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**Original Research**

# Medication follow-up in newborns with extremely low birth-weight

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## Abstract

**Objective**: The medication follow-up in infants with extremely low birth-weight in a neonatal intensive care unit is described, identifying drug-related problems (DRP), drug-related negative outcomes, and the relationship between the occurrence of DRP and birth-weight of newborns and their impact on pharmacotherapy and length of hospital stay.

**Methods**: A descriptive and exploratory study was performed in which medication follow-up of a population of infants with extremely low birth-weight admitted to the neonatal intensive care unit of a government-run maternity hospital was carried out by clinical pharmacists. Monitoring comprised assessment of patients' pharmacotherapy needs through visits to the neonatal unit, evaluation of prescriptions and information on medical records, identification of issues associated with pharmacotherapy and follow-up of the newborns' clinical evolution to determine whether desired results were achieved.

**Results**: The subjects were 33 infants characterized by extremely low weight at birth. Analysis of patients' pharmacotherapy showed that 39.4% (n=13) of the neonates presented some type of DRP, totaling 37 DRPs and a mean of 2.8 problems/patient. Fourteen drugs were identified with the occurrence of DRP. Vancomycin and cefepime were the most prevalent, with 18.9% (n=7). Occurrence of DRPs and several clinical characteristics of newborns and their pharmacotherapy were compared. The most prevalent drug-related negative outcomes identified were "untreated health problem" (40%, n=10) and "quantitative ineffectiveness" (32%, n=8). Pharmaceutical interventions were performed for all problems associated with pharmacotherapy, with a prevalence of "treatment day count correction" and "dose correction", both with 21.6% (n=8), and "correction of dosage" (16.2%, n=6).

**Conclusion**: The research evidenced the role of the clinical pharmacist in the solution and prevention of drug-related problems, contributing with the multidisciplinary team to obtain a safe and effective pharmacotherapy. Further, current study confirmed that there is an association between the characteristics of the newborns under analysis (eg. birth-weight, pharmacotherapy) and the occurrence of drug-related problems.



## Keywords

Infant, Extremely Low Birth Weight; Birth Weight; Intensive Care Units, Neonatal; Pharmaceutical Services; Pharmacists; Length of Stay; Patient Care Team; Follow-Up Studies; Brazil


## INTRODUCTION

Global statistics reveal that one in every ten low birth weight newborns are preterm infants with extremely low birth-weight (<1.0 kg). Although this group is less than 0.7% of all births, it comprises between 20 and 50% of all children who die before the first year of life.[1]

Extremely low weight at birth (less than 1000 g) contributes towards the aggravation of clinical conditions of newborns and their need for permanence in Neonatal Intensive Care Units (NICUs). In these units, newborns are often exposed to several therapies where they may receive between 15 and 20 intravenous drugs per day, most of which are not licensed for use in this population or they are used off-label.[2]


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In NICUs, drug doses are repeatedly calculated as they vary according to the newborns´ weight which, in turn, varies with great frequency. The very constant repetition of calculations is a possible source of error that requires attention when assisting newborns.[3]

In addition, when contrasted with children and adults, newborns have specific physiological characteristics such as different absorption, distribution, metabolism and excretion rates of drugs from the body, so that prescription, dispensing, monitoring and administration of medications are issues of great concern.[4]

The physiological limitations of newborns make them more susceptible to problems related to pharmacotherapy, requiring actions that increase the safety and quality of neonatal care. Because of this, in recent years, we have seen significant improvements in newborn care and monitoring not only due to the increased interest, knowledge and skills of health team professionals, but also due to the expansion of this team that now has clinical pharmacist as a member. This professional contributes to the proper use of medicines, the detection of possible problems related to their use in newborn and the promotion of activities related to education and research in the area.[5,6]

Current study describes the medication follow-up in infants with extremely low birth-weight in a neonatal intensive

care unit, with reports on the patients´ demographic profile, identifying problems related to drug use (DRP), drug-related negative outcomes and relating pharmacist interventions performed by clinical pharmacists during the research.

Current study also evaluated the possibility of a relationship between the occurrence of DRP and newborns´ birth-weight and their impact on pharmacotherapy and length of hospital stay.

