BMJ Open

A risk assessment of patient factors and medications in drug-related problems in neonatal intensive care

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024377
Article Type:	Research
Date Submitted by the Author:	23-May-2018
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Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS

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Running title: Drug-related problems in neonatal care

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Key words: Neonatal intensive & critical care; Health & safety; Adverse events

Abstract: 252 words

Text: 2,480 words

Tables and Figures: 4

ABSTRACT

Objectives: It is believed that drug-related problems (DRP) are potentially serious in neonates, however, information for neonatal intensive care units (NICU) is scarce. This study aims to identify patient factors and medications associated with the occurrence of DRPs in NICUs.

Design: Prospective cohort study.

Setting: NICU of a teaching hospital in Brazil.

Participants: The data were collected from the records of the clinical pharmacy service of all neonates admitted between January 2014 and November 2016, excluding neonates with length of stay in the NICU < 24 hours or without prescribed drugs.

Primary outcome measures: Risk factors and risk medicines for PRM.

Results: The study observed 600 neonates who spent a median of 14 NICU days (range 2 – 278 days). Most neonates (59.8%) were exposed to DRPs. The factors independently associated with DRPs were gestational age (adjusted odds-ratio (AOR) 0.85, 95% confidence interval (CI) 0.84–0.89), 5-minute APGAR < 7 (AOR 1.74, 95% CI 1.00–1.13), neurological disease (AOR 2.30, 95%CI 1.02–5.21), renal disease (AOR 5.88, 95%CI 1.93–17.9) and cardiac disease (AOR 2.80, 95%CI 1.50–5.22). The risk medications for DRP were vancomycin (AOR 3.88), amphotericin B (AOR 3.80), alprostadil (AOR 3.38), meropenem (AOR 3.33), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.69), amikacin (AOR 1.97), cefepime (AOR 1.80) and omeprazole (AOR 1.67). These medicines represent one-third of all prescribed drugs.

Conclusions: Gestational age, 5-minute APGAR < 7 and neurological, cardiac and renal disease are risk factors for DRP in NICUs. Alprostadil, omeprazole and several anti-infectives were associated with greater risk of DRPs.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study identifying patient variables and drugs associated with the occurrence of Drug-related problems (DRP), exclusively in Neonatal Intensive Care Unit (NICU) patients.
- The validity of the results is strengthened by the large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRPs and the adoption of a well-known DRP classification system.
- However, the data were obtained from a single institution, which may somehow impair the generalization of our findings.
- It is also possible that administration errors have been under-estimated by recording failures.

INTRODUCTION

The Intensive Care Unit (ICU) is a complex environment, characterized by polypharmacy, transfusions and frequent surgical procedures.[1] Neonatal Intensive Care Units (NICU) may pose additional hazards to patient safety because of the frequent usage of off-label and unlicensed medicines and of decimal dilutions of intravenous medicines.[2, 3] In addition, because of their physiological immaturity and rapid growth, neonates exhibit large interindividual variability in drug metabolism and excretion.[2] Such characteristics may predispose neonates to drug-related problems (DRP).

DRPs are events or circumstances that, actually or potentially, interfere in the patient's pharmacotherapy and that may lead to undesired clinical outcomes.[4] Those events include errors in the drug therapy processes (prescription, dispensation and administration) and adverse drug events (any untoward event related to medication that results in harm to the patient).[5 – 7]

In pediatric wards, about half of the patients are exposed to DRPs and most of these are preventable.[8] However, there is very little information on DRPs in children in intensive care units, especially among neonates.

It is believed that DRPs are particularly frequent and serious in neonates.[9, 10] Neonates are very sensitive to dose variations because of their particular pharmacokinetics and pharmacodynamics, consequence of the lower drug metabolism and clearance, low levels of plasma proteins, high proportion of body water and level of receptor expression and sensitivity.[11, 12] Some authors have shown that harm involving medicines is common in NICUs, with incidence rates ranging from 10 to 20 cases per 1,000 patient-days.[13, 14] Such harm can lead to prolonged hospitalization time and, in extreme cases, to the death of patients. It also generates an increase in hospital costs.[13, 15] Thus, the development of effective

preventive strategies directed to DRPs is of great relevance for the improvement of health careand one step towards this goal is the identification of patients susceptible to DRPs.[16]

Therefore, the purpose of this study was to identify risk factors for DRPs in NICU and to assess the risk associated with commonly used medications.

METHODS

This study was an observational, prospective cohort study that was conducted from January 2014 to November 2016 in the 20-bed NICU of a teaching maternity hospital specialized in high-risk pregnancy. All neonates with a NICU stay longer than 24 hours and who had at least one prescribed drug were included in the study. Neonates who were prescribed exclusively with electrolytes, parenteral nutrition, blood products, oxygen therapy, diagnostic agents, and vitamin and mineral supplements were excluded from the study, as those products were not considered as drugs.

The data collected from each neonate included sex, gestational age, birth weight, type of delivery (vaginal or caesarean), occurrence of premature rupture of membranes (PROM), 1-minute and 5-minute APGAR, a diagnosis of neurological, renal or cardiac disorder, and malformations. The APGAR is a score that evaluates the birth condition of newborns in the first and fifth minutes of life, values below seven being considered an ominous sign.[17]

Throughout the hospitalization period, every neonate was evaluated for the number of clinical problems, number of prescribed drugs and occurrence of DRPs. The identification of DRPs was performed by the NICU clinical pharmacy team (a chief pharmacist and four assistant pharmacists) through the review of medical charts, medication orders and nursing records. For each identified DRP, its causes were then classified according to the Pharmaceutical Care Network Europe system v.6.2.[4] This classification was carried out independently by two pharmacists (RDL and MTS), supported by the Neofax® textbook

(Thomson Reuters, New York, USA), as well as the Micromedex® (Truven Health Analytics, Michigan, USA) and Uptodate® (WoltersKluwer, Alphenaanden Rijn, NL) databases. A third pharmacist (TXC) was consulted when there was lack of consensus between the two evaluators.

Statistical analysis

The defined sample size of 600 subjects would afford 70% power to identify associations with an odds-ratio of 1.30 or more. All variables are described by mean ± standard deviation, or as absolute and relative frequency, as appropriate. For the identification of risk factors of DRP, the set of patient variables whose association with DRPs was statistically significant at the 0.10 significance level in univariate logistic regression was analyzed by backward stepwise multiple logistic regression, and those variables significant at the 0.05 level were retained in the final model. Results are presented as adjusted odds-ratios (AOR) and 95% confidence intervals (CI). For the estimation of the risk of DRP associated with medications commonly used in a NICU, each prescribed drug was analyzed by a multiple logistic regression model adjusted by the risk factors identified in the previous analysis. Statistical analysis was performed with Stata 11 (Stata Corporation, College Station, TX, USA).

RESULTS

During the 35-month study period, a total of 634 newborns were admitted to the NICU. Of these, 19 newborns were excluded (17 because they had no drugs prescribed and two patients in whom the length of stay was less than 24 hours). Six hundred fifteen newborns remained eligible but 15 (2.44%) were excluded from the analysis because they had missing pharmacotherapy follow-up data. The analysis set of 600 newborns was observed for a total of 16,335 NICU days, with a median of 14 days (range 2 – 278 days). The study population

consisted of 313 males (53.6%) and the mean gestational age was 31.9 ± 4.1 weeks. On average, 8.3 ± 6.1 medicines were prescribed to each newborn during the NICU stay. A total of 1,142 DRPs were identified, with a mean of 1.9 ± 2.6 DRPs per patient. More than half of the newborns had one or more DRPs (59.8%, 359). Seventy-six neonates died during the study (Table 1).

DRPs were associated with increased length of stay (39.8±41.8 days vs. 11.2±10.3 days, p<0.001), number of prescribed drugs (10.7±6.5 vs. 4.7±3.0, p<0.001) and number of clinical problems (5.54±2.78 vs. 3.38±1.57, p<0.001) but not with a fatal outcome (12.3% vs. 13.3%, p=0.71).

As shown in Table 2, univariate logistic regression analysis identified eight patient variables associated with DRPs: gestational age, birth weight, vaginal delivery, 1-minute and 5-minute APGAR, neurological disorder, renal disorder, and cardiovascular disorder. In the multivariate logistic regression model, five remained significant: lower gestational age (adjusted odds-ratio (AOR) 0.85), 5-minute APGAR <7 (AOR 1.74), neurological disorder (AOR 2.30), renal disorder (AOR 5.88) and cardiac disorder (AOR 2.80) were risk factors for DRPs.

Table 3 shows the medicines for which an estimate of the odds-ratio of DRP, adjusted for gestational age, 5-minute APGAR, neurological disorder, renal disorder, and cardiac disorder, could be obtained. The medications, and corresponding adjusted odds-ratios, are vancomycin (AOR 3.88), amphotericin B (AOR 3.80), alprostadil (AOR 3.38), meropenem (AOR 3.33), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.69), amikacin (AOR 1.97), cefepime (AOR 1.80) and omeprazole (AOR 1.67).

The frequency of prescription, and the prevalence of DRPs related to those medications are also displayed in Table 3. These nine drugs represent 28.1% (1398/4970) of all medications prescribed in the NICU and accounted for 50.6% (644/1273) of DRPs

involving medications. The most prescribed medicines in the group were gentamicin (10.5%, 523) and meropenem (3.1%, 154), and these drugs were also the most often involved in DRPs (17.3%, 220 and 7.9%, 101 respectively).

As for the causes of DRPs involving the nine medicines (Table 4), dose selection was the most common cause for amikacin (62.7%), gentamicin (62.3%), meropenem (39.6%), cefepime (38.1%) and ciprofloxacin (33.3%). DRPs involving omeprazole (53.57%), amphotericin B (45.5%) and alprostadil (25.0%) were most often related to drug use. Another cause involving alprostadil (25.0%) was adverse reactions. Vancomycin (40.4%) was most often implicated in errors of prescription logistics.

DISCUSSION

In our study, we observed that neonates with low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are more likely to have DRP during their stay in NICU. An assessment of the risk of DRP was made for alprostadil, amikacin, amphotericin B, cefepime, ciprofloxacin, gentamicin, meropenem omeprazole and vancomycin. Such medicines accounted for less than one-third of the drugs prescribed in the NICU, and were involved in half of DRPs, the majority being related to drug dose and to drug use.

Only a few studies have identified risk factors for the occurrence of DRP in hospitalized patients. Most of those studies were conducted in adult and pediatric wards for periods under six months and enrolled fewer than 400 patients.[18 – 21] We performed a study in the NICU involving 600 neonates for a period of three years and presenting a set of different predictor variables. Comparisons to the results of other studies are therefore difficult. Even so, several risk factors related to DRP identified in our study, such as age and clinical problems

(cardiac, neurological and renal disorders), were also observed in the works of Urbina et al.[16], Peterson et al.[20] and Blix et al.[22] although those studies were conducted in adult patients.

We also found that a low 5-minute APGAR was associated with a higher risk of DRP. This predictor is a specific neonatology parameter that measures the condition of the newborn at birth.[23] A low APGAR score usually represents a serious situation with the corresponding need for several therapeutic interventions which, in turn, increase the risk of DRP.

