Author's response to reviews

Title: Drug related problems in Neonatal Intensive Care Unit: incidence, characterization and clinical relevance

Authors:
Ramon Leopoldino (ramonweyler@gmail.com)
Marco Santos (marcomets@hornmail.com)
Tatiana Costa (tatycx1000@gmail.com)
Rand Martins (randrandall@gmail.com)
António Oliveira (oliveira.amg@gmail.com)

Version: 1 Date: 03 Sep 2018

Author's response to reviews:

Response to Reviewers

The authors are grateful to the reviewers for their comments that helped us to improve our paper. Below are the responses to the Technical comments and to the two reviewers.

Technical comments:

1. Please include e-mail addresses of all authors in the title page.
R: E-mail address of all authors was added in the title page.

Luke Grzeskowiak (Reviewer 1):

1. I appreciate that it would require additional work, but I think readers would greatly appreciate a table that lists the classification scheme and examples of DRPs identified in this study. i.e C3.1 Drug dose too low e.g. gentamicin prescribed 4mg instead of 6 mg daily. This could be included as a supplemental table/s.
R: We have included additional file 1 with details of the DRP classification scheme.
2. That is, how many DRPs are process related issues due to absence of an appropriate clinical practice guideline? Or are these still occurring despite a guideline suggesting the guideline is not being used appropriately? These are important learnings from such a study and deserve comments in discussion.

R: We added in the discussion (page 9) the sentence: “It should be noticed that in our study the DRPs occurred even though the NICU has an institutional clinical practice guideline.”

3. The study occurred over a 2-year period and identified distinct trends in terms of common DRPs. This raises another question as to whether or not anything was done at a process level in an effort to prevent DRPs? i.e. gentamicin dosing errors are common, were staff educated about this, was a guideline developed to try and reduce number of errors? Was number of DRPs related to gentamicin consistent across 2-year period?

R: All DRPs identified in the study were communicated to the NICU staff and most DRPs were intercepted. We could notice changes in the problems involving some medications, but there were no changes related to gentamicin. However, we emphasize that the temporal analysis of the DRPs was not object of study.

4. How were preventative pharmacist interventions handled in the study? That is, when medical staff ask the pharmacist to recommend an appropriate gentamicin dose this represents and important clinical pharmacy intervention. Was this classified as a DRP? This just requires short clarification in the methods to state whether only DRPs identified from medication charts were included, or whether potential DRPs avoided as a result of pharmacist intervention were also included.

R: We added in the methods (page 5) the sentence: “Inquiries from attending physicians or other healthcare professionals about pharmacotherapy were not considered as DRPs”. In addition, supplementary information was included in additional file 2.

5. I think it would be useful to include an example of a DRP rated at each severity level as well. This might be included just in discussion but helps highlight importance of clinical pharmacy interventions.

R: We did not classify DRPs according to severity. Rather, we classified DRPs according to their safety-relevance and have presented several examples in the Results section (page 7/8). We consider safety-relevance analysis more relevant than severity in the context of DRPs because it
combines the severity of a potential adverse event with its likelihood, offering a better measure of the potential risk to which the patient was exposed.

6. Is there any notion as to whether identified DRPs were the results of deliberate actions or accidental errors?

R: As most of the pharmaceutical interventions were accepted, it was concluded that the errors were accidental.

7. Out of interest, what was the margin of error for determining whether a drug was too high or too low? (i.e. more than 10% of original dose? More than 20%? Some errors simply occur due to rounding of medication doses and discrepancies less than 10% are unlikely to be clinically significant).

R: The margin of dose errors considered was 20%. We added this information in additional file 1.

8. My only real methodological concern relates to rating of DRP severity. Not including input from medical staff is a limitation as pharmacists may overstate the potential severity of DRPs. I think this should be noted in the discussion of study limitations.

R: Lewinsky tool allows an objective analysis of the safety-relevance of the DRPs. This analysis is done by listing the most serious injury a DRP can cause, as reported in clinical databases (Micromedex, Uptodate) and Neofax textbook, assigning a severity grade to that potential injury, and subsequently estimating the probability of such injury occurring. As the severity grade is potential, not actual, we believe there would be no difference whether a physician or a pharmacist assigns the grade. Nevertheless, this tool is not validated, and such limitation was added to the discussion (page 11): “The tool used to assess the safety-relevance of the DRPs is not validated, although it was previously applied by Lewinsky et al. [16] in community pharmacy users. We selected that tool because in the context of DRPs we considered safety-relevance analysis more relevant than just severity, because it combines the severity of a potential adverse event with its likelihood, offering a better measure of the potential risk to which the patient was exposed.”

9. Page 8 - please elaborate on comment regarding 'non-rational preparation of amphotericin B', as this is not inherently clear what this means.
R: Changed the sentence (Results section, page 8) from: “with the non-rational preparation (reconstitution and dilution) of amphotericin B being the most common” to: “with waste in the preparation (reconstitution and dilution) of amphotericin B (problem – P3.1) being the most common DRP.”

10. As was previously eluded to, there are a number of strategies for attempting to reduce/prevent DRPs. As an example, there is extensive literature relating to intervention for reducing medication errors and these are summarised in recent systematic reviews.

R: Information on strategies for reduction/prevention DRP were added in the discussion (page 11): “In addition to the performance of clinical pharmacists in the NICU, there are other strategies to reduce DRP as computerized physician order entry integrated with clinical and pharmacological databases, barcode dispensing and administration system, reporting system of errors and adverse events and programs of training and continuing education [27]. All those tools are in use at our NICU, except that the computerized physician order entry does not yet send alerts.”