## METHODS

Current exploratory study describes the medication follow-up on a population of extremely low birth-weight infants (ELBWIs) admitted to the NICU of a government-run maternity and school hospital in Fortaleza CE Brazil. This hospital is a reference institution in the state that offers the population a high quality standard in the services of obstetrics, gynecology, neonatology and high risk prenatal. At the time of the research, the hospital had 211 beds, 21 of which are from the neonatal intensive care unit.

Medication follow-up was performed between October 2013 and June 2014 by two clinical pharmacists, specialists on women's and children's health. Pharmacists spent 6 hours/day in the unit developing the medication follow-up.

The demographic and medication profile of the patients was analyzed. Regarding demographic, following variables were collected: sex; gestational age in weeks; birth weight in grams; length of in-hospital stay (days); monitoring time (days); diagnosis; mother's age.

Patients included in the study were monitored since their admission at the NICU until discharge to another low-risk treatment unit, transfer to another health institution or death.

Monitoring consisted in assessing the patient's pharmacotherapy needs through visits to the NICU and interaction with the health team, evaluation of prescriptions using NEOFAX form and information on the medical record.[7]

It also comprised identification of pharmacotherapy issues and their possible negative results classified according to the Third Consensus of Granada; performing pharmaceutical interventions when necessary and their classification following Farré Riba et al.[8,9] and follow-up of the clinical evolution of the newborn to evaluate results, according to the Pharmacist's Workup of Drug Therapy (PWDT) follow-up model10.The prescribed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) system of the World Health Organization.[11]

The patients included in the study were those admitted to the Neonatal Intensive Care Unit and whose birth-weight was less than 1000 g. These patients were identified by daily weight charts recorded in the prescriptions sent to the pharmacy service of the institution and by active research in their medical records.

Medication follow-up was performed with the "Medication follow-up Form" prepared by Pharmacy Service of the institution. The form consists of the following blocks in which patients' information was recorded: 1) Identification of the patient; 2) Laboratory tests; 3) Drugs prescribed; 4) DRP / drug-related negative outcomes / pharmacist interventions; 5) Clinical evolution.

ELBWIs with a NICU stay of less than 24 hours were excluded from current study because the researchers presume that there was not enough time for follow-up.

As a secondary outcome, current study also evaluated the possibility of a relationship between the occurrence of DRP and newborns´ birth-weight and their impact on pharmacotherapy and length of in-hospital stay by making statistical comparisons between these variables.

Analysis of results was given after data processing with SPSS version 17.0. According to the study of the variables, data were analyzed in a descriptive way, presented through tables. Numerical variables were given by means and standard deviations (SD) and categorical variables by proportions. Chi-square tests were used for categorical variables and Student's t-test for numerical variables at a 5% significance level.

The study was designed according to guidelines and regulatory norms for research involving human beings. The project was submitted to the Ethics Committee of the institution and assay started after approval (N. 408.053).

## RESULTS

### Primary outcomes

Forty-one neonates, complying with criteria for inclusion in the study, were admitted to the neonatal unit during the study period. However, five were excluded because they died in less than 24 hours, with no follow-up. In three cases, samples were lost since newborns were discharged without monitoring. The study comprised 33 infants characterized by extremely low birth-weight, what represents 80.5% of ELBWIs born during the study period.

Demographic characteristics of the newborns showed females were slightly predominant (54.5%, n=18). Table 1 presents other characteristics. Among the neonates, 45.5% (n=15) had a positive evolution of the clinical outcome and were discharged from the intensive care unit; 51.5% (n=17) died and only 1 newborn (3.0%) was transferred to another institution. Respiratory distress syndrome (60.6%, n=20), neonatal infection (30.3%, n=10), small for gestational age (15.2%, n=5), maternal-fetal incompatibility (12.1%, n=4) were the most prevalent diagnosis at birth. Intrauterine infection, severe anoxia and neonatal birth injuries rates equaled 3% (n=1). Mothers´ socio-demographic

