing

The clinical outcome of neonates can be improved with the use of safe and effective dosing regimens appropriately investigated in this population [11]. At present, health care professionals involved in neonatal care still routinely (> 90%) prescribe unlicensed drugs or use drugs in an off label manner in the neonatal intensive care setting. This also holds true for antibiotics, and results in extensive unexplained and irrational variability in dosing practices as has been highlighted recently. Considerable between unit variability in antibiotic dosing regimens has been observed in 44 French neonatal units with 444 different regimens for 41 antibiotics, with a mean number of 9 (SD 8), but up to 32 different regimens for a given antibiotic [12]. Similar, the ARPEC (Antibiotic Resistance and Prescribing in European Children) study illustrated that – based on inquiries in 84 pediatric hospitals in 19 European countries – comprehensive antibiotic guideline recommendations are generally lacking, with e.g. guidelines in 71% of the hospitals with 20 different antibiotic dosing regimens for neonatal sepsis [13]. This variability and lack of 'compliance' with dosing recommendations for neonates (BNFc, British National Formulary for children) has been confirmed in a Europe-wide point prevalence study. This is likely because these recommendations are not always evidence based [14].

Because the treatment aims at the infectious organism as target (considered similar between patient populations if similar time-concentration and target concentration profiles are reached) and not the host per se, it is reasonable to assume similarities in antimicrobial pharmacodynamics (PD) between populations (concentration–response relation). Three different main PK-PD patterns have been defined for maximum killing of the pathogen and these patterns depend on the properties of the antibiotic. These patterns are either (1) peak drug concentration > threshold (aminoglycosides), (2) area under the drug concentration time curve > threshold (vancomycin), or (3) time during which the drug concentration remains > threshold (beta-lactam). All these thresholds relate to the minimal inhibitory concentration (MIC) of a given pathogen.

These patterns are not different in neonates, but dosing should be further tailored to their PK characteristics [15,16]. We refer the readers who are interested on the development of PK/PD indices for antibiotics and it use in pediatrics to other papers on this topic since our intention here is to apply these main PK/PD patterns to neonatal dosing regimens [15–17]. If we subsequently assume that neonates are likely less immune-competent, we can shift target concentrations to further improve PD driven targets. To increase the bactericidal efficacy of beta-lactams in neonates, the percentage of free concentrations of the antibiotic > 4 times the MIC can be raised from 50% up to even 100% of the time in neonates [18]. A shift in target concentration is also needed when meningitis is documented since the target effect compartment includes the central nervous system, and dosing should be increased [18]. Using this paradigm, differences in PK and safety aspects are the primary or at least first focus to improve antibiotic prescription in neonates [19].

Clinical pharmacology in neonates: variability is the core characteristic

Similar to any other population, clinical pharmacology in neonates aims to predict drug-specific (side)-effects based on PK and PD. PK (*a*bsorption, *d*istribution, *m*etabolism, and *e*xcretion, *ADME*) describes the drug concentration over time ('*what the body does to the drug*') at a given compartment, like plasma, subcutaneous tissue, or the cerebrospinal fluid in case of meningitis. PD describes the link between drug concentrations and (side)-effects over time ('*what the drug does to the body*') [20]. All these ADME processes are subject to maturational as well as non-maturational changes. Maturational changes relate to age (postnatal, gestational, or postmenstrual age) or weight (birth weight, current weight) while non-maturational covariates relate to disease, environment, treatment interventions (co-medications, extra-corporeal membrane oxygenation, renal replacement therapies), or genetics (pharmacogenetics). This means that the final PK profile will be driven by maturational changes in physiology, but are further affected by co-morbidity [like renal failure, perinatal asphyxia, cardiac failure, sepsis, patent ductus arteriosus] or treatment modalities. As a consequence, neonatal dosing regimens for antibiotics are as heterogeneous as the neonates (10-fold variability in weight, 23–44 weeks age range) admitted to the NICU [21].

For antibiotics, this variability will be driven by differences in elimination, mainly by primary renal (glomerular filtration, renal tubular processes) route and in disposition (body composition, protein binding) [21,22]. Pharmacometric modeling and simulation approaches permit us to characterize population average, inter-subject and intra-subject variability of PK parameters (clearance, volume of distribution). It also permits to identify and quantify key factors ('covariates') that influence the PK patterns of antibiotics in neonates [21,22].

