Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey

Stéphanie Leroux,1,2,3 Wei Zhao,1,2,4,5 Pierre Bétrémieux,3 Patrick Pladys,3,6 Elie Saliba,7 Evelyne Jacqz-Aigrain,1,2,4 on behalf of the French Society of Neonatology

INTRODUCTION

Neonatal bacterial sepsis, classified as early or late onset, is a major cause of mortality and morbidity, particularly for premature neonates.1,2 Suspected infections are quite frequent in premature newborns and empirical antibiotic therapy is an emergency. If treatment is delayed or ineffective, neonatal sepsis can be rapidly fatal, making optimal use of antibiotics essential.

Previous work demonstrated a considerable variation of dosage regimens of vancomycin and gentamicin among UK neonatal intensive care units.3 This implies that either toxic or subtherapeutic treatment courses may exist in neonatal clinical care, which obviously impacts clinical outcomes, especially for drug with narrow therapeutic index, such as aminoglycosides and vancomycin. We speculated that the variation in the dosage regimens is a common problem for antibiotic therapy in neonates because of limited number of high quality pharmacokinetic–pharmacodynamic studies. We surveyed local guidelines for antibiotic therapy in all French NICUs to evaluate the current local dosage recommendations.

METHODS

Data collection

A total of 56 level 3 NICUs were identified from the directory of French paediatric intensive care network (Groupe Francophone de Réanimation et Urgences Pédiatriques): 54 metropolitan and 2 overseas. A senior doctor from each NICU was contacted by phone and/or email between May and June 2013 to participate in this survey.

Therapeutic guidelines and data extraction

All local therapeutic guidelines typically included various antibiotics, each of them with different dosage regimen defined by a dose and a dosing interval, based primarily on patients’ variables such as age, weight and/or renal function. The following were extracted for each antibiotic in all guidelines: (1) drug name; (2) lower and upper bound

Most antibiotics are used off-label in neonates.

Local practice is variable to manage antimicrobial therapy in neonates.

Previous work demonstrated a considerable variation of dosage regimens of vancomycin and gentamicin among UK neonatal intensive care units.
values for the daily doses (mg/kg/day) and dosing intervals (h); and (3) variables for dosage individualisation, when used (i.e., age or weight). Exclusion criteria included: (1) dosage recommendations for infants with a postmenstrual age over 44 weeks\(^4\) or (2) therapeutic guidelines for meningitis.

Data analysis
The number of antibiotics in each local guideline, the number of dosage regimens and the distribution (minimum, median, maximum) of the lower bound and upper bound of daily dose and dosing interval in each local guideline were described for each antibiotic. Median of daily doses and dosing intervals for all the guidelines were calculated for each antibiotic. Inter-centre variability was assessed by comparing the medians of the daily dose and dosing interval among NICUs using non-parametric statistical test of Kruskal–Wallis (\(n > 2\) medians) or Mann–Whitney-Wilcoxon \((n=2\) medians). Statistical analyses were conducted using R software (V3.0). A value of \(p < 0.05\) was considered statistically significant.

RESULTS
All 56 French level 3 NICUs were contacted: 3 declared no local antibiotic guidelines and 9 declined participation. Thus, 44 (79%) agreed to participate.

Each local guideline included a mean of 16 antibiotics (range 5–24). A total of 41 antibiotics were identified, including 19 beta-lactams, 4 aminoglycosides, 2 glycopeptides, 3 fluoroquinolones, 6 macrolides, 2 imidazoles, 1 sulphonamide and 4 other antibacterial agents. They are administered intravenously \((n=31)\), orally \((n=3)\) or both \((n=7)\). Intravenous administration was either intermittent \((n=37)\) or both intermittent and continuous \((n=1)\), with a loading dose strategy in 4 cases (metronidazole, ornidazole, teicoplanin, vancomycin). The different sources from which the local guidelines were developed are illustrated in figure 1.

Inter-centre variability in daily dose and dosing intervals
Antibiotics with significant inter-centre variability in median daily doses and dosing intervals are presented in table 1.