Table 1. Demographic characteristics of monitored newborns

| **Characteristics** (N=33) | **Minimum** | **Maximum** | **Mean** | **Standard deviation** |
|---|---|---|---|---|
| Gestational age (GA) in weeks | 22 | 31 | 26.7 | 2.3 |
| Birth-weight (BW) in grams | 410 | 940 | 734.5 | 145.7 |
| Length of in-hospital stay (days) | 2 | 121 | 36.8 | 32.8 |
| Monitoring time (days) | 1 | 118 | 32.3 | 31.6 |

Table 2. Rate of exposure of neonates to drugs classified according to ATC

| ATC Classification | N (%) |
|---|---|
| Blood and hematopoietic organs | 33 (100) |
| Anti-infective for systemic uses | 33 (100) |
| Respiratory system | 32 (97.0) |
| Cardiovascular system | 29 (87.9) |
| Alimentary tract and metabolism | 26 (78.9) |
| Nervous system | 19 (57.6) |
| Dermatological | 10 (30.3) |
| Systemic hormone preparation | 6 (18.2) |
| Sensory organs | 4 (12.1) |
| Could not be sorted | 1 (3.0) |

characteristics revealed mean age 25.4 years, with minimum age 15 years old and maximum age 43 years old (SD=7.5).

Pharmacotherapy analysis of the neonates monitored revealed 64 different drugs prescribed to the neonates, averaging 16.0 (4 and 32; SD=7.5) drugs per patient during hospitalization period in the NICU. The 10 most prevalent drugs were vitamin K, used by 100% of the newborns, surfactant (90.9%), crystalline penicillin (97.0%), gentamicin (81.8%), vancomycin (78.8%), cefepime (72.7%), furosemide (72.7%), aminophylline (57.6%), meropenem (54.5%) and fentanyl (51.5%).

ATC classification of drugs employed revealed a predominance of "hematopoietic blood and organ" and "systemic anti-infective" drugs, which were used in all patients under analysis. Table 2 shows the frequency of exposure of newborn to groups of drugs according to ATC.

Assessment of patients' pharmacotherapy demonstrated that 39.4% (n=13) of neonates presented some type of drug-related problems (DRP), totaling 37 DRPs (Table 3), averaging 2.8 problems/patient. The most frequent DRPs were "non-standardized medication" at the institution (24.3%, n=9) and "wrong days count of antimicrobial treatment" (21.6%, n=8). Thirteen drugs with DRP occurrence were identified (Table 4), the most prevalent of them were vancomycin and cefepime, both with 18.9% (n=7), iron glycinate chelate (16.2%; n=6) and meropenem (10.8%; n=4).

Among the drug-related negative outcomes, 91.9% (n=34) were presented as possible (avoided). However, the problem had already manifested (not avoided) in 8.1% (n=3) of the monitored cases. Table 5 shows that the most prevalent drug-related negative outcomes were "untreated health problem" (40%, n=10) and "quantitative ineffectiveness" (32%, n=8).

Table 4. Drugs associated with drug-related problems

| Drug (N=37) | N (%) |
|---|---|
| Vancomycin | 7 (18.9) |
| Cefepime | 7 (18.9) |
| Iron Glycinate chelate | 6 (16.2) |
| Meropenem | 4 (10.8) |
| Amikacin | 2 (5.4) |
| Zinc chelated | 2 (5.4) |
| Gentamicin | 2 (5.4) |
| Sildenafil | 2 (5.4) |
| Furosemide | 1 (2.7) |
| Hydrochlorothiazide | 1 (2.7) |
| Milrinone | 1 (2.7) |
| Vitamin K mixed micelles | 1 (2.7) |
| Total Parenteral Nutrition (TPN) | 1 (2.7) |
| **TOTAL** | **37 (100)** |

Table 3. Distribution of drug-related problems observed during the study according to the 3rd Granada Consensus

| Drug related problems (N=37) | N (%) |
|---|---|
| Non-standardized medication in the institution | 9 (24.39 |
| Wrong days counts of treatment | 8 (21.6) |
| Sub-dose | 6 (16.2) |
| Inadequate dosage | 6 (16.2) |
| Overdose | 3 (8.1) |
| Wrong concentration | 1 (2.7) |
| Lack of medication | 1 (2.7) |
| Risk of lack of medication | 1 (2.7) |
| Incorrect dilution volume | 1 (2.7) |
| Drug Interaction | 1 (2.7) |
| **TOTAL** | **37 (100)** |