The detection of the clinical variables associated with DRPs, as well as knowledge of the risk of DRPs associated with each medication, represents a first step for the development of preventive strategies for enhanced patient safety and improvements in the process of care. Blix et al.[22] were the first authors to present risk estimates for drugs, while other papers[8, 18 – 21, 24, 25] have only described drugs involved in DRPs. We were able to quantify the risk of DRP for a set of drugs that are involved in half of all DRPs, namely alprostadil, omeprazole and several antimicrobials (amikacin, cefepime, ciprofloxacin, gentamicin, meropenem, amphotericin B and vancomycin). Pawluk et al.[24] e Stavroudis et al.[25] claimed that the risk of DRP associated with a medicine is directly related to the frequency of prescription. However, our results show that the medicines with greater odds of DRPs (vancomycin and amphotericin B) were not the most prescribed. These results suggest that the risk of DRP is primarily associated with the chemical and pharmacological properties of a drug, therefore strongly related to the level of difficulty on setting the appropriate dose and on the drug's potential for adverse reactions, interactions and incompatibilities.

Inappropriate dose selection was the most common cause of DRPs for aminoglycosides, cefepime and meropenem. In neonates, the adjustment of dose and regimen of antibiotics is extremely complex, the main reason for this being the rapid change in weight during the first days of life, as well as significant heterogeneity in the maturation of organs and systems across newborns.[12, 26] The lower than the recommended doses of those medicines

administered in this study were often due to a delay in the adjustment of the medication dose to the rapid weight gain of the neonate.

We observed that amphotericin B, ciprofloxacin and omeprazole were associated with inappropriate drug use, specifically with drug administration error, with drug incompatibility being the most frequent cause. Neonates have a high risk of exposure to drug incompatibilities because of the limited number of intravenous accesses, often leading to simultaneous administration of incompatible drugs through the same intravenous line. In addition, the requirements for delivery of drugs in this population, such as dilutions and reduced infusion rates, can lead to incompatibilities because of high concentrations and longer time of contact between incompatible medicines.[27] Such problems may be implicated in therapeutic failures due to drug degradation and even to thromboembolic complications, including cases of deaths, due to the precipitate formed reaching the bloodstream.[28 – 30].

Another medicine that had potential incompatibilities as the main cause of DRP was alprostadil. However, this medicine stands out for the significant percentage of cases of suspected adverse reactions. Fever, leukocytosis, dyspnea are reactions commonly observed in the neonate soon after the administration of alprostadil.[31] Because of these reactions and complications, this medication is for intensive therapy only.

The most common cause of vancomycin-related problems was errors of prescription logistics. These errors are characterized by the lack of important information in the prescription for the safe administration of the medications, or by the non-justifiable prescription of non-standard medicines in the institution. The lack of information on the time length of the infusion on the prescription was the most common error involving vancomycin, an important problem because rapid infusions in less than 60 minutes can lead to macular or maculopapular skin rashes (red man syndrome).[32]

This study has some limitations. The data were obtained from a single institution, which may somehow impair the generalization of our findings. Furthermore, as DRPs were identified from patient records and medical reports, it is possible that administration errors have been under-estimated by recording failures. However, the same methodology has been adopted by other studies in DRPs and, considering the scarcity of papers related to the topic of risk factors for DRPs in NICU patients, we believe that our results are relevant. The large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRPs and the adoption of a well-known DRP classification system are methodological features that contribute to the validity of our results. To our knowledge, this is the first study identifying patient variables and drugs associated with the occurrence of DRPs, exclusively in NICU patients. The detection of those predictors is of great value for the identification of patients more prone to DRPs and, therefore, for the development of screening tools. Such tools can support the work of the healthcare team, especially the clinical pharmacist, with the strengthening of preventive strategies and the optimization of resources and time.

Further research is needed in order to deepen the study of factors associated with DRPs, aiming at the elaboration of risk stratification tools. Future studies should also analyze the influence of external factors on the incidence of DRPs, which have not been addressed in our study, such as the number and characteristics of the NICU team members, the workplace conditions, the intra-team and inter-team communication, and the organization of the hospital. Another issue of considerable importance would be the investigation of clinical outcomes of DRPs in NICUs.

CONCLUSION

In conclusion, low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are risk factors associated with the occurrence of DRPs. We also

list nine risk medications for DRP: vancomycin, amphotericin B, alprostadil, meropenem, ciprofloxacin, gentamicin, amikacin, cefepime and omeprazole. Although they are the most involved in DRPs, these medicines account for less than one-third of the drugs prescribed in NICU. Inappropriate dose selection and inappropriate drug use (mainly potential drug incompatibilities) were the main causes of DRP related to those medicines.

Acknowledgements We are grateful to all pharmacists of the maternity hospital, especially to the pharmacists Dr. Elaine Alves and Dr. Tayne Cortez for contributing to the elaboration of the research project, the pharmacy residents Kadine Pontes and Bruna Nunes for making available the records of pharmacotherapeutic follow-up of patients, and pharmacy students Mayara Alves and Amanda Nascimento for helping in data collection and tabulation. We also thank all members of the NICU, physicians, physiotherapists, nurses and auxiliaries.

Contributions RDL participated in all stages of the study. MTS and TXC participated in the study design and revision of the manuscript. RRM and AGO contributed to the design and analysis of the study and the writing and revision of the manuscript. All authors approved the final version of the manuscript.

Funding This study received fund from the National Council of Technological and Scientific Development (CNPq).

Competing interests None declared.

Ethics approval This study was approved by the Institutional Review Board of the University Hospital Onofre Lopes (No. 580.201/2014), who waived the need for written

informed consent because the study only evaluated data collected from clinical pharmacy records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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Table 1 – Demographic and clinical characteristics of the study population (n = 600)

Characteristics	**Value***
Gestational age (weeks)	31.9 ± 4.1
Female sex	271 (46.4%)
Birth weight (grams)	1779.4 ± 885.3
Length of stay (days)	28.2 ± 35.8
Vaginal delivery	214 (36.3%)
PROM	165 (31.5%)
1-minute APGAR < 7	266 (46.6%)
5-minute APGAR < 7	78 (13.3%)
Number of clinical conditions	4.7 ± 2.6
Neurological disorders	49 (8.2%)
Renal disorders	52 (8.7%)
Cardiac disorders	98 (16.4%)
Malformations	67 (11.2%)
Number of medications used	8.3 ± 6.1
DRP (n = 1142)	
Patients with DRP	359 (59.8%)
Average number of DRP per patient	1.9 ± 2.6
Death	76 (12.7%)

*Values are mean ± standard deviation or n (%).

PROM, premature rupture of membranes; DRP, drug-related problems.

Table 2– Factors associated with occurrence of drug-related problems in neonatal intensive care

Characteristics	Univariate analysis				Multivariate analysis			
	OR	95%CI		p	AOR	95%CI		p
Gestational age in weeks	0.87	0.84	0.91	<0.01	0.85	0.81	0.89	<0.01
Female sex	1.19	0.85	1.66	0.30				
Birthweight (grams)	0.99	0.99	0.99	<0.01				
Vaginal delivery	1.57	1.10	2.21	0.01				
PROM	1.28	0.87	1.86	0.20				
1-minute APGAR <7	1.57	1.12	2.20	<0.01				
5-minute APGAR <7	1.89	1.12	3.19	0.02	1.74	1.00	3.13	0.05
Neurological disorder	2.19	1.12	4.29	0.02	2.30	1.02	5.21	0.05
Renal disorder	9.17	3.26	25.79	<0.01	5.88	1.93	17.9	<0.01
Cardiac disorder	2.51	1.52	4.14	<0.01	2.80	1.50	5.22	<0.01
Malformations	1.54	0.89	2.65	0.12				

OR, odds-ratio; CI, confidence interval; AOR, adjusted odds-ratio; PROM, premature rupture of membranes.

Table 3 – Estimates of the risk of drug-related problems (DRP) associated with several drugs administered in NICUs, distributed by cases of DRP and frequency of prescription

Medicines	Adjusted Odds-ratio (95%CI)*	Cases of DRPs (n = 1,273)		Frequency of prescriptions (n = 4,970)	
		n	%	n	%
Vancomycin	3.88 (1.54 – 9.81)	99	7.8	102	2.0
Amphotericin B	3.80 (2.02 – 7.16)	44	3.4	48	1.0
Alprostadil	3.38 (1.67 – 6.84)	20	1.6	35	0.7
Meropenem	3.33 (1.72 – 6.49)	101	7.9	154	3.1
Ciprofloxacin	3.03 (1.34 – 6.85)	15	1.2	25	0.5
Gentamicin	2.69 (2.17 – 3.34)	220	17.3	523	10.5
Amikacin	1.97 (1.23 – 3.17)	75	5.9	177	3.6
Cefepime	1.80 (1.15 – 2.82)	42	3.3	189	3.8
Omeprazole	1.67 (1.06 – 2.62)	28	2.2	145	2.9

*Odds ratio adjusted for gestational age, 5-minute APGAR <7, neurological disorder, renal disorder and cardiac disorder. The p-value for each medicine was < 0.01.

CI, confidence interval.

Table 4 – Distribution of medicines associated with drug-related problems (DRP) in neonatal intensive care by main causes of DRP

	Causes of DRPs*			
Medicines	**Adverse reactions†**	**Dose selection**	**Drug use**	**Prescription logistics**
Alprostadil	5 (25.0%)	2 (10.0%)	5 (25.0%)	3 (15.0%)
Amikacin		47 (62.7%)	16 (21.3%)	8 (10.7%)
Amphotericin B		6 (13.6%)	20 (45.5%)	10 (22.7%)
Cefepime		16 (38.1%)	11 (26.2%)	14 (33.3%)
Ciprofloxacin		5 (33.3%)	3 (20.0%)	4 (26.7%)
Gentamicin		137 (62.3%)	78 (35,4%)	3 (1.4%)
Meropenem		40 (39.6%)	25 (24.8%)	28 (27.7%)
Omeprazole		1 (3.57%)	15 (53.57%)	12 (42.86%)
Vancomycin	1 (1.0%)	31 (31.3%)	24 (24.3%)	40 (40.4%)

*Causes of DRPs according to the Pharmaceutical Care Network Europe (PCNE) classification systemv.6.2.[4]

†Classified as others causes of DRP.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4/5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6/7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7/8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7/8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8/9/10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk assessment of patient factors and medications for drug-related problems from a prospective longitudinal study of newborns admitted to a neonatal intensive care unit

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024377.R1
Article Type:	Research
Date Submitted by the Author:	07-Dec-2018
Complete List of Authors:	Leopoldino, Ramon; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy Santos, Marco; Maternidade Escola Januário Cicco Costa, Tatiana; Universidade Federal do Rio Grande do Norte Maternidade Escola Januário Cicco Martins, Rand; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Department of Pharmacy Oliveira, António; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Department of Pharmacy
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care, Pharmacology and therapeutics
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS

Title: Risk assessment of patient factors and medications for drug-related problems from a prospective longitudinal study of newborns admitted to a neonatal intensive care unit

Running title: Drug-related problems in neonatal care

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Key words: Neonatal intensive & critical care; Health & safety; Adverse events

Abstract: 262 words

Text: 3,178 words

Tables and Figures: 4

ABSTRACT

Objective: To identify patient factors and medications associated with the occurrence of Drug Related Problems (DRP) in neonates admitted to Neonatal Intensive Care Units (NICU).

Design: Prospective longitudinal study.

Setting: NICU of a teaching hospital in Brazil.