**Daily dose**
The daily doses were significantly different among NICUs for 9 antibiotics, administrated intravenously.

Maintenance daily doses were significantly different among NICUs for 8 antibiotics (amikacin, penicillin G, imipenem/cilastatin, netilmicin, cloxacillin, oxacilline, metronidazole, ceftazidime); 4 of them (amikacin, imipenem/cilastatin, metronidazole, ceftazidime) were included in more than 70% of local guidelines and their median daily doses varied from 2 to 5 times. Table 1 compared their doses in local guidelines with doses recommended by Neofax and Redbook. Loading doses were significantly different for continuous infusion vancomycin \((p < 0.001)\), which was included in 78.4% of local guidelines. The loading dose varied 3 times \((7–20 \text{ mg/kg})\).

**Dosing intervals**
The dosing intervals were significantly different for 5 antibiotics: gentamicin \((p < 0.001)\), amikacin \((p < 0.001)\), netilmicin \((p < 0.001)\), tobramycin \((p < 0.001)\) and clindamycin \((p = 0.023)\). Gentamicin and amikacin were included in more than 70% of local guidelines and median dosing intervals varied 3.5 times \((12–42 \text{ h})\) (table 1).

**Dosage individualisation**
A total of 444 dosage regimens (407 intravenous and 37 oral) were used in French NICUs for 41 antibiotics. The number of

---

**Figure 1** Sources for local guidelines.
Drug therapy

In order to obtain a marketing authorisation for neonatal use and patient dependant. Therefore, appropriate neonatal dosing microorganisms provided by ratio, MIC is based on sensitivity and resistance breakpoints of 396 Leroux S, the inhibitory curve AUIC (i.e., the AUC24 to MIC ratio of the while dosing will be ultimately determined by the area under clinical suspicion. The initial choice of antibiotic therapy will treatment has to be started as early as possible and merely upon variations in neonates and developing evidence-based therapeutic per drug, with important differences in daily doses, dosing intervals and covariates used for dosage individualisation. These data highlighted the urgent need to optimise antibiotic prescriptions in neonates and developing evidence-based therapeutic consensus from already available data.

Antibiotics are extensively prescribed in neonates as infections are frequent and associated with a high risk of morbidity and mortality. However, few antibiotics have been evaluated in order to obtain a marketing authorisation for neonatal use and most of them are used off-label. As microbiologically evaluated infection is rare in neonates, treatment has to be started as early as possible and merely upon clinical suspicion. The initial choice of antibiotic therapy will depend on the clinical context and local bacterial epidemiology, while dosing will be ultimately determined by the area under the inhibitory curve AUIC (i.e., the AUC24 to MIC ratio of the antibiotic area under the concentration–time curve to the organism’s minimum inhibitory concentration). To determine such ratio, MIC is based on sensitivity and resistance breakpoints of microorganisms provided by ‘The European Committee on Antimicrobial Susceptibility Testing—EUCAST’ or by the ‘Clinical Laboratory Standards Institute’ while AUC is patient dependant. Therefore, appropriate neonatal dosing needs to integrate the rapid developmental changes of the neonatal period, as reflected by covariates influencing drug disposition. Depending on the drug, these covariates are markers of size and maturation and may include gestational, postnatal, post-menstrual age, creatine concentration liver function tests and so on. Additional variables may be tested: disease, associated drugs, cardiovascular and ventilatory support.

Accordingly, regulatory guidelines recommend pharmacokinetic modelling and simulation approaches to establish neonatal dosage recommendation of antibiotics, underlying the importance of well designed pharmacokinetic studies.

However, evidence-based dosing regimens to support optimal prescriptions are lacking for almost all antibiotics in neonates, as illustrated by the two extreme examples of amikacin and metronidazole.

(1) For amikacin, 19 different neonatal dosing regimens are proposed in the literature and 31 were identified in the present study. None of them were clinically validated resulting in the lack of consensus on the optimal dosage regimen to be used in neonates. A consensus on neonatal dosing can only be evidence-based and requires a validated pharmacokinetic model (with both internal and external validation) but also clinical evaluation of the proposed regimen by a prospective efficacy and safety study. As pharmacokinetic studies in neonates usually have a limited number of patients included in many centres, study-related factors (such as characteristics of the neonates included, analytical methods to measure biological covariates or drug concentrations.) may have an important impact when extrapolating the published results to different clinical settings. In such cases, population pharmacokinetic meta-analysis might ensure thorough understanding of study-related pharmacokinetic differences in drug disposition, a prerequisite for clinical evaluation of efficacy and safety.