The glomerular filtration rate (GFR) in neonates is mainly based on birth weight and postnatal age with a 2–4 fold increase in GFR in the first 4 weeks of life. The GFR is 20–45 ml/min/1.73 m^2 in the term neonate, with a subsequent progressive increase of 5–10 ml/min/1.73 m^2 for each week. Median GFR values in neonates aged 27–31 weeks gestation range from 7.9 to 30.3 on day 7, 10.7 to 33.1 on day 14, 12.5 to 34.9 on day 21, and 15.5 to 37.9 ml/min/1.73 m^2 on day 28, respectively [23]. However, renal elimination also covers renal tubular transport activity (absorption, excretion). Intriguingly, these processes do not mature simultaneously. Besides maturational changes, GFR patterns can also be affected by disease characteristics, like perinatal asphyxia or respiratory distress or co-medication (ibuprofen, indomethacin) [22,24].

When we focus on disposition, this relates to differences in plasma protein binding capacity and changes in body composition. The total albumin and plasma protein concentration display an age-dependent increase from 24–27 and 44–46 g/l between 24–28 weeks, to 30–32 and 50–52 g/l at 36 weeks of age [25]. Competitive binding of antibiotics (e.g. cefazolin, ceftriaxone) and bilirubin to albumin is a relevant issue. This is also reflected in the fact that ceftriaxone is contraindicated for use in neonates because of the risk of displacement of unconjugated bilirubin and subsequent neurotoxicity [26]. This protein binding capacity does not only influence drug distribution, but also drug action and elimination, since it is the unbound drug that will be distributed, is available for (renal) elimination and will exert a pharmacological effect. To illustrate this, differences in plasma protein binding explain the higher clearance of micafungin in neonates [27], but maturational differences in protein binding of vancomycin or cefazolin may also be covariates of clearance [28,29]. Compared to term neonates, preterm neonates have an even higher relative proportion of body water (80%), which gradually decreases with gestational and postnatal age to reach a plateau (35-40%) at the end of infancy. This is reflected in a proportional higher distribution volume (L/kg) for hydrophilic drugs to distribute in the extra-cellular body water compartment. These differences in both clearance and distribution will be of relevance to develop dosing regimens for beta-lactams, aminoglycosides, or vancomycin tailored for term and preterm neonates to attain these PK/PD indices [30].

Beta-lactam antibiotics

Beta-lactams are bactericidal by binding to penicillin-binding proteins responsible for peptidoglycan cross-linking, resulting in subsequent inhibition of bacterial wall synthesis. Beta-lactams include penicillins, cephalosporins, carbapenems, and monobactams. The

fraction of time during which the free antibiotic concentration remains above the minimum inhibitory concentration (MIC) (% *f*T > MIC) of the relevant pathogens [2] is the PK-PD target, and this target can be shifted to avoid resistance or to adapt for impaired immuno-competence, as in neonates.

Penicillin G clearance increased with increasing birth weight in a cohort of 20 preterm neonates (<32 weeks) in early neonatal life (day 1–3), suggesting that 25,000 IU, q12 h is adequate (time > MIC of at least 50%) in these cases instead of q8 h or q6 h in older (higher birthweight, higher postnatal age) newborns [31,32]. Postmenstrual age and serum creatinine were covariates of *ampicillin* clearance [33]. A simplified dosing regimen of 50 mg/kg, q12 h for GA of ≤ 34 weeks and PNA of ≤ 7 days, 75 mg/kg, q12 h for GA of ≤ 34 weeks and PNA of 8–28 days, and 50 mg/kg, q8 h for GA of > 34 weeks and PNA of ≤ 28 days achieved the surrogate efficacy target (time > MIC 100%) in 90% of events [33]. In the specific subset of neonates undergoing hypothermia because of hypoxic-ischemic encephalopathy (HIE), much lower doses (25–50 mg/kg/day, time > MIC of 50 and 100%, respectively) were suggested because of the associated renal impairment [34]. A similar pattern has recently been described for *amoxicillin* [35] *Cefazolin* is frequently administered for surgical prophylaxis and treatment of infections in neonates, but PK observations are limited and dosing regimens vary [13,14]. A neonatal PK model taking into account total and unbound cefazolin concentrations with saturable plasma protein binding was identified. Weight and postnatal age were the most relevant covariates, and a body weight- and PNA-adapted dosing regimen that resulted in similar exposure across different weight and age groups was proposed (25-50 mg/kg, q8–12 h, time > MIC 60%) [36]. *Cefotaxime* is one of the options to treat Gram-negative bacterial sepsis in neonates while dosing regimens vary considerably [13,14]. Leroux *et al.* recently reported on a population PK study to subsequently improve the dosing regimen, considering PK-PD, pathogens and safety. Covariate analysis showed that weight, gestational and postnatal age were relevant on clearance, and resulted in a dosing regimen of 50 mg/kg, two to four times a day, to improve dosing in older (postnatal age > 1 week and/or gestational age > 32 weeks, time > MIC75%) neonates [37]. *Meropenem* clearance was also affected by creatinine clearance and weight. A Monte Carlo simulation was performed in (pre)terms, exploring 20–40 mg/kg doses, q8 h–q12 h intervals and different infusion durations (0.5 or 4 h). The 8 h interval produced robust target attainments (time > MIC40%), but when more resistant organisms were to be treated (MIC of 4 to 8 mg/L), 40 mg/kg dose and prolonged infusion was suggested [38]. This prolonged infusion approach (20 mg/kg q8 h, 0.5 or 4 h) has recently proven to be more effective (better survival, faster reduction in inflammation) in neonates with culture proven Gram-negative sepsis [39]. *Doripenem* PK confirmed this general pattern with higher distribution volume and lower clearance in the most immature neonates compared to term neonates or young infants (time > MIC70-99%) [40].

