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How to Optimize the Evaluation and Use of Antibiotics in Neonates

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Introduction

Drugs are licensed to ensure that their use is safe, effective, and of high quality. However, in pediatric medicine more than 50% of infants, children, and adolescents admitted to a hospital will receive one or more unlicensed or off-label medicines. This circumstance occurs even more in neonates, who represent a particularly vulnerable subgroup of pediatric patients, especially if born prematurely. Although they account for only a low percentage of total drug use in the pediatric age group, up to 90% of medicines in this very young population are used unlicensed or off-label, especially during their stay in a neonatal intensive care unit (NICU).^{1–4} Therefore, the uncertainty about efficacy and the potential risk of adverse events with such a high incidence of unlicensed and off-label drug use is much more relevant for neonates than for older children.⁵

This review, based on the authors' experience with the FP7 TINN (Treat Infections in Neonates) project,⁶ addresses the numerous challenges faced by neonatologists and pediatric clinical pharmacologists to assure safe and effective use and evaluation of antibiotics in neonates.

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Challenge 1: To Understand Neonatal Pharmacology

Irrespective of the kind of drugs prescribed in neonates, understanding the impact of growth and development on the changes in absorption, distribution, metabolism, and excretion of drugs used during the neonatal period is essential.^{7,8}

In neonates, distribution of antibiotics is affected by body composition. The relatively larger extracellular (70%–75% in neonates vs 50%–55% in adults) and total-body water compartments (40% in neonates vs 20% in adults) as well as the lower fat amount (15% in infants vs 20% in adults) affect the distribution of hydrophilic drugs, which are mainly distributed in body water, and to a lesser extent, the distribution of lipophilic drugs. Lower protein binding increases the free fraction of drugs that are highly bound in older children and adults. Drug-metabolizing enzyme activity in neonates by cytochrome P450 oxidases (phase I enzymes) and conjugating enzymes (phase II enzymes) is low, resulting in reduced metabolic clearance of drugs with a high variability between patients. The glomerular filtration rate is much lower in neonates than in older infants, children, or adults, affecting renal clearing capacity. The maturation of renal structure and function includes prolongation and maturation of renal tubules, increase in renal blood flow, and improvement of filtration efficiency, reflected by the rapid changes in the pharmacokinetics (PK) of renally excreted drugs such as amikacin.⁹ The developmental differences and changes in the aforementioned physiology explain that the neonatal population is divided into groups based on gestational and postnatal age.¹⁰

For the majority of antibacterial agents used in the neonatal population, renal excretion is the most important and rate-limiting step in the clearance of the antibiotic or antibiotics prescribed and administered to the ill neonate. It is therefore imperative to have a useful measure of renal function in this vulnerable and rapidly developing, and therefore changing, population.

Challenge 2: To Understand the Specific Characteristics of Neonatal Sepsis

Neonatal sepsis, classified as early-onset and late-onset sepsis, is a major cause of mortality and morbidity, with specific pathogen distribution and infection rates in the different neonatal age groups.¹¹

Sepsis in neonates during the first 48 to 72 hours after birth is defined as early neonatal sepsis. It is usually caused by vertical transmission of group B streptococcal infection.^{12,13} The increased periparturient use of antibacterial agents in women colonized with group B streptococcus appears to have reduced neonatal infection.^{14,15} Data on maternal risk factors for infection and effective strategies to detect maternal colonization are required before validating treatment protocols during labor and delivery.^{16,17}

Sepsis in neonates after the first 2 to 3 days of life is called late-onset neonatal sepsis. It is predominantly caused by gram-positive organisms, with coagulase-negative staphylococci responsible for half the cases of sepsis. The rate of infection is inversely related to birth weight and gestational age and is associated with an increased risk of death.^{18,19} Among others, previous antimicrobial exposure is an important risk factor.²⁰

However, the classic separation between early-onset and late-onset infection may be questioned, as recent data in neonates suggest that extensive antibiotic use results in changes in the spectrum of organisms from predominantly gram-positive to predominantly gram-negative pathogens, with a significant increase in the incidence of *Escherichia coli*.^{19,21}