Participants: The data were collected from the records of the clinical pharmacy service of all neonates admitted between April 2014 and January 2017, excluding neonates with length of stay in the NICU < 24 hours or without prescribed drugs.

Primary outcome measures: The occurrence of one or more DRP (conditions interfering in the patient's pharmacotherapy with potential undesired clinical outcomes).

Results: The study observed 600 neonates who had a median length of stay in the NICU of 13 days (range 2 to 278 days). DRP were identified in most neonates (60.5%). In a multivariate logistic regression model, the factors independently associated with DRP were gestational age (adjusted odds-ratio (AOR) 0.85, 95% confidence interval (CI) 0.81–0.89), 5-minute APGAR < 7 (AOR 1.74, 95% CI 1.00–3.13), neurological disease (AOR 2.49, 95%CI 1.09–5.69), renal disease (AOR 5.75, 95%CI 1.85–17.8) and cardiac disease (AOR 2.36, 95%CI 1.31–4.24). The medications with greater risk for DRP were amphotericin B (AOR 4.80), meropenem (AOR 4.09), alprostadil (AOR 3.38), vancomycin (AOR 3.34), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.43), cefepime (AOR 1.88), amikacin (AOR 1.82) and omeprazole (AOR 1.66). These medicines represent one-third of all prescribed drugs.

Conclusions: Gestational age, 5-minute APGAR < 7 and neurological, cardiac and renal disease are risk factors for DRP in NICUs. Alprostadil, omeprazole and several anti-infectives were associated with greater risk of DRP.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study identifying patient variables and drugs associated with the occurrence of Drug-related problems (DRP), exclusively in Neonatal Intensive Care Unit (NICU) patients.
- The validity of the results is strengthened by the large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRP and the adoption of a well-known DRP classification system.
- However, the data were obtained from a single institution, which may somehow impair the generalization of our findings.
- It is also possible that administration errors have been under-estimated by recording failures.

INTRODUCTION

The Intensive Care Unit (ICU) is a complex environment, characterized by polypharmacy, transfusions and frequent surgical procedures.[1] Neonatal Intensive Care Units (NICU) may pose additional hazards to patient safety because of the frequent usage of off-label and unlicensed medicines and of decimal dilutions of intravenous medicines.[2, 3] In addition, because of their physiological immaturity and rapid growth, neonates exhibit large interindividual variability in drug metabolism and excretion.[2] Such characteristics may predispose neonates to drug-related problems (DRP).

DRP are events or circumstances that, actually or potentially, interfere in the patient's pharmacotherapy and that may lead to undesired clinical outcomes.[4] Those events include errors in the drug therapy processes (prescription, dispensation and administration) and adverse drug events (any untoward event related to medication that results in harm to the patient).[5 – 7]

In paediatric wards, DRP occur in about half of the patients and most of these are preventable.[8] However, there is very little information on DRP in children in intensive care units, especially among neonates.

It is believed that DRP are particularly frequent and serious in neonates.[9, 10] Neonates are very sensitive to dose variations because of their particular pharmacokinetics and pharmacodynamics, consequence of the lower drug metabolism and clearance, low levels of plasma proteins, high proportion of body water and level of receptor expression and sensitivity.[11, 12] Some authors have shown that harm involving medicines is common in NICUs, with incidence rates ranging from 10 to 20 cases per 1,000 patient-days.[13, 14] Such harm can lead to prolonged hospitalization time and, in extreme cases, to the death of patients. It also generates an increase in hospital costs.[13, 15] Thus, the development of effective preventive strategies directed to DRP is of great relevance for the improvement of health care and one step towards this goal is the identification of patients susceptible to DRP.[16]

Therefore, the purpose of this study was to identify risk factors for the occurrence of one or more DRP in NICU, to assess the risk associated with commonly used medications and to describe the causes of DRP in the medications with greater risk of DRP in neonates.

METHODS

This was an observational, prospective, longitudinal study conducted from April 2014 to January 2017 in the 20-bed NICU of a teaching maternity hospital specialized in high-risk pregnancy. All neonates admitted to the NICU during the study period were prospectively evaluated for inclusion in the study. Inclusion criteria were a NICU stay longer than 24 hours and at least one prescribed drug. Neonates who were prescribed exclusively with electrolytes, parenteral nutrition, blood products, oxygen therapy, diagnostic agents, and vitamin and mineral supplements were excluded from the study, as those products were not considered as drugs.

In the absence of information in the literature on risk factors for DRP in neonates, the patient variables selected as candidates for assessment in a multivariate risk model were those that could be collected at NICU admission on every neonate and that reflect serious conditions that are usually associated with enhanced pharmacotherapy. The data collected from each neonate included sex, gestational age, birth weight, type of delivery (vaginal or caesarean), occurrence of premature rupture of membranes (PROM), 1-minute and 5-minute APGAR, a diagnosis of neurological, renal or cardiac disorder, and malformations. The APGAR is a score that evaluates the birth condition of newborns in the first and fifth minutes of life, values below seven being considered an ominous sign.[17] In addition to those risk factors that may be predictors of DRP, patient variables representing the complexity of care (number of unique medications prescribed, number of different clinical problems, and NICU length of stay in days) were also collected from each patient.

The study also wanted to identify medications that were associated with increased risk of DRP in neonates and, therefore, all the medications prescribed to each neonate during the NICU stay were recorded.

The identification of DRP was actively performed on a daily basis by the NICU clinical pharmacy team (a chief pharmacist and four assistant pharmacists) through the analysis of medical charts, medication orders and nursing records, seeking entries that might indicate the occurrence of a DRP. The pharmacists involved in this research were permanent members of the clinical pharmacy team allocated to the NICU of our institution. The identification of DRP and their notification to the medical team is an important part of their routine work and all were experienced in the detection of DRP. For each identified DRP, its causes were then classified according to the Pharmaceutical Care Network Europe system v.6.2[4] (see supplementary file 1). This classification was carried out independently by two pharmacists (RDL and MTS), supported by the Neofax® textbook (Thomson Reuters, New York, USA), as well as the Micromedex® (Truven Health Analytics, Michigan, USA) and Uptodate® (WoltersKluwer, Alphenaanden Rijn, NL) databases that provided authoritative information on adverse drug reaction and drug-drug interactions. Whenever the two evaluators disagreed upon the classification of the cause of a DRP, a third pharmacist (TXC) was called in to break the tie.

Statistical analysis

The target sample size was set at 600 patients, a number that would afford 70% power to identify associations with an odds-ratio of 1.30 or greater for patient factors with a prevalence over 30%[18]. All variables are described by mean±standard deviation, median (range), or as absolute and relative frequency, as appropriate. For the identification of risk factors of DRP, an initial selection of patient variables at NICU admission were tested for association with the occurrence of one or more DRP with logistic regression. All variables were binary, except gestational age and birth weight that were continuous. The set of patient variables whose

association with DRP was statistically significant at the 0.10 significance level in univariate logistic regression was analysed by stepwise backward multiple logistic regression, and those variables significant at the 0.05 level were retained in the final model. Variables collected only at discharge from the NICU were analysed in a separate model. Results of these analyses are presented as odds-ratios adjusted by the other variables in the model (AOR) and 95% confidence intervals (CI). The model was $\ln[p(\text{DRP}=1)/p(\text{DRP}=0)] = \beta_0 + \beta_i x_i$, where β_0 is the regression constant, β_i the partial regression coefficients and x_i the independent variables.

It was hypothesized that some medications could be singled out because they are associated with a significantly higher risk of DRP, through a combination of complex dosing and/or administration, and of frequency of use. Those drugs would be high-risk medications requiring close monitoring from the clinical pharmacy team. In the NICU setting, very often several medications are prescribed concurrently, sometimes by simultaneously through the same intravenous line, and accounting for the interplay of all medications administered to a patient at a given in a statistical model would be unmanageable. Therefore, the estimation of the risk of DRP associated with each medication was based on a simpler model, where the risk of DRP observed with a given medication was compared to the average risk observed with all other medications prescribed to this patient population, controlling for the risk factors for DRP identified in the previous analysis. For this analysis, a set of multiple logistic regressions with each drug as independent variable and adjusted by the risk factors identified in the previous analysis was evaluated and, for those medications where a statistically significant association with the occurrence of one or more DRP was found at the 5% significance level, results are presented as adjusted odds-ratios of DRP with that medication to the average risk of all the other medications prescribed. The model was $\ln[p(\text{DRP}=1)/p(\text{DRP}=0)] = \beta_0 + \beta_1 x_1 + \beta_i x_i$, where β_0 is the regression constant, β are the partial regression coefficients, x_1 a binary variable coding for the medication, and x_i the co-variables. In the drugs identified in the previous analysis as

high-risk medications, the respective causes of DRP are presented descriptively. The interaction of each of those high-risk medications with each risk factor previously identified was tested with multiple logistic regression, with significant interactions assumed at the $p<0.10$ level. The model was $\ln[p(\text{DRP=1})/p(\text{DRP=0})] = \beta_0 + \beta_1 x_1 + \beta_i x_i + \beta_j x_1 x_i$, where β_0 is the regression constant, β are the partial regression coefficients, x_1 a binary variable coding for the medication, x_i the co-variables and $\beta_j x_1 x_i$ the interaction of the medication with each co-variable. Statistical analysis was performed with Stata 11 (Stata Corporation, College Station, TX, USA).

Patient and Public Involvement

Patients were not involved in the study.

RESULTS

During the 34-month study period, a total of 627 newborns were admitted to the NICU. Of these, 15 newborns were excluded (13 because they had no drugs prescribed and two patients in whom the length of stay was less than 24 hours). Six hundred twelve newborns remained eligible but 12 (1.96%) were excluded from the analysis because they had missing pharmacotherapy follow-up data. The analysis set of 600 newborns was observed for a total of 15,836 NICU days, with a median of 13 days (range 2 – 278 days). The study population consisted of 265 females (45.1%) and the mean gestational age was 32.1±4.1 weeks. On average, 8.2±6.0 medicines were prescribed to each newborn during the NICU stay. A total of 1,115 DRP were identified, with a mean of 1.9±2.6 DRP per patient. There were 237 (39.5%) patients with no DRP, 132 (22.0%) with one DRP, 71 (11.8%) with two DRP, and 160 (26.7%) with three or more DRP. Multiple DRP in the same patient could occur concurrently or simultaneously. Sixty-eight neonates (11.3%) died during the study (Table 1).

As shown in Table 2, univariate logistic regression analysis identified eight patient variables at admission that were associated with DRP: lower gestational age, lower birth weight, vaginal delivery, 1-minute and 5-minute APGAR< 7, neurological disorder, renal disorder, and cardiovascular disorder. In the multivariate logistic regression model, five remained significant: lower gestational age (adjusted odds-ratio (AOR) 0.85), 5-minute APGAR <7 (AOR 1.74), neurological disorder (AOR 2.49), renal disorder (AOR 5.75) and cardiac disorder (AOR 2.36) were risk factors at admission for DRP. The *c*-statistic for the multivariate model with five variables was 0.72.

DRP were associated with increased length of stay (38.2±39.6 days vs. 10.8±9.9 days, AOR 1.04, p<0.001), number of prescribed drugs (10.6±6.3 vs. 4.6±3.0, AOR 1.22, p<0.001) and number of clinical problems (5.57±2.86 vs. 3.39±1.51, AOR 1.22, p<0.001). There was no evidence of an association with a fatal outcome (11.4% vs. 11.3%, p=0.702).