Aminoglycosides

The bactericidal efficacy of aminoglycosides in Gram-negative infections, combined with its synergism with beta-lactam antibiotics, limited bacterial resistance and low costs have resulted in the frequent use of aminoglycosides as part of antimicrobial pharmacotherapy in neonates [41]. The ideal dosing regimen would maximize the C_{max}, because the higher the concentration, the more extensive and the faster the degree of bacterial killing. For aminoglycosides, it is best to have a peak/MIC ratio of at least 8-10. [15]. Animal studies and clinical trials in older children and adults documented that a 'one dose per day' regimen of aminoglycosides is superior to a multiple doses per day regimen. In neonates, the currently available evidence is limited to the fact that these target concentrations (gentamicin) are reached more often (higher peak, lower trough level) [42]. While the pharmacodynamic action and bacterial target is obviously the same in neonates compared to children and adults, relevant differences exist in PK [9,41]. In essence, these maturational differences are contradicting, with a higher distribution volume (*so in need for higher mg/kg doses to reach the Peak/MIC ratio*) and lower clearance (*so in need of time intervals even beyond 48 h in the most immature neonates to reach sufficiently low trough levels*) [9,41]. Non-maturational factors are ibuprofen or indomethacin co-administration or HIE with hypothermia.

The suggested targets for *gentamicin* and *tobramycin* are similar (a peak/MIC ratio of at least 8-10). A weight driven dosing interval (5 mg/kg, q24–48 h) resulted in target gentamicin concentrations for both peak and trough levels in the majority of neonates (n = 93/113) [43], while Fjalstad *et al.* reported on the outcome using the same approach (dosing interval q24–48 h) but with a slightly higher gentamicin dose (6 mg/kg) [44]. Using a model-based dosing approach, 4.5–5.5 mg/kg with a dosing interval based on birth weight, postnatal age, and ibuprofen resulted in improved attainment of target concentrations. Similar, but based on a *netilmicin* population PK study, the suggested optimal dosing for netilmicin was 5 mg/kg, q36 h, 5 mg/kg, q24 h, 6 mg/kg, q24 h and 7 mg/kg, q24 h for neonates < 28, 28-30, 31-33, and > 33 weeks of postmenstrual age [45]. However, none of these dosing regimens underwent prospective validation. In contrast, an *amikacin* dosing regimen has been developed and validated, considering current weight, postnatal age and ibuprofen use. This regimen (15-20 mg/kg, q20–48 h,+10–12 h when ibuprofen is co-administered) has been developed based on data collected during routine care, and has subsequently undergone prospective validation [46]. Using a similar

methodological approach, it was observed that amikacin clearance was decreased by 40% in term neonates undergoing cooling for HIE, with the suggestion to increase the dosing interval from 24 to 36 h in these cases [47].

Vancomycin

Studies in adults documented that the PK/PD index of favorable clinical outcome is an AUC over a 24 h period at steady-state divided by the MIC of the suspected pathogen (AUC/MIC) of at least 400 in a *Staphylococcus aureus* lower respiratory tract infections model [48]. The subsequent translation to vancomycin dosing guidelines in neonates is uncertain. This is because PK covariates (protein binding, renal tubular transport) are still only partially understood. In addition, there are differences in pathogens (*Staphylococcus epidermidis*) and target effect compartment (blood) compared to the target in adults. Several dosing schedules have been proposed, based on age (i.e. postmenstrual and postnatal), body weight or serum creatinine. Additional factors like ECMO, indomethacin or ibuprofen co-administration have also been suggested [49].

