Author's response to reviews

Title: The use of ciprofloxacin and fluconazole in Italian neonatal intensive care units: a nationwide survey

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Author's response to reviews: see over
Dear Editor,

The manuscript has not changed, but we are including this additional phrase in this cover letter, as requested: The authors confirm that they have the permission of the TINN group to publish this manuscript and that the main manuscript has also been submitted, but has not yet been published.

(Original cover letter)

We are submitting a manuscript entitled “The use of ciprofloxacin and fluconazole in Italian neonatal intensive care units: a nationwide survey” for publication in BMC Pediatrics as a research article.

We originally submitted this manuscript to BMC Pediatrics in January (MS: 2128053192658525) and, at the end of February, received an email stating that it had not been accepted for publication, but that, if the reviewers’ comments were addressed in a revised version, it could be resubmitted as a new article.

We therefore addressed all the reviewers’ concerns and are submitting the revised version of the manuscript as a new submission. Our replies to the reviewers’ comments are listed in detail below. The comments consisted mainly in clarifying some points, adding some interesting comments suggested by the reviewers, and adding a few specific references. One of the two reviewers commented on the excessive length of the article and suggested shortening it. We attempted to condense some sections where possible, however, both reviewers suggested adding comments or details to different parts of the paper, so the overall length did not change drastically. The contact author has also been modified in this new version and is Chiara Pandolfini instead of Maurizio Bonati.

The article discusses data on the use of fluconazole and ciprofloxacin for the treatment and prevention of neonatal sepsis in neonatal intensive care units in Italy collected via an online questionnaire. The survey is part of a large European Commission Seventh Framework Project, TINN (Treat Infections in Neonates).

We feel that the readers of BMC Pediatrics would be interested in the use of these two drugs because, despite their importance in treating a very serious condition in newborns, especially premature newborns, not enough information on their use exists. The results of this survey highlight this lack of information through the wide differences in the manner in which these drugs are employed in the different NICUs and the reported need, on the part of the NICUs, for additional safety and efficacy information and for guidance by pediatric associations.

There are no competing interests.

We thank you for your time and consideration and look forward to hearing from you.

Sincerely,

Maurizio Bonati, Chiara Pandolfini, and co-authors
REVIEWER COMMENTS AND REPLIES

Reviewer: David Kaufman
Reviewer's report:
Major:
1. Incidence from Benjamin 2010 should replace reference 1, it is more accurate reflecting all invasive Candida infections and was 9% in infants <1000 grams compared to reference 1 which was 7% from Bloodstream/CSF data only.
   Ok. Changed reference and adjusted text accordingly.

2. Fluconazole prophylaxis use may be higher in Italy due to time period studied, more publications and data are available since the Burwell study was performed.
   Rates of prophylaxis use were higher in Italy compared to all other EU NICUs surveyed contemporaneously. However, the following phrase, i.e. “The rate is probably higher because Italy….” in the Discussion section under “Fluconazole use” was deleted because misleading. More publications have been added.

3. Was prevalence known by data or simply inquired about (e.g. self reported).
   All data discussed in the article comes from the survey administered to the NICUs. The word “reported” (“The reported prevalence of fungal infections”) was added in paragraph 2 of the Results section.

4. Was prevalence in table 1 for infants <1000 grams, <1500 grams, for entire NICU and before fluconazole prophylaxis initiated if yes?
   This was not specified in the questionnaire, but it is presumed that the rate reported is the current rate, despite prophylaxis.

5. Page13, line 6. Add clarity to sentence. Incidence from Benjamin 2010 should replace reference 1, it is more accurate reflecting all invasive Candida infections and was 9% in infants <1000 grams compared to reference 1 which was 7% from Bloodstream/CSF data only. Specify in sentence after the parentheses that “our Italian study” was in level III etc…
   We substituted the reference (also related to comment 1) and changed the text accordingly, delineating the care levels more clearly.

6. P13
   “There is great difficulty in diagnosing invasive fungal infection early and the consequences of such an infection are severe; prophylaxis is therefore a valuable option and should be considered” ---In lieu of the articles proposal for national and international guidelines, “should be considered” falls short of specific guidelines.
   We have modified the phrase, eliminating “should be considered” and substituted the reference to a more recent one that stresses the importance (and efficacy) of prophylaxis to an even greater extent.

7. P15. The US survey was not from the American Academy of Pediatrics Section on Perinatal Pediatrics, the list of NICUs surveyed was obtained from the AAP section on Perinatal Pediatrics.
   OK. Deleted the part of the phrase that stated this.

8. One additional point is that NICUs using fluconazole prophylaxis should
choose a different antifungal for treatment.

OK. Added a phrase specifying this point on pg 15, and a reference to the Kaufman 2010 article.

9. Another point, is that for fluconazole prophylaxis, twice weekly dosing schedule has been well studied in addition to dosage.

   OK. Modified the phrase on page 14 “Studies have been performed to test…” so that it specifies this point.

10. Another point is that a study of cipro, due to its broad spectrum, may increase resistance to it and increase fungal infections in those patients and their NICU.

   Although interesting we have decided not to add this point because the article is already very long.

11. P16: It would truly move things forward it centers reported their rates of infections to a central public body. The goal would be a worthwhile component to add to this initiative. Transparency and accurate data on incidence leads to the high motivation and the best, evidenced based practices to be instituted.

   This is a good point. This initiative is already underway and does not foresee the possibility, resource-wise, of setting up a centralised body for collecting such data. However, it is possible to take advantage of this network to begin to diffuse this idea. A phrase has been added on page 16. “The collection of data on rates of infection…”.