Table 3 shows the medicines with a statistically significant increased risk of DRP compared to all the other prescribed medicines, adjusted for gestational age, 5-minute APGAR score <7, neurological disorder, renal disorder and cardiac disorder, could be obtained. The medications, and corresponding adjusted odds-ratios, were amphotericin B (AOR 4.80), meropenem (AOR 4.09), alprostadil (AOR 3.38), vancomycin (AOR 3.34), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.43), cefepime (AOR 1.88), amikacin (AOR 1.82) and omeprazole (AOR 1.66). Related to increase in the occurrence of DRP, there were statistically significant interactions between renal disease and the prescription of amphotericin (p=0.084) and of meropenem (p=0.054), and between a 5-minute APGAR score < 7 and prescription of vancomycin (p=0.038).

The frequency of prescription, and the prevalence of DRP related to those medications are also displayed in Table 3. These nine drugs represent 28.4% (1,395/4,917) of all medications prescribed in the NICU and accounted for 49.6% (622/1,252) of DRP involving medications.

The most prescribed medicines in the group were gentamicin (10.5%, 518) and meropenem (3.1%, 152), and these drugs were also the most often involved in DRP (16.9%, 211 and 8.0%, 100 respectively).

As for the causes of DRP involving the nine medicines (Table 4), dose selection was the most common cause for gentamicin (62.6%), amikacin (64.4%), meropenem (38.0%), cefepime (42.1%) and ciprofloxacin (30.77%). DRP involving omeprazole (53.57%), amphotericin B (45.7%) were most often related to drug use process. Alprostadil was mainly involved in others causes as wrong drug preparation technique (18.75%) and suspected adverse reaction (31.25%). Vancomycin was most often implicated in errors of prescription logistics (41.24%).

DISCUSSION

In our study, we observed that neonates with low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are more likely to have DRP during their stay in NICU. An assessment of the risk of DRP was made for alprostadil, amikacin, amphotericin B, cefepime, ciprofloxacin, gentamicin, meropenem, omeprazole and vancomycin. Such medicines accounted for less than one-third of the drugs prescribed in the NICU, and were involved in half of DRP, the majority being related to drug dose and to drug use.

Only a few studies have identified risk factors for the occurrence of DRP in hospitalized patients. Most of those studies were conducted in adult and pediatric wards for periods under six months and enrolled fewer than 400 patients.[19 – 22] We performed a study in the NICU involving 600 neonates for a period of three years and presenting a set of different predictor variables. Comparisons to the results of other studies are therefore difficult. Even so, several risk factors related to DRP identified in our study, such as age and clinical problems (cardiac,

neurological and renal disorders), were also observed in the works of Urbina et al.[16], Peterson et al.[21] and Blix et al.[23] although those studies were conducted in adult patients.

We also found that a low 5-minute APGAR was associated with a higher risk of DRP. This predictor is a specific neonatology parameter that measures the condition of the newborn at birth.[24] A low APGAR score usually represents a serious situation with the corresponding need for several therapeutic interventions which, in turn, increase the risk of DRP.

The detection of the clinical variables associated with DRP, as well as knowledge of the risk of DRP associated with each medication, represents a first step for the development of preventive strategies for enhanced patient safety and improvements in the process of care. Blix et al.[23] were the first authors to present risk estimates for drugs, while other papers[8, 19 – 22, 25, 26] have only described drugs involved in DRP. We were able to quantify the risk of DRP for a set of drugs that are involved in half of all DRP, namely alprostadil, omeprazole and several antimicrobials (amikacin, cefepime, ciprofloxacin, gentamicin, meropenem, amphotericin B and vancomycin). Pawluk et al.[25] e Stavroudis et al.[26] claimed that the risk of DRP associated with a medicine is directly related to the frequency of prescription. However, our results show that the medicines with greater odds of DRP (vancomycin and amphotericin B) were not the most prescribed. These results suggest that the risk of DRP is primarily associated with the chemical and pharmacological properties of a drug, therefore strongly related to the level of difficulty on setting the appropriate dose and on the drug's potential for adverse reactions, interactions and incompatibilities.

Inappropriate dose selection was the most common cause of DRP for aminoglycosides, cefepime and meropenem. In neonates, the adjustment of dose and regimen of antibiotics is extremely complex, the main reason for this being the rapid change in weight during the first days of life, as well as significant heterogeneity in the maturation of organs and systems across newborns.[12, 27] The lower than the recommended doses of those medicines administered in this

study were often due to a delay in the adjustment of the medication dose to the rapid weight gain of the neonate.

We observed that amphotericin B, ciprofloxacin and omeprazole were associated with inappropriate process of drug use, specifically with drug administration error, with drug incompatibility being the most frequent cause. Neonates have a high risk of exposure to drug incompatibilities because of the limited number of intravenous accesses, often leading to simultaneous administration of incompatible drugs through the same intravenous line. In addition, the requirements for delivery of drugs in this population, such as dilutions and reduced infusion rates, can lead to incompatibilities because of high concentrations and longer time of contact between incompatible medicines.[28] Such problems may be implicated in therapeutic failures due to drug degradation and even to thromboembolic complications, including cases of deaths, due to the precipitate formed reaching the bloodstream.[29 – 31].

Another medicine that had potential incompatibilities as the main cause of DRP was alprostadil. However, this medicine stands out for the significant percentage of cases of suspected adverse reactions. Fever, leukocytosis, dyspnea are reactions commonly observed in the neonate soon after the administration of alprostadil.[32] Because of these reactions and complications, this medication is for intensive therapy only.

The most common cause of vancomycin-related problems was errors of prescription logistics. These errors are characterized by the lack of important information in the prescription for the safe administration of the medications, or by the non-justifiable prescription of non-standard medicines in the institution. The lack of information on the time length of the infusion on the prescription was the most common error involving vancomycin, an important problem because rapid infusions in less than 60 minutes can lead to macular or maculopapular skin rashes (red man syndrome).[33]

This study has some limitations. The data were obtained from a single institution, which may somehow impair the generalization of our findings. Furthermore, as DRP were identified from patient records and medical reports, it is possible that administration errors have been under-estimated by recording failures. However, the same methodology has been adopted by other studies in DRP and, considering the scarcity of papers related to the topic of risk factors for DRP in NICU patients, we believe that our results are relevant. The large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRP and the adoption of a well-known DRP classification system are methodological features that contribute to the validity of our results. To our knowledge, this is the first study identifying patient variables and drugs associated with the occurrence of DRP, exclusively in NICU patients. The detection of those predictors is of great value for the identification of patients more prone to DRP and, therefore, for the development of screening tools. Such tools can support the work of the healthcare team, especially the clinical pharmacist, with the strengthening of preventive strategies and the optimization of resources and time.

Further research is needed in order to deepen the study of factors associated with DRP, aiming at the elaboration of risk stratification tools. Future studies should also analyse the influence of external factors on the incidence of DRP, which have not been addressed in our study, such as the number and characteristics of the NICU team members, the workplace conditions, the intra-team and inter-team communication, and the organization of the hospital. Another issue of considerable importance would be the investigation of clinical outcomes of DRP in NICUs.

CONCLUSION

In conclusion, low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are risk factors associated with the occurrence of DRP. We also

list nine medications with a risk for DRP above the average risk of other medications: alprostadil, amikacin, amphotericin B, cefepime, ciprofloxacin, gentamicin, meropenem, omeprazole and vancomycin. Although they are the most involved in DRP, these medicines account for less than one-third of the drugs prescribed in NICU. Inappropriate dose selection and inappropriate drug use (mainly potential drug incompatibilities) were the main causes of DRP related to those medicines.

Acknowledgements We are grateful to all pharmacists of the maternity hospital, especially to the pharmacists Dr. Elaine Alves and Dr. Tayne Cortez for contributing to the elaboration of the research project, the pharmacy residents Kadine Pontes and Bruna Nunes for making available the records of pharmacotherapeutic follow-up of patients, and pharmacy students Mayara Alves and Amanda Nascimento for helping in data collection and tabulation. We also thank all members of the NICU, physicians, physiotherapists, nurses and auxiliaries.

Contributions RDL participated in all stages of the study. MTS and TXC participated in the study design and revision of the manuscript. RRM and AGO contributed to the design and analysis of the study and the writing and revision of the manuscript. All authors approved the final version of the manuscript.

Funding This study received fund from the National Council of Technological and Scientific Development (CNPq).

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Institutional Review Board of the University Hospital Onofre Lopes (No. 580.201/2014), who waived the need for written informed consent because the study only evaluated data collected from clinical pharmacy records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Table 1 – Demographic and clinical characteristics of the study population (n = 600)

Characteristics	**Value***
Gestational age (weeks)	32.1±4.1
Female sex	265 (45.1%)
Birth weight (kilograms)	1.80±0.88
Length of stay (days)	13 (2 – 278)
Vaginal delivery	207 (35.2%)
PROM	162 (31.5%)
1-minute APGAR < 7	266 (45.8%)
5-minute APGAR < 7	76 (12.9%)
Number of clinical conditions	4.7±2.6
Neurological disorders	49 (8.2%)
Renal disorders	52 (8.7%)
Cardiac disorders	107 (17.9%)
Malformations	69 (11.5%)
Number of medications used	8.2±6.0
DRP (n=1,115)	
Patients with DRP	363 (60.5%)
Average number of DRP per patient	1.9 ± 2.6
Death	68 (11.3%)

*Values are mean±standard deviation, median (range), or n (%).

PROM, premature rupture of membranes; DRP, drug-related problems.

Table 2– Factors associated with occurrence of drug-related problems in neonatal intensive care

Variables	Univariate analysis				Multivariate analysis			
	OR	95%CI		p	AOR	95%CI		p
Collected at patient admission								
Gestational age in weeks	0.87	0.83	0.91	<0.001	0.85	0.81	0.89	0.003
Female sex	1.32	0.94	1.84	0.105				
Birth weight (kilograms)	0.55	0.46	0.68	<0.001				
Vaginal delivery	1.49	1.10	2.12	0.025				
PROM	1.21	0.83	1.78	0.322				
1-minute APGAR <7	1.49	1.06	2.08	0.020				
5-minute APGAR <7	2.03	1.18	3.48	0.010	1.74	1.00	3.13	0.050
Neurological disorder	2.12	1.09	4.17	0.028	2.49	1.09	5.69	0.031
Renal disorder	8.90	3.17	25.04	<0.001	5.75	1.85	17.8	0.002
Cardiac disorder	2.08	1.31	3.32	<0.001	2.36	1.31	4.24	0.004
Malformations	1.35	0.79	2.29	0.267				
Collected at NICU discharge								
Number of unique medications	1.36	1.28	1.44	<0.001	1.22	1.13	1.32	<0.001
Length of stay in days	1.08	1.06	1.10	<0.001	1.04	1.02	1.06	<0.001
Number of clinical problems	1.60	1.44	1.77	<0.001	1.22	1.13	1.32	<0.001

OR, odds-ratio; CI, confidence interval; AOR, adjusted odds-ratio; PROM, premature rupture of membranes.