Pharmacist interventions were performed in all problems associated with pharmacotherapy. Table 6 shows that the most prevalent were "treatment day count correction" and "dose correction", both with 21.6% (n = 8), and "correction of dosage" (16.2%, n=6). The evaluation of interventions with regard to impact and significance showed that 81.1% (n=30) of pharmacist interventions were related to "effectiveness" and 18.9% (n=7) were related to "toxicity". Most pharmacist interventions were classified as "very significant" (67.6%, n=25), followed by those classified as "significant" (24.3%, n=9) and "extremely significant" (5.4%, n=2). Intervention in a single case (2.7%) was classified as "inappropriate". Finally, the rate of acceptance of interventions was 86.5% (n=32).

Further, 89.2% (n=33) of interventions were performed with physicians; 5.4% (n=2) with a pharmacist from an outpatient pharmacy; and 5.4% (n=2) with a nurse (n=37), with an 86.5% (n=32) general acceptance. When no acceptance occurred, justifications involved termination of treatment with the drug related (n=2); physician without integral information on the newborn available at that instance (n=2); physician judged his conduct to be the most correct option for the patient" (n=1).

**Secondary outcomes**

Regarding the analyzes involving the possibility of a relationship between the occurrence of DPR and the birth weight of the newborn and its impact on pharmacotherapy and length of stay, it has been observed that newborns with DRP also presented higher birth-weight (mean=832 g) than those without DRP (mean=671.2 g). Difference between weight means was statistically significant (Student's t test $p<0.05$).

Average hospitalization time and the presence or absence of DRP were also compared and revealed that, among the newborns who presented DRP, the mean in-hospital stay

Table 5. Distribution of drug-related negative outcomes observed during the study according to the 3rd Granada Consensus

| Drug-related negative outcomes (N=37) | N (%) |
|---|---|
| Untreated health problem | 17 (45.9) |
| Effect of unnecessary medication | 4 (10.8) |
| Non-quantitative ineffectiveness | 1 (2.7) |
| Quantitative ineffectiveness | 10 (27.1) |
| Non-quantitative insecurity | - |
| Quantitative insecurity | 3 (13.5) |
| **TOTAL** | **37 (100)** |

| Table 6. Pharmaceutical interventions during the study | |
|---|---|
| **Pharmaceutical interventions (N=37)** | **N (%)** |
| Treatment days count correction | 8 (21.6) |
| Dose correction | 8 (21.6) |
| Replacement of medication or purchase | 6 (16.2) |
| Correction of dosage | 6 (16.2) |
| Acquisition of the drug by outpatient pharmacy | 2 (5.4) |
| Replacement of medicine | 2 (5.4) |
| Adoption of standard schedules | 2 (5.4) |
| Requested purchase | 1 (2.7) |
| Correction of concentration | 1 (2.7) |
| Dilution correction | 1 (2.7) |
| **TOTAL** | **37 (100)** |

was longer (66.23 days) when compared to those without DRP (17.7 days). This difference was statistically significant ($p<0.05$), it suggested that the longer the hospitalization time, the greater the chances of DRP occurrence.

It has also been recorded that the mean number of drugs used was greater among patients with DRP (22.7 drugs) than among those without DRP (11.7 drugs). Consequently, a greater therapy complexity rate exists among those medication issues.

## DISCUSSION

The profile of monitored neonates showed the usual fragility characteristics of their clinical status. Although very few studies on ELBWIs are available, several authors reported similar characteristics among newborns evaluated in their research.[12,13] Hernández & Sánchez reported a slight predominance between the subgroup with gestational age between 28-29 weeks and the 26-27 week range, with the latter ranking second as the most prevalent.[1] It should be noted that the lowest gestational age observed in current study was 22 weeks, which, according to the literature, is the limit of human viability, with marked increases over the weeks of gestation.[14]

Mean birth-weight was close to that described by Cunha et al. (2013), with 805.6 g. Birth-weight in ELBW population has been considered as a primary factor for survival. Small differences (for instance, 100 g) in weight in this group may mean a greater chance of survival. Previous studies has shown that survival improves considerably above 750 g birth-weight.[15,16]