Suspected infections are quite frequent in neonatal care, but microbiologically evaluable infections are rare: 1 to 2 cases per 1000 live births. Treatment is an emergency, and if treatment is delayed or ineffective, neonatal sepsis can be rapidly fatal; therefore, empiric parenteral antibiotics are always administered when this condition is suspected, mostly on clinical grounds alone.²²

In addition to systemic bacterial infections, invasive candidiasis is also an important and often fatal pathogen in the preterm neonate of very low birth weight. Invasive candidiasis frequently results in increased morbidity, prolonged stay, death, or neurologic damage. Despite antifungal treatment, 20% of infants who develop invasive candidiasis die as a result of disease, and neurodevelopmental impairment occurs in nearly 60% of the survivors. Data from the literature and one large multi-center randomized controlled trial have shown that antifungal prophylaxis provides an effective approach to decrease the morbidity and mortality of invasive candidiasis in the premature infant, primarily in centers with a high incidence of fungal infection.²³ Although important, the use of antifungal agents is not within the scope of this review.

Challenge 3: To Understand the Pharmacodynamics of Antibiotics

Pharmacokinetics (PK) is the study of the time course of antimicrobial concentrations in the body, whereas pharmacodynamics (PD) defines the relationship between antimicrobial concentrations and its effect. The 3 PK parameters that are most important for evaluating antibiotic efficacy are the peak serum (plasma) concentration (C_{max}), the trough concentration (C_{min}), and the area under the serum concentration versus time curve (AUC). The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC) of the pathogen, that is, the lowest concentration of an antibiotic that completely inhibits the bacterial growth in vitro. Integrating the PK parameters with the MIC has resulted in 3 PK/PD parameters: the peak/MIC ratio, the T>MIC (percentage of dose interval in which the serum level exceeds the MIC), and the 24-hour AUC/MIC ratio (determined by dividing the 24-hour AUC by the MIC). Based on these parameters, the bacterial killing activity is primarily defined as time dependent or concentration dependent.²⁴

For concentration-dependent killing antibiotics with prolonged persistent effects (eg, aminoglycosides, fluoroquinolones), the 24-hour AUC/MIC ratio and the peak/MIC ratio are important predictors of antibiotic efficacy. The optimal dosing regimen should maximize concentration, because the higher the concentration, the more extensive and faster the degree of killing.

For time-dependent killing antibiotics (eg, penicillins, cephalosporins, carbapenems), the dosing regimen should maximize the duration of exposure.

For time-dependent killing antibiotics with moderate persistent killing (eg, vancomycin, azithromycin), the optimal dosing regimen maximizes the amount of drug received.

PK/PD markers, highly correlated with clinical cure, pathogen eradication, and even resistance development, have been identified for many antibacterial agents in adults. As a consequence, in neonates it is highly recommended to perform PK/PD studies instead of simple PK studies. However, as the isolation of the infective agent is infrequent, the PK/PD relationship is rarely based on the “true MIC” and the MIC distribution for wild-type pathogens, based on large epidemiologic and microbiological studies, are used.^{25,26}

Challenge 4: To Get the Dose Right

As PK parameters of drug disposition vary widely between neonates, identical dosing regimens may provide different total exposure and PK profiles.²⁷ Therefore, “to get the dose right” is one of the greatest challenges in neonatal drug development.²⁸

Until recently, dosages were extrapolated from adult data by the use of simple allometric methods, based on empiric scaling factors such as body weight or body surface area, and PK studies were conducted a posteriori in treated neonates. Pharmacokinetic studies, either classic (rich sampling) or population (sparse sampling), are now recommended although they remain difficult to perform.^{29–31} Whatever the approach, in clinical practice it boils down to getting the dose right by exposing either a low number of neonates to high sampling³² or a high number of neonates to limited sampling without knowing if the selected dose is optimal.^{33–35} An intermediate proposal might be to perform an initial rich pilot study with 2 to 4 samples drawn in a limited number of infants, which consequently can be further validated by a population PK study embodied in a larger PK and/or efficacy trial. However, such a recommendation does not support the selection of the first dose to be administered in neonates.