(2) For metronidazole, only 2 population pharmacokinetic studies with a limited number of neonates (n=32) have been published even though the drug has been used for many

---

### Table 1: The daily doses and dosing intervals of antibiotics with significant inter-centre variability: comparison with Neofax and RedBook

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Minimal daily doses</th>
<th>Maximal daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survey results</td>
<td>Neofax</td>
</tr>
<tr>
<td>Amikacin</td>
<td>(Min–max)</td>
<td>(mg/kg/day)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>4.0–15.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>50.0–200.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Imipenem/cilastin</td>
<td>20.0–75.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2.0–6.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>50.0–180.0</td>
<td>NA</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>25.0–180.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>3.75–30.0</td>
<td>3.75</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>25.0–200.0</td>
<td>60.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Minimal dosing intervals</th>
<th>Maximal dosing intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survey results</td>
<td>Neofax</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>6–8</td>
<td>8</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8–48</td>
<td>24</td>
</tr>
</tbody>
</table>

NA, not available.
years for treating complicated abdominal infections in neonates. Additional data are obviously required as treated patients are highly variable from extremely low birth weight to term neonates.

The French inter-NICU variability reported in this survey almost certainly reflects more common situations encountered in European countries or at the international level. Indeed, such heterogeneity in clinical practice is in agreement with previous data evaluating the dosage recommendations of vancomycin and gentamicin or ciprofloxacin. The National Institute of Health and Care Excellence guidance recommends a unique gentamicin starting dose of 5 mg/kg every 36 h for early onset neonatal infection treatment; however, the current clinical practice is variable for gentamicin therapy. In UK survey, 24 different combinations of dose were revealed and the dosing interval varied markedly from 12 to 48 h. In a French survey, we found 25 different combinations of doses and the dosing interval varied from 8 to 48 h. For vancomycin, clinical practice is even more variable in France, as both of continuous infusion and intermittent infusion were routinely used. Our results are also consistent with the previous findings by Porta et al who reported wide variation between four children’s hospitals in the type and dose of antibiotic used in paediatrics based on daily prescription data.

We further compared the doses in local guidelines with dosages recommended by Neofax and Redbook as they are frequently used reference books by neonatologists. Inconsistencies were highlighted, e.g. for ceftazidime, Neofax recommends 30 mg/kg per dose every 8 or 12 h according to postmenstrual age and postnatal age, while Redbook recommends 50 mg/kg per dose every 8 or 12 h according to body weight and postnatal age. Reaching a consensus on antibiotic therapy in neonates is urgently required, but will need close collaboration between paediatric pharmacologists and neonatologists.

Such variability in local guidelines, along with the paucity and poor quality of randomised controlled trials, highlights the difficulties in studying cases assessing the effects of antibiotics in neonates despite regulatory initiatives that encourage drug studies in neonatology. Several factors may explain this situation: (1) signs of neonatal sepsis (either early or late onset sepsis) are unspecific and antibiotic treatment has to be started as early as possible and merely upon clinical suspicion; (2) the empirical treatment varies between units, as it depends on local epidemiology and clinical context; (3) antibiotics with proven efficacy and safety in older paediatric patients or even adults frequently enter neonatal care because clinicians perceive them to have a more adapted spectrum of activity and/or better risks to benefit ratio than the currently used antibiotics; and (4) in such emergency situations, and whatever the study design (pharmacokinetics and safety or randomised controlled trial for efficacy), informed consent is difficult to obtain.

In conclusion, this survey analysed the multiple dosage regimens to be followed to prescribe antibiotics in the French NICUs. A wide inter-centre variability was evidenced in terms of daily doses, dosing intervals and covariates used for dosage individualisation. Obviously, evidence-based dosage regimens of antibiotics should be validated for neonatal treatment on the basis of developmental pharmacokinetics-pharmacodynamics.