The maternal profile showed a mean age of mothers equivalent to the reproductive period, between 20 and 30 years, similar to other studies, but a few decades ago, the occurrence of pregnancy in adolescence or in advanced ages has been documented in several studies and was considered a risk factor for prematurity. [13,17]

Analysis of the pharmacotherapy of newborns showed agreement between most prescribed drug classes, according to ATC classification, and the main diagnoses at birth. Although not apparently related to the main diagnostic impressions described, Vitamin K had a high prevalence among the prescribed drugs. Its use is described in the clinical protocols of the institution under analysis and has been indicated for the prophylaxis of hemorrhagic disease of the newborns. In fact, they are more susceptible to the disease due to lower levels of coagulation factors, lower vitamin K reserves and low vitamin intake when fed on human milk.[18]

The surfactant is also among the most prescribed items, since it is associated with the treatment of Respiratory Discomfort Syndrome, which is considered one of the major causes of prolonged hospitalization in NICUs.[19] ATC classification revealed the predominance of drugs that act on "blood and hematopoietic organs", "systemic anti-infectives", "respiratory system" and "cardiovascular system" among the drug groups. López Martínez et al. also reported a similar pharmacotherapy profile.[20] Penicillin and gentamicin are among the most commonly used antimicrobials in neonatology, according to Neubert *et al*.[21]

Consequently, drugs are mostly administered intravenously, the preferred route for drug administration in neonates because it does not involve the absorption stage and its action is fast. However, the almost immediate action of the drugs by such administration is in itself a point that requires care, since it is practically impossible to correct erroneously administered doses. The possibility for adverse effects is thus raised.[22]

In addition, due to its invasive characteristics, the intravenous route favors blood infection risks. This factor should be taken into consideration when one observes the significant number of newborns diagnosed with neonatal infection. The careful monitoring of drug use by this route is required.

Antimicrobials, especially vancomycin, cefepime and meropenem, were prevalent drugs in prescriptions and they were also the most closely related to the occurrence of drug-related problems. It is known that the chance of failures is greater in proportion to the increasing duration of treatment with a given drug, to care intensity, disease severity and/or the complexity of the care system. These factors seem to have contributed towards failures observed during the use of these items.[23] Other studies have also confirmed that this class of medications is commonly associated with medication errors (dosage errors).[25,26] Therefore, it is of great importance that the pharmacist monitors the use of these drugs, be available to solve doubts at the prescription process and participate in the elaboration of antimicrobial protocols.

Iron glycinate chelate was also one of the most involved drugs with PRM. The drug was prescribed even though it was not standardized in the institution. In these cases, as iron glycinate chelate is a safer drug and with less adverse effects than the standard drug (ferrous sulfate), the pharmacist performed interventions in order to acquire the safest drug for the treatment of newborns.[26]

When analyzing DRPs in current research, most failures occurred at the medical prescription stage, also reported by Silva & Vendramin, such as, for example, DRPs related to counting misaligned duration of treatment, sub-dose, overdose or dosage.[23] The above fact underscores the significance of the participation of the pharmaceutical professional as a collaborator in the prescription process, assisting in the evaluation of information related to the dose, dosage, interactions between medicines or with nutrients, as well as about the standardized pharmaceutical specialties available at the health institution.

The occurrence of errors associated with "mismatch of days of treatment" occurred mainly with antimicrobials. Its possible cause may have been that the count was done manually at the institution, whilst the number of days of treatment should be updated daily by the prescriber. Another explanation is the fact that the institution is an educational institution. Several professionals are actually not fully adapted to perform such routines as the registration of the day of treatment in the prescriptions.

Similar factors included "lack of medication", or rather, when a standard item was not available at the institution, and "risk of medication failure" associated with situations where the stock of the drug in question was reduced and rationing required. In the case of the administration of drugs in the form of injectable solutions, as the unused contents of ampoules should be discarded, it was suggested the adoption of standard schedules in which the drug could be made available for more than one patient per period. This method minimizes drug loss as little as possible and the stock will be made to last until the acquisition of new samples.