Validation of the population PK models is required to test their predictive performance. For example, many models have been developed for vancomycin, an antibacterial agent widely used in staphylococcal infections, and an external validation has shown that, among potential other factors, the analytical techniques to measure serum creatinine as well as vancomycin concentrations had a clear impact on the prediction of vancomycin concentrations, and that dosage individualization of vancomycin in neonates should be considered.

Modeling and simulation can guide initial dosage recommendations in neonates, taking into account available information on drug characteristics, efficacy, and safety.³⁶ The use of physiologically based pharmacokinetic (PBPK) models are especially aiming at simulation of drug concentrations in the circulation and in tissue(s) at the individual or population level. These models can also account for age-related variability and, consequently, may be used to predict the PK of drugs in children from data in adults or from one pediatric “old” age group to a younger one.³⁷ Such models have already shown that they might be of great interest for use in neonates.³⁶ However, they will be even better performing with additional physiologic data that are still missing in preterm infants, including biological parameters.

Challenge 5: To Choose the Right Empiric Treatment and Dosage Schedule

Antibiotics are prescribed extensively in NICUs, as shown recently by a large cohort study over an 8-year period.³⁸ The major risk of such extensive use of broad-spectrum antibiotics is the induction and emergence of resistance, which is particularly true when using third-generation cephalosporins, a combination of broad-spectrum antibiotics, and/or prolonged antibacterial treatment. Major consequences of the emergence of resistant bacterial strains may include prolonged hospital stay, adverse drug reactions, and adverse neurodevelopmental outcomes associated with infection. Additional consequences include changes of the microbial flora or an increased risk of nosocomial infection.

For all these reasons and to optimize treatment, antibiotics should be selected based on the epidemiology of neonatal infections, and adapted to susceptibility patterns. For this reason, many countries have established surveillance networks to monitor changes in pathogens, and to detect changes in antibiotic sensitivity and occurrence of bacterial resistance. Moreover, data on the epidemiology of specific infections in various countries are available, such as group B streptococcus, methicillin-resistant *Staphylococcus aureus*, and fungal infections. In addition, surveys are conducted to search for modifications in clinical practices and/or drug prescriptions.

Antibiotics are usually administered intravenously either at repeated doses with a constant dosage interval or as a continuous infusion, depending on the antibiotic. For drugs with linear elimination given at a fixed dosage regimen, drug concentrations reach a steady state after 4 to 5 half-lives. In neonates, elimination is often longer than in infants or children, and a loading dose may be recommended to reach steady-state concentrations earlier.

Challenge 6: To Promote Adapted Monitoring

Therapeutic drug monitoring (TDM) aims at measuring individual drug exposure based on validated concentrations or PK parameters that better reflect drug effect than drug dosage.³⁹ Optimal interpretation of the results requires a validated therapeutic range. One major limitation of TDM in neonates is that, for many medications, target concentrations are not defined in children but are only based on data obtained in adults. Indeed, for antibiotics the target range validated in adults is always used in children, including neonates, although additional data are required to validate that such bacteriologic targets are associated with efficacy in neonatal sepsis.

An important issue in neonatal TDM is the availability of bioanalytical assays validated for use of very small sample volumes. To optimize TDM, analytical methods adapted to the age of the patients, particularly for neonates, have to be developed and validated. Immunoassay techniques are widely used for TDM but, although often regarded as specific for the parent drug, the antibody may cross-react with other compounds, including metabolites of the drug. Therefore, the concentrations are often overestimated. In general, these differences do not affect significantly the clinical value of TDM, although they have an impact on the target concentration and contribute to the variability of drug concentrations reported in the literature.