Table 3 – Estimates of the risk of drug-related problems (DRP) associated with several drugs administered in NICUs, distributed by cases of DRP and frequency of prescription

Medicines	Adjusted Odds-ratio (95%CI)*	Cases of DRP		Frequency of prescriptions	
		n	%	n	%
Amphotericin B	4.80 (1.49 – 15.40)	46	3.7	48	1.0
Meropenem	4.09 (1.74 – 9.60)	100	8.0	152	3.1
Alprostadil	3.38 (1.67 – 6.84)	16	1.3	33	0.7
Vancomycin	3.34 (1.17– 9.52)	97	7.7	100	2.0
Ciprofloxacin	3.03 (1.34 – 6.85)	13	1.0	24	0.5
Gentamicin	2.43 (1.00 – 5.89)	211	16.9	518	10.5
Cefepime	1.88 (1.13 – 3.13)	38	3.0	193	3.9
Amikacin	1.82 (1.09 – 3.07)	73	5.8	181	3.7
Omeprazole	1.66 (1.02 – 2.59)	28	2.2	146	3.0
Total		4,917	100,0	1,252	100,0

*Odds ratio adjusted for gestational age, 5-minute APGAR <7, neurological disorder, renal disorder and cardiac disorder. The *p*-value for each medicine was < 0.05.

CI, confidence interval.

Table 4 – Type and frequency of the causes of DRP in medicines associated with high-risk of drug-related problems (DRP) in neonatal intensive care

Medicines	Causes of DRP*				
	Drug selection	Dose selection	Drug use process	Logistics	Others†
Alprostadil		2 (12.5%)	6 (37.5%)		8 (50.0%)
Amikacin		47 (64.4%)	14 (19.2%)	8 (10.9%)	4 (5.5%)
Amphotericin B		7 (15.2%)	21 (45.7%)	11 (23.9%)	7 (15.2%)
Cefepime		16 (42.1%)	10 (26.32%)	11 (28.95%)	1 (2.63%)
Ciprofloxacin	3 (23.08%)	4 (30.77%)	2 (15.38%)	4 (30.77%)	
Gentamicin		132 (62.6%)	73 (34.6%)	4 (1.9%)	2 (0.9%)
Meropenem	1 (1.0%)	38 (38.0%)	25 (25.0%)	29 (29.0%)	7 (7.0%)
Omeprazole		1 (3.57%)	15 (53.57%)	12 (42.86%)	
Vancomycin	1 (1.0%)	28 (28.9%)	24 (24.74%)	40 (41.24%)	4 (4.12%)

*Causes of DRP according to the Pharmaceutical Care Network Europe (PCNE) classification systemv.6.2.[4]

†Others included drug form, treatment duration, and others specific causes (e. g. adverse reaction and wrong drug preparation technique).

Supplementary file 1 – PCNE systems v6.2 and operational definitions of the study for the classification of drug related problems (DRP)

Code – Categories	**Operational definition**
Problems	
P1 – Treatment effectiveness	There is a (potential) problem with the (lack of) effect of the pharmacotherapy.
P1.1 – No effect of drug treatment/therapy failure	The drug treatment cannot lead or does not lead to the improvement of the patient's symptoms (e.g. early sepsis not responsive to treatment of ampicillin and gentamicin).
P1.2 – Effect of drug treatment not optimal	The drug treatment may lead or lead to a partial improvement of the patient's symptoms (e.g. paracetamol sub-dose leading to a partial pain relief).
P1.3 – Wrong effect of drug treatment	Not applicable for the study.
P1.4 – Untreated indication	There are symptoms that need treatment but are not being treated at the moment (e.g. patient has a fever but is not in drug treatment).
P2 – Adverse reactions	Patient suffers, or will possibly suffer, from an adverse drug event.
P2.1 – Non-allergic adverse drug event	The drug treatment may be related to an unintended, non-allergic adverse event with doses normally used for the intended indication (e.g. tachycardia reportedly related to the use of caffeine).
P2.2 – Allergic adverse drug event	The drug treatment may be related to an unintended, allergic adverse event with doses normally used for the intended indication (e.g. skin rash reportedly related to the use of penicillin).
P2.3 – Toxic adverse drug-event	The drug treatment may lead or lead to an unintended adverse event occurring in doses higher than that normally used for the intended indication (e.g. captopril overdose leading to hypotension).
P3 – Treatment costs	The drug treatment is more expensive than necessary.
P3.1 – Drug treatment more costly than necessary	The medicine is more expensive than other medicines available or there is a waste in its preparation (reconstitution and dilution).
P3.2 – Unnecessary drug-treatment	The prescribed medication is not necessary or no longer necessary.
P4 – Others	Other problems not specified above
P4.1 – Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes	Not applicable for the study.
P4.2 – Unclear problem/complaint	Problem not clarified or without defined classification.

Causes	
C1 – Drug selection	The cause of the DRP is related to the selection of the drug.
C1.1 – Inappropriate drug (including contraindication)	Selected drug is inappropriate for the intended indication or is contraindicated for the patient (e.g. ampicillin prescribed to allergic patient).
C1.2 – No indication for drug	There is no indication for the selected drug.
C1.3 – Inappropriate combination of drugs, or drugs and food	The selected drug interacts or may interact physically, physico-chemical or chemically with other drugs or foods (e.g. patient is receiving ciprofloxacin and fluconazole, medicines that may increase the risk of QT interval prolongation and, consequently, ventricular arrhythmias).
C1.4 – Inappropriate duplication of therapeutic group or active ingredient	The physician order inappropriately has medicines of same therapeutic group or active ingredients to treat different symptoms (e.g. ibuprofen indicated for closure of the ductus arteriosus and paracetamol indicated for fever present in the same physician order).
C1.5 – Indication for drug-treatment not noticed	The appropriate drug is not used to treat the symptom because the existence of the symptom is not noticed (e.g. patient has a fever that is not noticed and, therefore, is not in drug treatment).
C1.6 – Too many drugs prescribed for indication	The physician order inappropriately has medicines indicated to treat the same symptoms (e.g. ranitidine and omeprazole both indicated for gastrointestinal haemorrhage present in the same physician order).
C1.7 – More cost-effective drug available	There are cheaper and effective (or more effective) medications to treat the symptoms.
C1.8 – Synergistic/preventive drug required and not given	There is a requirement to use a medication to improve an existing treatment or to prevent the development of another symptom, but it is not used. (e.g. ferrous sulfate requirement for the prevention of anemia).
C1.8 – New indication for drug treatment presented	The patient presents a new symptom that is not being treated (e.g. patient has a recent fever and requires drug treatment).
C2 – Drug form	The cause of the DRP is related to the selection of the drug form.
C2.1 – Inappropriate drug form	The drug has an inappropriate form and/or formula for the patient (e.g. oral caffeine solution prescribed for neonate with feeding intolerance).
C3 – Dose selection	The cause of the DRP is related to the selection of the dosage schedule.
C3.1 – Drug dose too low	Selected dose is 20% lower than the minimum dose defined for the intended indication (e.g.

	cefepime prescribed 45 mg/kg instead of 60 mg/kg daily).
C3.2 – Drug dose too high	Selected dose is 20% higher than the maximum dose defined for the intended indication (e.g. oxacillin prescribed 150 mg/kg instead of 100 mg/kg daily).
C3.4 – Dosage regimen not frequent enough	Selected dosing frequency is less than that defined for the intended indication (e.g. gentamicin prescribed every 48 hours instead of every 36 hours).
C3.5 – Dosage regimen too frequent	Selected dosing frequency is higher than that defined for the intended indication (e.g. amikacin prescribed every 24 hours instead of every 36 hours).
C3.6 – No therapeutic drug monitoring	Monitoring serum levels of the drug is required, but it is not done.
C3.7 – Pharmacokinetic problem requiring dose adjustment	Not applicable for the study.
C3.8 – Deterioration/improvement of disease state requiring dose adjustment	Change in disease state requiring dose adjustment (e.g. vancomycin dose adjustment because of the improvement in renal function in patients with renal impairment).
C4 – Treatment duration	The cause of the DRP is related to the duration of therapy.
C4.1 – Duration of treatment too short	Duration of treatment is shorter than that defined for the indication treated (e.g. penicillin prescribed for eight days instead of ten days).
C4.2 – Duration of treatment too long	Duration of treatment is longer than that defined for the indication treated (e.g. meropenem prescribed for sixteen days instead of fourteen days).
C5 – Drug use process	The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label).
C5.1 – Inappropriate timing of administration and/or dosing intervals	Drug administered at wrong times or intervals (e.g. gentamicin dose scheduled for 16 hours but administered at 18 hours).
C5.2 – Drug under-administered	Drug administered at a frequency lower than the physician order (e.g. ranitidine prescribed twice daily but administered only once).
C5.3 – Drug over-administered	Drug administered at a frequency higher than the physician order (e.g. aminophylline prescribed twice daily but administered three time).
C5.4 – Drug not taken/administered at all	Drug dose is not administered in full (e.g. ampicillin dose administered in half).
C5.5 – Wrong drug administered	Drug is administered wrong (e.g. norepinephrine was administered in the wrong route).

C5.6 – Drug abused (unregulated overuse)	Not applicable for the study.
C5.7 – Patient unable to use drug/form as directed	Not applicable for the study.
C6 – Logistics	The cause of the DRP can be related to the logistics of the prescribing and dispensing process.
C6.1 – Prescribed drug not available	Prescribed drug is not available in the institution and there is no other effective drug (e.g. ursodiol is prescribed but not available in the hospital and there is no other drug alternative).
C6.2 – Prescribing error (necessary information missing)	Missing necessary information on the drug prescription that may generate a medication error (e.g. vancomycin is prescribed, but there is no information on the minimum recommended time for administration).
C6.3 – Dispensing error (wrong drug or dose dispensed)	Drug is dispensed wrong or dispensed in the wrong dosage form or dose (e.g. dispensed intravenous furosemide instead of oral).
C7 – Patient	The cause of the DRP can be related to the personality or behaviour of the patient.
C7.1 – Patient forgets to use/take drug	Not applicable for the study.
C7.2 – Patient uses unnecessary drug	Not applicable for the study.
C7.3 – Patient takes food that interacts	Not applicable for the study.
C7.4 – Patient stored drug inappropriately	Not applicable for the study.
C8 – Others	Other causes not specified above.
C8.1 – Others specific causes	The problem arises due to other specific causes (e.g. adverse events related to alprostadil, cefepime prepared wrongly and etc.).
C8.2 – No obvious cause	Not applicable for the study.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4/5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6/7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7/8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7/8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8/9/10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk assessment of patient factors and medications for drug-related problems from a prospective longitudinal study of newborns admitted to a neonatal intensive care unit

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024377.R2
Article Type:	Research
Date Submitted by the Author:	18-Mar-2019
Complete List of Authors:	Leopoldino, Ramon; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Pharmacy Santos, Marco; Maternidade Escola Januário Cicco Costa, Tatiana; Universidade Federal do Rio Grande do Norte/ Maternidade Escola Januário Cicco Martins, Rand; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Department of Pharmacy Oliveira, António; Universidade Federal do Rio Grande do Norte Centro de Ciencias da Saude, Department of Pharmacy
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care, Pharmacology and therapeutics
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS

Title: Risk assessment of patient factors and medications for drug-related problems from a prospective longitudinal study of newborns admitted to a neonatal intensive care unit

Running title: Drug-related problems in neonatal care

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Key words: Neonatal intensive & critical care; Health & safety; Adverse events

Abstract: 262 words

Text: 3,178 words

Tables and Figures: 4

ABSTRACT

Objective: To identify patient factors and medications associated with the occurrence of Drug Related Problems (DRP) in neonates admitted to Neonatal Intensive Care Units (NICU).