Among the observed drug-related negative outcomes, the prevalence of "untreated health problems" refers to the frequent prescription of non-standard items and alerts to re-evaluate the institution's standardization of medications to avoid discontinuation of treatments and the occurrence of negative clinical outcomes.

The emergence of negative results related to quantitative ineffectiveness is a consequence of the main DRPs reported in current study, including the mismatch of days of antimicrobial treatment, subdose and inadequate posology. These situations may reduce the amount of drugs offered to the patient and impairing improvement of the patient's clinical condition.

The prevalence of avoided drug-related negative outcomes is a positive point with regard to the performance of the clinical pharmacist. The professional was able to identify imminent problems and were avoided through interventions with the multi-professional team, preventing negative consequences associated with pharmacotherapy.

After analyzing the interventions, an agreement was reached that took into consideration the problems related to detected drugs and the guidelines proposed by the pharmacist. Regarding to the significance of the intervention, most were related to actions that aimed at obtaining greater effectiveness of the proposed therapeutics. A smaller portion of interventions focused on reducing toxicity associated with drug use.

More than half of the pharmaceutical interventions performed were classified as "very significant". The interventions were classified as "extremely significant" in two situations since they were related to the acquisition of the drug sildenafil, not available in the institution and used as therapy option to control pulmonary hypertension, generating an increase in the effectiveness of the therapy performed and improving patient´s survival.

Further, one case was classified as "inappropriate" intervention. In this case, the available data in the literature and protocols were taken into account. However, due to the patient´s unstable clinical conditions, the medical team opted for an off-label procedure, based on a more subjective analysis of the case, since the newborn did not respond to the conventional doses.

Overall, pharmacist interventions performed had a positive impact on patient care and were especially important in cases of dose and treatment days count correction. According to Drovandi *et al*. (2018), clinical pharmacists play a significant role in reducing drug-related problems and improving patient outcomes. Medication errors like over and underdosing, missed doses, medication history gaps, allergies, and near-misses can all be avoided by involving the pharmacist in the care of the pediatric patient.

The physician was the professional mostly contacted for the required interventions, since the most prevalent problems detected were related to the medical prescription. The non-acceptance of some pharmacist interventions still demonstrates some resistance regarding the insertion of the clinical pharmacist in the health team. They are barriers that have to be overcome by the pharmacist who has increasingly been able to provide support in more specific areas of knowledge, albeit less explored, as is the case of neonatology.

Regarding secondary outcomes, results also demonstrated that DRPs may be associated with the patient's birth-weight and impact on pharmacotherapy and hospitalization period. They help one understand that among the infants who presented DRP, the birth-weight was higher than in the group without DRP. However, it has been verified that neonates of this last group are prone to die since they present lower average weight rates and, consequently, less probability of survival. They feature less hospital stay, short period of exposure to drug therapy and lower chances of drug-related problems.

Among neonates who presented higher birth-weight averages, hospital stay was longer, similar to DRP occurrence. It is worth mentioning that among the newborns that had problems related to medication, the number of drugs used during hospitalization was higher, favoring the occurrence of several factors that make the therapeutic regimen more complex. It involves more daily doses of the medications, more units per dose, total doses per day.[24]

Among the limitations observed throughout the study, the occurrence of periods of strike of the services provided by the public institution came to affect the hospitalization rates, which may have reduced the size of the population studied.

## CONCLUSIONS

Current study demonstrated that it is possible to follow the medication in infants with extremely low birth-weight in a neonatal intensive care unit. The analysis of pharmacotherapy for newborns evidenced possible failures in stages directly related to drug prescription, identifying the main drug-related problems, as well as drugs most involved in this process (antimicrobials) for which activities can be planned by clinical pharmacist to reduce negative

results by training and by a continuous evaluation of the risks associated with pharmacotherapy.

Most of the pharmacists' interventions performed were significant, evidencing the role of the clinical pharmacist in the detection, solution and prevention of drug-related problems, while contributing to the achievement of safe and effective pharmacotherapy. It is also possible to associate the occurrence of problems related to medications and the characteristics of newborns studied, such as birth-weight, length of in-hospital stay and number of prescribed pharmaceutical specialties, which highlights the importance of monitoring pharmacotherapy in this population.

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## CONFLICT OF INTEREST

There are no conflicts of interest.

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