Dried blood spot (DBS) sampling is an interesting option for TDM in neonates, as it is less invasive, it avoids classic venous blood sampling, it requires smaller blood volumes (less than 100 μ L), its storage is simpler, and its transfer is easier at room temperature.^{40–44} DBS is increasingly used for TDM of a wide spectrum of drugs including antibiotics, although assay sensitivity and specificity are still a challenge. The interpretation of drug concentrations measured during TDM should take into account all aspects and conditions of monitoring (including dose and dosage schedule, the type of biological sample, analytical techniques used, initiation of treatment, potential drug interactions, and so forth) and use of reference concentrations to make recommendations for dosage adjustments.

It is important to bear in mind that detailed information on neonatal disease and clinical conditions, biological parameters of interest, drug, dosage regimen and associated therapies, and time of sampling relative to the time of drug administration are essential to interpret TDM.⁴⁵

Challenge 7: To Promote Drug Evaluation in Neonates

Profound changes occurred over the past 10 to 20 years as the American and European regulations on the pediatric use of drugs encouraged the development of medicines for all pediatric age groups,^{46,47} with the intention of having a major impact on drug evaluation in pediatric patients of all ages.^{48–50}

However, there are major practical and ethical issues in evaluating medicines in preterm and term neonates. The gold standard for evaluating efficacy of antibacterial agents is a randomized controlled trial (RCT). However, for many reasons these kinds of trials are very difficult to conduct in neonates. Indeed, neonates are still less likely to be involved in an RCT.^{51,52} In a recent study, the authors analyzed published RCTs conducted to evaluate antibiotics in neonates since 1995, and have shown that the number of RCTs of antimicrobial agents in neonates is small, as well as being poorly designed, conducted, and reported. Moreover, the necessity of conducting RCT trials, when antibacterial efficacy has already been established in other age groups, is questionable, and suitable methodological approaches are required to allow optimal drug evaluation. Specific guidelines, designed by experts, are available for the investigation of medicinal products in the term and preterm neonate,⁵³ as well as guidelines related to clinical trials in small populations, PK studies, and pharmacovigilance.⁵⁴

As previously stated, neonatal bacterial infections are mainly suspected and are confirmed in only a limited number of cases, and antibiotic treatment protocols are designed in a probabilistic manner, according to local bacteriologic epidemiology and resistance patterns.

In these situations, evaluation of antibiotics remains a challenge,^{55–57} as “new antibiotics” are introduced to the therapeutic arsenal because of their expected therapeutic benefits. Accordingly, individual clinicians are reluctant to randomize patients to an agent that they already use with highly expected benefit, which is particularly true for drug-resistant bacterial infections that require effective antibiotics, even if evaluation in neonates is limited. This fact explains why, in the absence of validated dosing regimens, major

differences in dose administration and schedules may occur between countries or even between NICUs in the same country, as shown for ciprofloxacin.

In most cases, antibiotics have proven efficacy in adults and older children, and it is accepted that medicines that work in adults and older children do not always need to be tested extensively in neonates. This aspect is described as bridging and extrapolation, and is summarized in the Decision Tree of the European Medicines Agency (EMA)/Food and Drug Administration (Fig. 1). However, intrinsic neonatal factors such as the innate immune immaturity that may result in a broader dissemination of the infection and/or other medical factors, in addition to important limitations in diagnostic means, may influence the antibiotic's clinical efficacy; this is the reason why data on therapeutic response (clinical efficacy) must also be collected.

As random allocation of treatment is difficult, or even impossible, for all the reasons previously discussed, effects of clinical treatment may be assessed by means of observational, nonrandomized studies. However, these studies may be hampered by several reasons for bias. When the efficacy of an antibiotic has already been demonstrated in adults, necessary data on effectiveness in neonatal use can be provided by the combination of PK/PD and clinical observational studies.⁵⁸ Indeed, observational studies generally have an important role in quantifying drug effects under the conditions of usual practice (effectiveness) whereas RCTs demonstrate drug effects under restricted conditions in terms of disease, comorbidities and concomitant treatment (efficacy). Various approaches are available such as adjustment for predefined pretreatment variables or the creation of a propensity score (ie, probability of being treated according to predefined prognostic factors).^{59,60} Therefore in most cases, applications for a product license concerning antibiotics in neonates should include reliable information on the product's dosing recommendations and safety by means of trials that do not necessarily include a randomization step for treatment allocation.