Design: Prospective longitudinal study.

Setting: NICU of a teaching hospital in Brazil.

Participants: The data were collected from the records of the clinical pharmacy service of all neonates admitted between April 2014 and January 2017, excluding neonates with length of stay in the NICU < 24 hours or without prescribed drugs.

Primary outcome measures: The occurrence of one or more DRP (conditions interfering in the patient's pharmacotherapy with potential undesired clinical outcomes).

Results: The study observed 600 neonates who had a median length of stay in the NICU of 13 days (range 2 to 278 days). DRP were identified in most neonates (60.5%). In a multivariate logistic regression model, the factors independently associated with DRP were gestational age (adjusted odds-ratio (AOR) 0.85, 95% confidence interval (CI) 0.81–0.89), 5-minute APGAR < 7 (AOR 1.74, 95% CI 1.00–3.13), neurological disease (AOR 2.49, 95%CI 1.09–5.69), renal disease (AOR 5.75, 95%CI 1.85–17.8) and cardiac disease (AOR 2.36, 95%CI 1.31–4.24). The medications with greater risk for DRP were amphotericin B (AOR 4.80), meropenem (AOR 4.09), alprostadil (AOR 3.38), vancomycin (AOR 3.34), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.43), cefepime (AOR 1.88), amikacin (AOR 1.82) and omeprazole (AOR 1.66). These medicines represent one-third of all prescribed drugs.

Conclusions: Gestational age, 5-minute APGAR < 7 and neurological, cardiac and renal disease are risk factors for DRP in NICUs. Alprostadil, omeprazole and several anti-infectives were associated with greater risk of DRP.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study identifying patient variables and drugs associated with the occurrence of Drug-related problems (DRP), exclusively in Neonatal Intensive Care Unit (NICU) patients.
- The validity of the results is strengthened by the large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRP and the adoption of a well-known DRP classification system.
- However, the data were obtained from a single institution, which may somehow impair the generalization of our findings.
- It is also possible that administration errors have been under-estimated by recording failures.

INTRODUCTION

The Intensive Care Unit (ICU) is a complex environment, characterized by polypharmacy, transfusions and frequent surgical procedures.[1] Neonatal Intensive Care Units (NICU) may pose additional hazards to patient safety because of the frequent usage of off-label and unlicensed medicines and of decimal dilutions of intravenous medicines.[2, 3] In addition, because of their physiological immaturity and rapid growth, neonates exhibit large interindividual variability in drug metabolism and excretion.[2] Such characteristics may predispose neonates to drug-related problems (DRP).

DRP are events or circumstances arising from the patient's pharmacotherapy that may actually or potentially interfere with health outcomes.[4] Those events include errors in the drug therapy processes (prescription, dispensation and administration) and adverse drug events (any untoward event related to medication that results in harm to the patient).[5 – 7]

In paediatric wards, DRP occur in about half of the patients and most of these are preventable.[8] However, there is very little information on DRP in children in intensive care units, especially among neonates.

It is believed that DRP are particularly frequent and serious in neonates.[9, 10] Neonates are very sensitive to dose variations because of their particular pharmacokinetics and pharmacodynamics, consequence of the lower drug metabolism and clearance, low levels of plasma proteins, high proportion of body water and level of receptor expression and sensitivity.[11, 12] Some authors have shown that harm involving medicines is common in NICUs, with incidence rates ranging from 10 to 20 cases per 1,000 patient-days.[13, 14] Such harm can lead to prolonged hospitalization time and, in extreme cases, to the death of patients. It also generates an increase in hospital costs.[13, 15] Thus, the development of effective preventive strategies directed to DRP is of great relevance for the improvement of health care and one step towards this goal is the identification of patients susceptible to DRP.[16]

Therefore, the purpose of this study was to identify risk factors for the occurrence of one or more DRP in NICU, to assess the risk associated with commonly used medications and to describe the causes of DRP in the medications with greater risk of DRP in neonates.

METHODS

This was an observational, prospective, longitudinal study conducted from April 2014 to January 2017 in the 20-bed NICU of a teaching maternity hospital specialized in high-risk pregnancy. All neonates admitted to the NICU during the study period were prospectively evaluated for inclusion in the study. Inclusion criteria were a NICU stay longer than 24 hours and at least one prescribed drug. Neonates who were prescribed exclusively with electrolytes, parenteral nutrition, blood products, oxygen therapy, diagnostic agents, and vitamin and mineral supplements were excluded from the study, as those products were not considered as drugs.

In the absence of information in the literature on risk factors for DRP in neonates, the patient variables selected as candidates for assessment in a multivariate risk model were those that could be collected at NICU admission on every neonate and that reflect serious conditions that are usually associated with enhanced pharmacotherapy. The data collected from each neonate included sex, gestational age, birth weight, type of delivery (vaginal or caesarean), occurrence of premature rupture of membranes (PROM), 1-minute and 5-minute APGAR, a diagnosis of neurological, renal or cardiac disorder, and malformations. The APGAR is a score that evaluates the birth condition of newborns in the first and fifth minutes of life, values below seven being considered an ominous sign.[17] In addition to those risk factors that may be predictors of DRP, patient variables representing the complexity of care (number of unique medications prescribed, number of different clinical problems, and NICU length of stay in days) were also collected from each patient.

The study also wanted to identify medications that were associated with increased risk of DRP in neonates and, therefore, all the medications prescribed to each neonate during the NICU stay were recorded.

The identification of DRP was actively performed on a daily basis by the NICU clinical pharmacy team (a chief pharmacist and four assistant pharmacists) through the analysis of medical charts, medication orders and nursing records, seeking entries that might indicate the occurrence of a DRP. The pharmacists involved in this research were permanent members of the clinical pharmacy team allocated to the NICU of our institution. The identification of DRP and their notification to the medical team is an important part of their routine work and all were experienced in the detection of DRP. For each identified DRP, its causes were then classified according to the Pharmaceutical Care Network Europe system v.6.2[4] (see supplementary file 1). This classification was carried out independently by two pharmacists (RDL and MTS), supported by the Neofax® textbook (Thomson Reuters, New York, USA), as well as the Micromedex® (Truven Health Analytics, Michigan, USA) and Uptodate® (WoltersKluwer, Alphenaanden Rijn, NL) databases that provided authoritative information on adverse drug reaction and drug-drug interactions. Whenever the two evaluators disagreed upon the classification of the cause of a DRP, a third pharmacist (TXC) was called in to break the tie.

Statistical analysis

The target sample size was set at 600 patients, a number that would afford 70% power to identify associations with an odds-ratio of 1.30 or greater for patient factors with a prevalence over 30%[18]. All variables are described by mean±standard deviation, median (range), or as absolute and relative frequency, as appropriate. For the identification of risk factors of DRP, an initial selection of patient variables at NICU admission (sex, gestational age, birth weight, type of delivery, occurrence of PROM, 1-minute and 5-minute APGAR, a diagnosis of neurological, renal or cardiac disorder, and malformations) were tested for association with the occurrence

of one or more DRP with logistic regression. All variables were binary, except gestational age and birth weight that were continuous. The set of patient variables whose association with DRP was statistically significant at the 0.10 significance level in univariate logistic regression was analysed by stepwise backward multiple logistic regression, and those variables significant at the 0.05 level were retained in the final model. Variables collected only at discharge from the NICU (number of unique medications, length of stay and number of clinical problems) were analysed in a separate logistic model consisting of those three variables. Results of these analyses are presented as odds-ratios adjusted by the other variables in the model (AOR) and 95% confidence intervals (CI). The model was $\ln[p(\text{DRP}=1)/p(\text{DRP}=0)] = \beta_0 + \beta_i x_i$, where β_0 is the regression constant, β_i the partial regression coefficients and x_i the independent variables.

It was hypothesized that some medications could be singled out because they are associated with a significantly higher risk of DRP, through a combination of complex dosing and/or administration, and of frequency of use. Those drugs would be high-risk medications requiring close monitoring from the clinical pharmacy team. In the NICU setting, very often several medications are prescribed concurrently, sometimes by simultaneously through the same intravenous line, and accounting for the interplay of all medications administered to a patient at a given in a statistical model would be unmanageable. Therefore, the estimation of the risk of DRP associated with each medication was based on a simpler model, where the risk of DRP observed with a given medication was compared to the average risk observed with all other medications prescribed to this patient population, controlling for the risk factors at NICU admission for DRP that were identified in the previous analysis. For this analysis, a set of multiple logistic regressions with each drug as independent variable and adjusted by the risk factors at NICU admission identified in the previous analysis was evaluated and, for those medications where a statistically significant association with the occurrence of one or more DRP was found at the 5% significance level, results are presented as adjusted odds-ratios of

DRP with that medication to the average risk of all the other medications prescribed. The model was $\ln[p(\text{DRP=1})/p(\text{DRP=0})] = \beta_0 + \beta_1 x_1 + \beta_i x_i$, where β_0 is the regression constant, β are the partial regression coefficients, x_1 a binary variable coding for the medication, and x_i the co-variables. In the drugs identified in the previous analysis as high-risk medications, the respective causes of DRP are presented descriptively. The interaction of each of those high-risk medications with each risk factor previously identified was tested with multiple logistic regression, with significant interactions assumed at the $p<0.10$ level. The model was $\ln[p(\text{DRP=1})/p(\text{DRP=0})] = \beta_0 + \beta_1 x_1 + \beta_i x_i + \beta_j x_1 x_i$, where β_0 is the regression constant, β are the partial regression coefficients, x_1 a binary variable coding for the medication, x_i the co-variables and $\beta_j x_1 x_i$ the interaction of the medication with each co-variable. Statistical analysis was performed with Stata 11 (Stata Corporation, College Station, TX, USA).

Patient and Public Involvement

Patients were not involved in the study.

RESULTS

During the 34-month study period, a total of 627 newborns were admitted to the NICU. Of these, 15 newborns were excluded (13 because they had no drugs prescribed and two patients in whom the length of stay was less than 24 hours). Six hundred twelve newborns remained eligible but 12 (1.96%) were excluded from the analysis because they had missing pharmacotherapy follow-up data. The analysis set of 600 newborns was observed for a total of 15,836 NICU days, with a median of 13 days (range 2 – 278 days). The study population consisted of 265 females (45.1%) and the mean gestational age was 32.1±4.1 weeks. On average, 8.2±6.0 medicines were prescribed to each newborn during the NICU stay. A total of 1,115 DRP were identified, with a mean of 1.9±2.6 DRP per patient. There were 237 (39.5%)

patients with no DRP, 132 (22.0%) with one DRP, 71 (11.8%) with two DRP, and 160 (26.7%) with three or more DRP. Multiple DRP in the same patient could occur concurrently or simultaneously. Sixty-eight neonates (11.3%) died during the study (Table 1).

As shown in Table 2, univariate logistic regression analysis identified eight patient variables at admission that were associated with DRP: lower gestational age, lower birth weight, vaginal delivery, 1-minute and 5-minute APGAR< 7, neurological disorder, renal disorder, and cardiovascular disorder. In the multivariate logistic regression model, five remained significant: lower gestational age (33.5 ± 3.7 vs. 31.2 ± 4.1 weeks, adjusted odds-ratio (AOR) 0.85, p<0.01), 5-minute APGAR <7 (73.7% vs. 26.3%, AOR 1.74, p<0.01), neurological disorder (75.5% vs. 24.5%, AOR 2.49, p=0.03), renal disorder (92.3% vs. 7.7%, AOR 5.75, p<0.01) and cardiac disorder (73.8% vs. 26.2%, AOR 2.36, p<0.01) were risk factors at admission for DRP. The *c*-statistic for the multivariate model with five variables was 0.72.