The currently recommended vancomycin dosing only results in a therapeutic target of AUC/MIC > 400 in a limited number of neonates (25%), and the same holds true when target trough samples (30–35%) are considered [50,51]. To further illustrate the extent of the uncertainty, vancomycin has been dosed below or above recommendations with extensive variability in daily dosing (−100% up to + 60%) in the earlier mentioned European point prevalence study [14]. Vancomycin is usually administered intermittently, with a target trough concentration of 10–15 μg/mL, but there is preliminary experience with continuous administration (after an initial loading dose) [51]. The clinical utility and safety of a model-based patient-tailored dose of vancomycin has been demonstrated in 190 neonates, resulting in a vancomycin target attainment (15–25 mg/L) rate of 72% instead of the former 41% [51]. This dosing regimen was based on a loading dose with a subsequent maintenance dose (determined by birth weight, current weight, postnatal age, recent serum creatinine value), using an individual patient calculator. The European Medicines Agency recently also updated their recommendations. A loading dose of 15 mg/kg is suggested, with a subsequent maintenance doses of 10 mg/kg, q12 h (postnatal age < 8 days) or q8 h (8–28 days) in neonates, with the recommendation to use therapeutic drug monitoring (TDM) [52].

Discussion: How to create progress

Major progress has been made on the knowledge of PK of antibiotics and its covariates in neonates, as illustrated for beta-lactams, aminoglycosides and – to a much lesser extent – for vancomycin. This information has subsequently been converted to dosing recommendations, aiming at similar target exposures as used in non-neonatal populations.

At best, decisions on dosing regimens should be driven by high-quality data with focus on efficacy and safety. These data should pave the way to conduct comparative studies to assess the efficacy and safety of these commonly used drugs in neonates. However, one can question the need for randomized controlled efficacy trials in neonates when efficacy is already established in other populations [17,53]. This concept of extrapolation is part of the pediatric study decision tree [17]. This is because the intervention has the pathogen as target (considered similar between patient populations if similar time-concentration profiles are reached) and not the host per se. A bacteriologic response is expected to be similar to that in other populations so that PK-PD studies can support antibiotic administration in neonates by determining the appropriate dose required for targeted exposure. This should be supported by PK data in the different neonatal subpopulations and covering the relevant maturational and non-maturational factors to proof that indeed the target concentration patterns are reached.

However, it is too simple to stop the product development and knowledge building at that point. It is reasonable to at least validate these dosing regimens to confirm that indeed the target exposure range is attained. At present, the number of such validation studies is still limited [18,43]. Opportunistic sampling strategies, either samples collected for TDM or scavenged samples may be an effective strategy, but heterogeneous sampling times may also introduce systematic errors and affect PK estimates [54]. Second, the target concentration rate may be different in neonates (innate immune immaturity, maturational toxicity). Using the beta-lactam examples to illustrate this uncertainty, the time > MIC applied to develop the dosing regimens varies between and 40 and 100 % [31–40].

In addition, the very same PK estimates can be used to develop more advanced dosing regimens (loading dose, followed by either continuous or prolonged infusion). At present, the shift toward such advanced dosing regimens is limited in neonates. This is in part also because of difficulties related to venous access, stability, compatibility with other drugs co-administered and dosing accuracy [55]. Further improvements in dosing strategies should also consider the use of a loading dose. This is because of the higher distribution volume that may delay attainment of a given minimal concentration, despite the lower clearance.

In conclusion, relevant information on the PK of antibiotics and its covariates have been generated, but the next steps are to validate the dosing regimens suggested as well as consider more sophisticated advanced dosing regimens based on this PK information. This approach should pave the way to conduct comparative studies to assess the efficacy and safety of these commonly used drugs in neonates.

List of abbreviations

NICU neonatal intensive care unit

PK pharmacokinetics
PD pharmacodynamics
NICE National Institute for health and Care Excellence
CRP C-reactive protein
SD standard deviation
ARPEC antibiotic resistance and prescribing in European children
BNFc British National Formulary, for children
ADME absorption, distribution, metabolism, excretion
GFR glomerular filtration rate
MIC minimal inhibitory concentration
PNA postnatal age
GA gestational age
HIE hypoxic-ischemic encephalopathy
C_{max} maximal concentration
AUC area under the curve
ECMO extracorporeal membrane oxygenation
TDM therapeutic drug monitoring

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