Challenge 8: How to Predict Toxicity—Room for Juvenile Animal Studies

When evaluating antimicrobials, the targets are pathogenic bacteria, and consequently any effects on human cells and tissues are, by definition, adverse.²⁷ This fact underscores the importance of safety evaluation, as the profile of adverse reactions may greatly differ between newborns and older children or adults. RCTs are often too limited in patients' sample size or too short in duration to detect any adverse events, which can be rare or may occur many years after treatment discontinuation. Indeed, most of the available information about adverse events has been derived from observational studies even in the adult population. Observational studies, either case-control or large-scale observational follow-up studies, enable adequate assessment of drug safety and have been proved to be more adequate than RCTs in evaluating safety issues.⁶¹ Observational controlled studies should be implemented to obtain information on antibiotic safety in neonates, until 1 or 2 years of age, and should be completed by longer follow-up studies including patients who were exclusively treated with the test antibiotic until school age (6–7 years) as recommended by regulatory guidelines.⁶²

Juvenile animal studies are recommended by the EMA.⁶³ As an example, juvenile mice studies were performed in the TINN project to evaluate the potential effects of ciprofloxacin, namely, impact on growth, neurodevelopmental toxicity, and articular toxicity. As previously stated, juvenile animal toxicity studies can be useful, although considerations on species' specificity and concerns about the physiologic comparability with humans are numerous.

Challenge 9: To Develop Adapted Formulations

Formulations for use in neonates are required because in most cases, available age-appropriate formulations are either too concentrated, requiring multiple dilutions associated with dilution errors, or too diluted, associated with liquid overload, or even contain excessive quantities of drugs that are thrown away.^{63,64} Although extensively debated and with a strong consensus among all specialists that there is a need for formulations specifically adapted to neonates, it is clear that all currently available incentives will not, in the majority of cases, result in a neonatal formulation that is commercially viable, at least in indications where the number of neonates to be treated is low.

Summary

A pediatric study decision tree was designed to help researchers extrapolate existing knowledge on drugs from adult studies and ultimately avoid unnecessary trials in pediatrics.⁶⁵

For antibiotics, the bacteriologic response is expected to be similar to that in adults. Therefore, PK/PD studies can support antibiotic administration in neonates by determining the appropriate dose required for targeted exposure. Extrapolating a PK/PD relationship from adults and/or children to neonates with limited PK data collected for model validation in neonates,⁶⁶ as well as using PBPK models to link dose, concentration, and response data, should be implemented.

Nevertheless, because neonatal infections present with several unique characteristics related to individual neonatal and environmental factors, the clinical response data might differ between age groups, and additional data on antibiotic response should also be collected. RCTs and methodologies specific to the neonatal population are very difficult to conduct for many reasons, but they still should be considered.

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Key Points

- A pediatric study decision tree was designed to help researchers extrapolate existing knowledge on drugs from adult studies and ultimately avoid unnecessary trials in pediatrics.
- For antibiotics, the “bacteriologic response” is expected to be similar to that in adults. Therefore, pharmacokinetic (PK)/pharmacodynamic (PD) studies can support antibiotic administration in neonates by determining the appropriate dose required for targeted exposure.
- Extrapolating a PK/PD relationship from adults and/or children to neonates with limited PK data collected for model validation “in neonates,” as well as using physiologically based PK models to link dose, concentration, and response data, should be implemented.
- Because neonatal infections present with several unique characteristics related to individual neonatal and environmental factors, the clinical response data might differ between age groups, and additional data on antibiotic response should also be collected. Randomized controlled trials and methodologies specific to the neonatal population are difficult to conduct for many reasons, but they still should be considered.

Fig. 1.

Pediatric study decision tree. (From U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Exposure-response relationships—study design, data analysis, and regulatory applications. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, 2003. Available at: <http://www.fda.gov/cber/guidelines.htm>.)