11. Future research exploring risk factors for DRPs are suggested, but it may be worth including a section in the discussion regarding how certain evidence-based interventions may or may not be useful for preventing DRPs? That is, what % of DRPs identified in this study could have been prevented? Or, are many unlikely to be avoided? The unit already has comprehensive clinical pharmacy services which is fantastic and this likely reduces DRPs (as it has been shown to reduce medication errors at least).

R: We added in the discussion (page 10) the sentence: “In our study, we estimate that nearly nine out of ten DRP were preventable.”

12. Table 2: I think it would be beneficial to present breakdown of results for problems (i.e. P1.1 not just at parent level P1). This helps reader understand the types of problems occurring more effectively. P4 - Others require some clarification as it is completely unclear what types of DRPs this constitutes.

R: Table 2 was changed to present the sub-headings of each DRP.
Reviewer 2:

1. The lack of data on DRP in neonates may also relate to the high off label practices, and therefore the lack of guidance on how to qualify for DRP, likely due to the extensive variability in PK within the neonatal population. The authors have selected the Lewinski tool, and subsequently used Neofax 2011, Micromedex and Uptodate, but the Lewinski tool is not validated for this population Neofax has not been updated since 2001 and even dosing suggestions differ between the different sources. How have authors handled these differences (eg meropenem in the top 3 of your list)?

R: Micromedex, Uptodate and Neofax were not used to identify DRPs. These clinical databases were only used to identify the most serious injury that a DRP can cause (first step of Lewinsky’s safety-relevance analysis). The identification of the DRPs was carried out based on the institutional clinical practice guideline, information that was included in additional file 2.

2. Similar, the probability and degrees of severity read as very arbitrary, not validated.

R: The lack of validation of the Lewinsky tool was described as one of the limitations of the study (page 11). The following text was added in the Discussion: “The tool used to assess the safety-relevance of the DRPs is not validated, although it was previously applied by Lewinsky et al. [16] in community pharmacy users. We selected that tool because in the context of DRPs we considered safety-relevance analysis more relevant than just severity, because it combines the severity of a potential adverse event with its likelihood, offering a better measure of the potential risk to which the patient was exposed.”

3. How to assess gentamicin or vancomycin problems? based on TDM or dosing guidelines, but if so, how valid are these dosing guidelines (cfr Wilbaux reference in the list)?

R: Dose errors were identified according to the institutional clinical practice guideline. The process of identification and classification DRP are explained in additional file 2 and details of the DRP classification scheme were added in additional file 1.

4. The conversion from adverse (drug) reaction to DRP suggest causality assessment, and how has this been done?

R: We added in the Methods section (page 5) the sentence: “Adverse events for which there were conclusive reports in the literature relating them to one of the drugs being administered were considered adverse drug reactions”.
5. The assessment does not consider wrong drug, like aminophylline instead of caffeine. Perhaps this decision is based on local rational decisions, but this is not supported by the available evidence on efficacy and tolerance.

R: We agree that aminophylline is not the best therapeutic option for the management of neonatal apnea because caffeine has a similar therapeutic effect and is less toxic. However, its use is not contraindicated in neonates, and therefore not a medication error in our view, being described by Schoen et al. (Schoen K, Yu T, Stockmann C, Spigarelli MG, Sherwin CMT. Use of methylxanthine therapies for the treatment and prevention of apnea of prematurity. Paediatr Drugs. 2014; 16(2): 169–177) and Eichenwald et al. (Eichenwald EC, AAP COMMITTEE ON FETUS AND NEWBORN. Apnea of Prematurity. Pediatrics. 2016;137(1):e20153757) and present in the clinical databases Micromedex and Uptodate.

6. Based on the study design (single unit, methods) I agree that this analysis may provide information as an audit, but that the relevance is very limited for other settings.

R: Although the study is done in a single institution, the prospective collection of the data in a large sample and the adoption of a standard DRP classification system strengthen its results. The NICU where the study was conducted is like most other NICUs in tertiary care hospital and we believe that our results can safely be generalized to any NICU in a similar setting. Most published studies on this and related topics were also conducted in a single center.

7. Supplements were excluded, but iron was kept in the analysis, any rationale?

R: Changed the sentence (methods – page 4) from: “Electrolyte and parenteral nutrition solutions, whole blood or blood products, oxygen therapy, diagnostic agents and vitamin and mineral supplements were not considered as medicines” to: “Electrolyte and parenteral nutrition solutions, whole blood or blood products, oxygen therapy and diagnostic agents were not considered as medicines. Vitamin and mineral supplements were also not considered, except for ferrous sulfate and phytonadione because these supplements have a well-defined dosage and therapeutic indication, and require pharmacotherapeutic follow-up”.

8. How to discriminate between advice to doctors or to nurses?

R: In additional file 2, we add the sentence: “pharmaceutical interventions related to prescribed drugs and adverse events were directed to physicians, and those related to drug preparation and administration were directed to nurses”.
9. Was there any association between DRP and mortality?

The assessment of the causal relationship between DRP and mortality was not the aim of this study. This type of analysis is very complex in critically ill patients, and the design of this study is not the best for analysing that relationship controlling for confounders.

10. Treatment costs appear in the table, but are not discussed in the methods section, nor elsewhere, so how has this concept been handled?

R: Treatment costs is a type of DRP defined by the PCNE classification system as “the drug treatment is more expensive than necessary”. Details of this classification are shown in additional file 1.