**Author affiliations**

1. Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP, Paris, France
2. EA7233, Université Paris Diderot-Université Paris Descartes, Paris, France
3. Division of Neonatology, Department of Child and Adolescent Medicine, CHU de Rennes, Rennes, France
4. Clinical Investigation Center CIC1426, INSERM, Paris, France
5. Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan, China
6. INSERM U1099, Institut des Neurosciences Cliniques de Rennes, Rennes, France
7. Paediatric and Neonatal Intensive Care Unit, CHRU Tours, Tours, France

**Acknowledgements** We acknowledge all neonatologists from paediatric and neonatal intensive care network (listed in alphabetic order) who participated in this survey (CH: centre hospitalier): Amiens CHU (C. Gougolos), Angers CHU Hôpital Dieu (S. Le boudec, B. Lebouche), Arras CH (B. Thenet, L. Desnoulez), Bayonne CH de Côte Basque (P. Louvecrè), Biarritz Hôpital Biarritz (D. Devictor, L. Chevret), Brest CHRU Morvan Breiz (A. Garenne, J. Mouel, R. Caen), Hôpital Côte de Nacre (B. Guillou, A. Cencir), Calais CHM (M. Thielleau, L. Egeret), Clamart Hôpital Antoine Béclère (O. Romain), Chambery CH (M. Deiber), Cherbourg CH public du Cotentin (S. Saumureau), Clermont-Ferrand Hôpital Etaing (B. Bœuf, V. Pointier), Creteil—CH Intercommunal (C. Danan, X. Durmeyer), Grenoble CHU Hôpital Couple Enfant (T. Debillon, L. Marcus, F. Audeoud), Lens CH Docteur Schaffner (C. Moreot, S. Klosowsky), Lille Hôpital Jeanne de Flandre (L. Stam, A. Fily), Lyon Hôpital Femme Mère Enfant (O. Clairis, F. Plaisant), Lyon Hôpital Croix Rousse (J. C. Picaud, I. Jordan), Marseille Hôpital Nord (U. Simeoni, S. Hassid), Marseille Hôpital de la Conception (U. Simeoni, L. Ligi), Montpellier hôpital Arnaud de Villeneuve (G. Gambone, R. Mesnage), Montpellier Hôpital Arnaud de Villeneuve (L. Nkhléle), Nantes Hôpital Mère-Enfant (J. R. Roccé), Nice Hôpital Archet 2 (C. Dagaveille), Nîmes CHU Careneau (J. B. Mariette), Noumea Hôpital Magenta (L. Tauzin), Paris Hôpital Cochin (P. J. Jarreau), Paris Hôpital Necker Enfants-Malades (P. Hubert, M. Nicloux), Paris Hôpital Robert Debré (O. Baud, V. Biran); Paris Hôpital Tronseau (D. Mitanchez, F. Kieffer), Perpignan Hôpital Saint Aimé (J. Thevenot, R. Mesnage), Poissy CH Intercommunal (P. Boileau, G. Cirialo), Rennes Hôpital René Dubos (R. Boit), Reims Hôpital Maison Blanche (P. Hourvin), Rouen Hôpital Charles Nicolle (S. Marret), Rennes Hôpital sud Anne de Bretagne (P. Pladys, P. Bettemieux), Saint Brieuc Hôpital Yves Le Foll (E. Boutejac), Saint Denis La Reunion CHU Felix Guyon (S. Saperus, D. Ramfial), Strasbourg Hôpital Haupteipierre (D. Astruc, L. Palpacuer), Tours Hôpital Clocheville (E. Sallia, A. Bouissou), Troyes CH (I. Arnauld), Valenciennes CH (F. Lapeyre, M. Hassan), Vannes CH Bretagne Atlantique (H. Journel, H. Bourdial).

**Collaborators** Société Française de Neonatologie (http://fsdn.perinat-france.org/SFN).

**Contributors** SL, ZW and EJ-A defined the study. SL contacted the NICUs with the participation of PB, PP and ES. SL, ZW and EJ-A planned the analysis. SL performed the analysis and wrote the first draft of the manuscript. WZ and EJ-A reviewed the manuscript; the last version was validated by all authors.

**Funding** This work was supported by “Treat Infections in Neonates network” (TINN1 and TINN2, EU-funded FP7 projects, Grant Agreement numbers no 223614 TINN1; no 260908 TINN2) and Global Research in Paediatrics—Network of Excellence (GRIP, EU-funded FP7 project, Grant Agreement number 261060).

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Drug therapy


11 http://www.eucast.org