DRP were associated with increased length of stay (38.2±39.6 days vs. 10.8±9.9 days, AOR 1.04, p<0.001), number of prescribed drugs (10.6±6.3 vs. 4.6±3.0, AOR 1.22, p<0.001) and number of clinical problems (5.57±2.86 vs. 3.39±1.51, AOR 1.22, p<0.001). There was no evidence of an association with a fatal outcome (11.4% vs. 11.3%, p=0.702).

Table 3 shows the medicines with a statistically significant increased risk of DRP compared to all the other prescribed medicines, adjusted for gestational age, 5-minute APGAR score <7, neurological disorder, renal disorder and cardiac disorder. The medications, and corresponding adjusted odds-ratios, were amphotericin B (AOR 4.80), meropenem (AOR 4.09), alprostadil (AOR 3.38), vancomycin (AOR 3.34), ciprofloxacin (AOR 3.03), gentamicin (AOR 2.43), cefepime (AOR 1.88), amikacin (AOR 1.82) and omeprazole (AOR 1.66). Related to increase in the occurrence of DRP, there were statistically significant interactions between renal disease and the prescription of amphotericin (p=0.084) and of meropenem (p=0.054), and between a 5-minute APGAR score < 7 and prescription of vancomycin (p=0.038).

The frequency of prescription, and the prevalence of DRP related to those medications are also displayed in Table 3. These nine drugs represent 28.4% (1,395/4,917) of all medications prescribed in the NICU and accounted for 49.7% (622/1,252) of problems involving medications. The most prescribed medicines in the group were gentamicin (10.5%, 518) and meropenem (3.1%, 152), and these drugs were also the most often involved in DRP (16.9%, 211 and 8.0%, 100 respectively).

As for the causes of DRP involving the nine medicines (Table 4), dose selection was the most common cause for gentamicin (62.6%), amikacin (64.4%), meropenem (38.0%), cefepime (42.1%) and ciprofloxacin (30.77%). DRP involving omeprazole (53.57%), amphotericin B (45.7%) were most often related to drug use process. Alprostadil was mainly involved in others causes as wrong drug preparation technique (18.75%) and suspected adverse reaction (31.25%). Vancomycin was most often implicated in errors of prescription logistics (41.24%).

DISCUSSION

In our study, we observed that neonates with low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are more likely to have DRP during their stay in NICU. An assessment of the risk of DRP was made for alprostadil, amikacin, amphotericin B, cefepime, ciprofloxacin, gentamicin, meropenem, omeprazole and vancomycin. Such medicines accounted for less than one-third of the drugs prescribed in the NICU, and were involved in half of DRP, the majority being related to drug dose and to drug use.

Only a few studies have identified risk factors for the occurrence of DRP in hospitalized patients. Most of those studies were conducted in adult and pediatric wards for periods under six months and enrolled fewer than 400 patients.[19 – 22] We performed a study in the NICU involving 600 neonates for a period of three years and presenting a set of different predictor

variables. Comparisons to the results of other studies are therefore difficult. Even so, several risk factors related to DRP identified in our study, such as age and clinical problems (cardiac, neurological and renal disorders), were also observed in the works of Urbina et al.[16], Peterson et al.[21] and Blix et al.[23] although those studies were conducted in adult patients.

We also found that a low 5-minute APGAR was associated with a higher risk of DRP. This predictor is a specific neonatology parameter that measures the condition of the newborn at birth.[24] A low APGAR score usually represents a serious situation with the corresponding need for several therapeutic interventions which, in turn, increase the risk of DRP.

The detection of the clinical variables associated with DRP, as well as knowledge of the risk of DRP associated with each medication, represents a first step for the development of preventive strategies for enhanced patient safety and improvements in the process of care. Blix et al.[23] were the first authors to present risk estimates for drugs, while other papers[8, 19 – 22, 25, 26] have only described drugs involved in DRP. We were able to quantify the risk of DRP for a set of drugs that are involved in half of all DRP, namely alprostadil, omeprazole and several antimicrobials (amikacin, cefepime, ciprofloxacin, gentamicin, meropenem, amphotericin B and vancomycin). Pawluk et al.[25] e Stavroudis et al.[26] claimed that the risk of DRP associated with a medicine is directly related to the frequency of prescription. However, our results show that the medicines with greater odds of DRP (vancomycin and amphotericin B) were not the most prescribed. These results suggest that the risk of DRP is primarily associated with the chemical and pharmacological properties of a drug, therefore strongly related to the level of difficulty on setting the appropriate dose and on the drug's potential for adverse reactions, interactions and incompatibilities.

Inappropriate dose selection was the most common cause of DRP for aminoglycosides, cefepime and meropenem. In neonates, the adjustment of dose and regimen of antibiotics is extremely complex, the main reason for this being the rapid change in weight during the first

days of life, as well as significant heterogeneity in the maturation of organs and systems across newborns.[12, 27] The lower than the recommended doses of those medicines administered in this study were often due to a delay in the adjustment of the medication dose to the rapid weight gain of the neonate.

We observed that amphotericin B, ciprofloxacin and omeprazole were associated with inappropriate process of drug use, specifically with drug administration error, with drug incompatibility being the most frequent cause. Neonates have a high risk of exposure to drug incompatibilities because of the limited number of intravenous accesses, often leading to simultaneous administration of incompatible drugs through the same intravenous line. In addition, the requirements for delivery of drugs in this population, such as dilutions and reduced infusion rates, can lead to incompatibilities because of high concentrations and longer time of contact between incompatible medicines.[28] Such problems may be implicated in therapeutic failures due to drug degradation and even to thromboembolic complications, including cases of deaths, due to the precipitate formed reaching the bloodstream.[29 – 31].

Another medicine that had potential incompatibilities as the main cause of DRP was alprostadil. However, this medicine stands out for the significant percentage of cases of suspected adverse reactions. Fever, leukocytosis, dyspnea are reactions commonly observed in the neonate soon after the administration of alprostadil.[32] Because of these reactions and complications, this medication is for intensive therapy only.

The most common cause of vancomycin-related problems was errors of prescription logistics. These errors are characterized by the lack of important information in the prescription for the safe administration of the medications, or by the non-justifiable prescription of non-standard medicines in the institution. The lack of information on the time length of the infusion on the prescription was the most common error involving vancomycin, an important problem

because rapid infusions in less than 60 minutes can lead to macular or maculopapular skin rashes (red man syndrome).[33]

This study has some limitations. The data were obtained from a single institution, which may somehow impair the generalization of our findings. Furthermore, as DRP were identified from patient records and medical reports, it is possible that administration errors have been under-estimated by recording failures. However, the same methodology has been adopted by other studies in DRP and, considering the scarcity of papers related to the topic of risk factors for DRP in NICU patients, we believe that our results are relevant. The large cohort size, the prospective data collection, the longitudinal design, the in-situ evaluation of DRP and the adoption of a well-known DRP classification system are methodological features that contribute to the validity of our results. To our knowledge, this is the first study identifying patient variables and drugs associated with the occurrence of DRP, exclusively in NICU patients. The detection of those predictors is of great value for the identification of patients more prone to DRP and, therefore, for the development of screening tools. Such tools can support the work of the healthcare team, especially the clinical pharmacist, with the strengthening of preventive strategies and the optimization of resources and time.

Further research is needed in order to deepen the study of factors associated with DRP, aiming at the elaboration of risk stratification tools. Future studies should also analyse the influence of external factors on the incidence of DRP, which have not been addressed in our study, such as the number and characteristics of the NICU team members, the workplace conditions, the intra-team and inter-team communication, and the organization of the hospital. Another issue of considerable importance would be the investigation of clinical outcomes of DRP in NICUs.

CONCLUSION

In conclusion, low gestational age, low 5-minute APGAR, neurological disorder, renal disorder and cardiac disorder are risk factors associated with the occurrence of DRP. We also list nine medications with a risk for DRP above the average risk of other medications: alprostadil, amikacin, amphotericin B, cefepime, ciprofloxacin, gentamicin, meropenem, omeprazole and vancomycin. Although they are the most involved in DRP, these medicines account for less than one-third of the drugs prescribed in NICU. Inappropriate dose selection and inappropriate drug use (mainly potential drug incompatibilities) were the main causes of DRP related to those medicines.

Acknowledgements We are grateful to all pharmacists of the maternity hospital, especially to the pharmacists Dr. Elaine Alves and Dr. Tayne Cortez for contributing to the elaboration of the research project, the pharmacy residents Kadine Pontes and Bruna Nunes for making available the records of pharmacotherapeutic follow-up of patients, and pharmacy students Mayara Alves and Amanda Nascimento for helping in data collection and tabulation. We also thank all members of the NICU, physicians, physiotherapists, nurses and auxiliaries.

Contributions RDL participated in all stages of the study. MTS and TXC participated in the study design and revision of the manuscript. RRM and AGO contributed to the design and analysis of the study and the writing and revision of the manuscript. All authors approved the final version of the manuscript.

Funding This study received fund from the National Council of Technological and Scientific Development (CNPq).

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the Institutional Review Board of the University Hospital Onofre Lopes (No. 580.201/2014), who waived the need for written informed consent because the study only evaluated data collected from clinical pharmacy records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Table 1 – Demographic and clinical characteristics of the study population (n = 600)

Characteristics	**Value***
Gestational age (weeks)	32.1±4.1
Female sex	265 (45.1%)
Birth weight (kilograms)	1.80±0.88
Length of stay (days)	13 (2 – 278)
Vaginal delivery	207 (35.2%)
PROM	162 (31.5%)
1-minute APGAR < 7	266 (45.8%)
5-minute APGAR < 7	76 (12.9%)
Number of clinical conditions	4.7±2.6
Neurological disorders	49 (8.2%)
Renal disorders	52 (8.7%)
Cardiac disorders	107 (17.9%)
Malformations	69 (11.5%)
Number of medications used	8.2±6.0
DRP (n=1,115)	
Patients with DRP	363 (60.5%)
Average number of DRP per patient	1.9 ± 2.6
Death	68 (11.3%)

*Values are mean±standard deviation, median (range), or n (%).

PROM, premature rupture of membranes; DRP, drug-related problems.

Table 2– Factors associated with occurrence of drug-related problems in neonatal intensive care

Variables	Univariate analysis				Multivariate analysis			
	OR	95%CI		p	AOR	95%CI		p
Collected at patient admission								
Gestational age in weeks	0.87	0.83	0.91	<0.001	0.85	0.81	0.89	0.003
Female sex	1.32	0.94	1.84	0.105				
Birth weight (kilograms)	0.55	0.46	0.68	<0.001				
Vaginal delivery	1.49	1.10	2.12	0.025				
PROM	1.21	0.83	1.78	0.322				
1-minute APGAR <7	1.49	1.06	2.08	0.020				
5-minute APGAR <7	2.03	1.18	3.48	0.010	1.74	1.00	3.13	0.050
Neurological disorder	2.12	1.09	4.17	0.028	2.49	1.09	5.69	0.031
Renal disorder	8.90	3.17	25.04	<0.001	5.75	1.85	17.8	0.002
Cardiac disorder	2.08	1.31	3.32	<0.001	2.36	1.31	4.24	0.004
Malformations	1.35	0.79	2.29	0.267				
Collected at NICU discharge								
Number of unique medications	1.36	1.28	1.44	<0.001	1.22	1.13	1.32	<0.001
Length of stay in days	1.08	1.06	1.10	<0.001	1.04	1.02	1.06	<0.001
Number of clinical problems	1.60	1.44	1.77	<0.001	1.22	1.13	1.32	<0.001

OR, odds-ratio; CI, confidence interval; AOR, adjusted odds-ratio; PROM, premature rupture of membranes.

Table 3 – Estimates of the risk of drug-related problems (DRP) associated with several drugs administered in NICUs, distributed by cases of DRP and frequency of prescription

Medicines	Adjusted Odds-ratio (95%CI)*	Cases of DRP		Frequency of prescriptions	
		n	%	n	%
Amphotericin B	4.80 (1.49 – 15.40)	46	3.7	48	1.0
Meropenem	4.09 (1.74 – 9.60)	100	8.0	152	3.1
Alprostadil	3.38 (1.67 – 6.84)	16	1.3	33	0.7
Vancomycin	3.34 (1.17– 9.52)	97	7.7	100	2.0
Ciprofloxacin	3.03 (1.34 – 6.85)	13	1.0	24	0.5
Gentamicin	2.43 (1.00 – 5.89)	211	16.9	518	10.5
Cefepime	1.88 (1.13 – 3.13)	38	3.0	193	3.9
Amikacin	1.82 (1.09 – 3.07)	73	5.8	181	3.7
Omeprazole	1.66 (1.02 – 2.59)	28	2.2	146	3.0
Others		630	50.3	3,522	71.6
Total		1,252	100.0	4,917	100.0

*Odds ratio adjusted for gestational age, 5-minute APGAR <7, neurological disorder, renal disorder and cardiac disorder. The *p*-value for each medicine was < 0.05.

CI, confidence interval.

Table 4 – Type and frequency of the causes of DRP in medicines associated with high-risk of drug-related problems (DRP) in neonatal intensive care

Medicines	Causes of DRP*				
	Drug selection	Dose selection	Drug use process	Logistics	Others†
Amphotericin B		7 (15.2%)	21 (45.7%)	11 (23.9%)	7 (15.2%)
Meropenem	1 (1.0%)	38 (38.0%)	25 (25.0%)	29 (29.0%)	7 (7.0%)
Alprostadil		2 (12.5%)	6 (37.5%)		8 (50.0%)
Vancomycin	1 (1.0%)	28 (28.9%)	24 (24.74%)	40 (41.24%)	4 (4.12%)
Ciprofloxacin	3 (23.08%)	4 (30.77%)	2 (15.38%)	4 (30.77%)	
Gentamicin		132 (62.6%)	73 (34.6%)	4 (1.9%)	2 (0.9%)
Cefepime		16 (42.1%)	10 (26.32%)	11 (28.95%)	1 (2.63%)
Amikacin		47 (64.4%)	14 (19.2%)	8 (10.9%)	4 (5.5%)
Omeprazole		1 (3.57%)	15 (53.57%)	12 (42.86%)	

*Causes of DRP according to the Pharmaceutical Care Network Europe (PCNE) classification systemv.6.2.[4]

†Others included drug form, treatment duration, and others specific causes (e. g. adverse reaction and wrong drug preparation technique).

Supplementary file 1 – PCNE systems v6.2 and operational definitions of the study for the classification of drug related problems (DRP)

Code – Categories	**Operational definition**
Problems	
P1 – Treatment effectiveness	There is a (potential) problem with the (lack of) effect of the pharmacotherapy.
P1.1 – No effect of drug treatment/therapy failure	The drug treatment cannot lead or does not lead to the improvement of the patient's symptoms (e.g. early sepsis not responsive to treatment of ampicillin and gentamicin).
P1.2 – Effect of drug treatment not optimal	The drug treatment may lead or lead to a partial improvement of the patient's symptoms (e.g. paracetamol sub-dose leading to a partial pain relief).
P1.3 – Wrong effect of drug treatment	Not applicable for the study.
P1.4 – Untreated indication	There are symptoms that need treatment but are not being treated at the moment (e.g. patient has a fever but is not in drug treatment).
P2 – Adverse reactions	Patient suffers, or will possibly suffer, from an adverse drug event.
P2.1 – Non-allergic adverse drug event	The drug treatment may be related to an unintended, non-allergic adverse event with doses normally used for the intended indication (e.g. tachycardia reportedly related to the use of caffeine).
P2.2 – Allergic adverse drug event	The drug treatment may be related to an unintended, allergic adverse event with doses normally used for the intended indication (e.g. skin rash reportedly related to the use of penicillin).
P2.3 – Toxic adverse drug-event	The drug treatment may lead or lead to an unintended adverse event occurring in doses higher than that normally used for the intended indication (e.g. captopril overdose leading to hypotension).
P3 – Treatment costs	The drug treatment is more expensive than necessary.
P3.1 – Drug treatment more costly than necessary	The medicine is more expensive than other medicines available or there is a waste in its preparation (reconstitution and dilution).
P3.2 – Unnecessary drug-treatment	The prescribed medication is not necessary or no longer necessary.
P4 – Others	Other problems not specified above
P4.1 – Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes	Not applicable for the study.
P4.2 – Unclear problem/complaint	Problem not clarified or without defined classification.

Causes	
C1 – Drug selection	The cause of the DRP is related to the selection of the drug.
C1.1 – Inappropriate drug (including contraindication)	Selected drug is inappropriate for the intended indication or is contraindicated for the patient (e.g. ampicillin prescribed to allergic patient).
C1.2 – No indication for drug	There is no indication for the selected drug.
C1.3 – Inappropriate combination of drugs, or drugs and food	The selected drug interacts or may interact physically, physico-chemical or chemically with other drugs or foods (e.g. patient is receiving ciprofloxacin and fluconazole, medicines that may increase the risk of QT interval prolongation and, consequently, ventricular arrhythmias).
C1.4 – Inappropriate duplication of therapeutic group or active ingredient	The physician order inappropriately has medicines of same therapeutic group or active ingredients to treat different symptoms (e.g. ibuprofen indicated for closure of the ductus arteriosus and paracetamol indicated for fever present in the same physician order).
C1.5 – Indication for drug-treatment not noticed	The appropriate drug is not used to treat the symptom because the existence of the symptom is not noticed (e.g. patient has a fever that is not noticed and, therefore, is not in drug treatment).
C1.6 – Too many drugs prescribed for indication	The physician order inappropriately has medicines indicated to treat the same symptoms (e.g. ranitidine and omeprazole both indicated for gastrointestinal haemorrhage present in the same physician order).
C1.7 – More cost-effective drug available	There are cheaper and effective (or more effective) medications to treat the symptoms.
C1.8 – Synergistic/preventive drug required and not given	There is a requirement to use a medication to improve an existing treatment or to prevent the development of another symptom, but it is not used. (e.g. ferrous sulfate requirement for the prevention of anemia).
C1.8 – New indication for drug treatment presented	The patient presents a new symptom that is not being treated (e.g. patient has a recent fever and requires drug treatment).
C2 – Drug form	The cause of the DRP is related to the selection of the drug form.
C2.1 – Inappropriate drug form	The drug has an inappropriate form and/or formula for the patient (e.g. oral caffeine solution prescribed for neonate with feeding intolerance).
C3 – Dose selection	The cause of the DRP is related to the selection of the dosage schedule.
C3.1 – Drug dose too low	Selected dose is 20% lower than the minimum dose defined for the intended indication (e.g.

	cefepime prescribed 45 mg/kg instead of 60 mg/kg daily).
C3.2 – Drug dose too high	Selected dose is 20% higher than the maximum dose defined for the intended indication (e.g. oxacillin prescribed 150 mg/kg instead of 100 mg/kg daily).
C3.4 – Dosage regimen not frequent enough	Selected dosing frequency is less than that defined for the intended indication (e.g. gentamicin prescribed every 48 hours instead of every 36 hours).
C3.5 – Dosage regimen too frequent	Selected dosing frequency is higher than that defined for the intended indication (e.g. amikacin prescribed every 24 hours instead of every 36 hours).
C3.6 – No therapeutic drug monitoring	Monitoring serum levels of the drug is required, but it is not done.
C3.7 – Pharmacokinetic problem requiring dose adjustment	Not applicable for the study.
C3.8 – Deterioration/improvement of disease state requiring dose adjustment	Change in disease state requiring dose adjustment (e.g. vancomycin dose adjustment because of the improvement in renal function in patients with renal impairment).
C4 – Treatment duration	The cause of the DRP is related to the duration of therapy.
C4.1 – Duration of treatment too short	Duration of treatment is shorter than that defined for the indication treated (e.g. penicillin prescribed for eight days instead of ten days).
C4.2 – Duration of treatment too long	Duration of treatment is longer than that defined for the indication treated (e.g. meropenem prescribed for sixteen days instead of fourteen days).
C5 – Drug use process	The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label).
C5.1 – Inappropriate timing of administration and/or dosing intervals	Drug administered at wrong times or intervals (e.g. gentamicin dose scheduled for 16 hours but administered at 18 hours).
C5.2 – Drug under-administered	Drug administered at a frequency lower than the physician order (e.g. ranitidine prescribed twice daily but administered only once).
C5.3 – Drug over-administered	Drug administered at a frequency higher than the physician order (e.g. aminophylline prescribed twice daily but administered three time).
C5.4 – Drug not taken/administered at all	Drug dose is not administered in full (e.g. ampicillin dose administered in half).
C5.5 – Wrong drug administered	Drug is administered wrong (e.g. norepinephrine was administered in the wrong route).

C5.6 – Drug abused (unregulated overuse)	Not applicable for the study.
C5.7 – Patient unable to use drug/form as directed	Not applicable for the study.
C6 – Logistics	The cause of the DRP can be related to the logistics of the prescribing and dispensing process.
C6.1 – Prescribed drug not available	Prescribed drug is not available in the institution and there is no other effective drug (e.g. ursodiol is prescribed but not available in the hospital and there is no other drug alternative).
C6.2 – Prescribing error (necessary information missing)	Missing necessary information on the drug prescription that may generate a medication error (e.g. vancomycin is prescribed, but there is no information on the minimum recommended time for administration).
C6.3 – Dispensing error (wrong drug or dose dispensed)	Drug is dispensed wrong or dispensed in the wrong dosage form or dose (e.g. dispensed intravenous furosemide instead of oral).
C7 – Patient	The cause of the DRP can be related to the personality or behaviour of the patient.
C7.1 – Patient forgets to use/take drug	Not applicable for the study.
C7.2 – Patient uses unnecessary drug	Not applicable for the study.
C7.3 – Patient takes food that interacts	Not applicable for the study.
C7.4 – Patient stored drug inappropriately	Not applicable for the study.
C8 – Others	Other causes not specified above.
C8.1 – Others specific causes	The problem arises due to other specific causes (e.g. adverse events related to alprostadil, cefepime prepared wrongly and etc.).
C8.2 – No obvious cause	Not applicable for the study.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4/5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5/6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6/7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7/8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7/8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8/9/10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.