12. It would be worthy to illustrate that while prophylaxis for <1000 grams based on incidence may vary, the rate for infants at the lower gestational ages (23, 24, 25 weeks) is high in all studies. Rates should also be calculated over a 3 to 5 year period depending on the number of admissions to get an accurate reflection of the incidence of invasive fungal infections for these low gestational ages for the best decision making.

   OK. Added phrase in text on pg.13 for the first part of this suggestion. For the second part, the point is true, a systematic, longitudinal survey of this duration would be appropriate.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer: Brian McCrossan
Reviewer's report:
There are a number of positive points about this study.
It attempts to address an important question
It is a nation wide study
Italy is at the forefront in research into fungal prophylaxis in preterm neonates.
The study produces some interesting data which informs this field:
The rate of invasive fungal infection was not affected by the use of fluconazole prophylaxis in NICUs.
Descriptions of the factors influencing use of fungal prophylaxis across NICUs
Variability in dosing regimes
However, there are a number of weaknesses in the study not all of which are acknowledged in the manuscript.
Firstly the manuscript appears to be very long. A word count was not included but it is probably somewhere between 3,500 & 4,000 words. There are also too many paragraphs. We have tried to compact the paragraphs and adjust some phrases in order to be more concise, however, the author guidelines say that there is no explicit limit on the length of articles submitted.

This study is data lifted from a larger pan-european study. The original research has not been published yet. I think this is quite a major weakness in the manuscript. The full, European data article is under submission and its data has been presented at multiple meetings. The data presented here gives a more homogeneous, focused picture, since all NICUs are Italian and all provide the same level of care.

There are previous studies reporting surveys of fungal prophylaxis practices in NICUs. Clerihew et al 2006, O'Grady et al 2008 & Burwell 2006. None of these studies are referenced in this manuscript. Clerihew et al 2006 has been cited and data added from it in the discussion under fluconazole use. The O'Grady study has been cited and its results have been confronted with those of the current study. The Burwell 2006 study was already referenced in the manuscript (it was cited especially for its methodology, which we used, in part, in our survey (pg.6)).

I shall discuss other problems as they appear in the manuscript.

Background

Define GA - Gestational age.

OK. Defined.

Page 2, paragraph 2 line 4: This should be 2 sentences: “2007 on. The most important were a multi-center RCT”

OK.

Methods

1. Not enough detail is given about the following:
Who developed the questionnaire
Was the questionnaire validated before being sent out.

OK. More details provided in the methods section. “…by the TINN partners, based in part on a US survey.[39] The survey was tested by the partners.”

Is this data a section of a larger study that is to be published elsewhere

Yes, this is mentioned in the last phrase of the introduction section. The full, European data article is under submission.

It would be normal practice to describe a 1-5 Likert scale as 4 = important & 5 = very important.

Calling 4 & 5 “very important” skews the impression of the results.

The classification “very important” was used in order to make the comments of this survey’s data more comparable with the results of the Burwell et al 2006 article. The fact that a similar methodology was used is stated in the methods section “A methodology similar to that employed in the US survey…” In any case, the concept used in dichotomizing the responses was explained in detail, so readers should be aware of what “very important” refers to.
Results
1. It seems that 2 separate questions are under consideration: Ciprofloxacin use and fluconazole use. It may be better to concentrate the manuscript on fluconazole use and cut out the sections pertaining to ciprofloxacin.

The manuscript is based on the two drugs because they are the basis of the TINN Project. The authors decided to report on both drugs in this article because the data gives a more complete picture of the heterogeneity of drug uses in NICUs and the consequent urgency and importance of correcting the situation.

Page 5, paragraph 4: It is quite a false analysis to compare a group with 5 patients in it with another containing 33 and then conclude there is no significant difference. It would be very difficult to demonstrate such a difference.

The phrase was changed and the word “seemed” was used. The specific limit concerning the small sample size has been added at the end of the discussion section.

Page 7, paragraph 4, be more explicit about which guideline is being quoted. There is also some guidance from the European Association of Perinatal Medicine. As part of the “European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update” it is recommended that: Units should develop protocols for antifungal prophylaxis in VLBW babies based on the local incidence and risk factors. A suggested regimen is fluconazole 3mg/kg body weight twice weekly for 6 weeks.

OK, these partial guidelines have been cited and the dose commented on.

Page 7, paragraph 4, lines 4-5: should this not be every 48 hrs rather than 24 hours?
Yes, this has been corrected.

Page 7, paragraph 5: This data suggests indifference Likert score = 3.5 & 3.3. At any rate the questionnaire does not ask that specific question ie “would a statement from paediatric societies influence your decision to prescribe fluconazole?” Instead an extrapolation from the question is being made here.

The phrase was worded differently.

Page 8, paragraph 1, line 2 - state the numerator and denominator (56%)
OK, added.

Page 9 I’m not sure how relevant this data is to the manuscript although it is not uninteresting.
This data is relevant to the TINN project because it reveals the centres’ interest in participating in a trial in this therapeutic area, and launching such a trial is part of the TINN consortium’s aims.

Discussion
I am bit surprised that there is such a low return rate. Although it is a national study, neonatology is a small subspecialty with colleagues working fairly close together. Italy has a national society which presumably could have facilitated greater participation. This low return rate does undermine the results.

Yes, the return rate was not high, but the data does represent the NICU contexts from the North to the South. Also, Italy was, among the countries involved, the one with the greatest participation.
Page 10, paragraph 4, line 2/3: change to: “resistance have recently been reported and seem positive so far” 
OK, changed.

Page 13 paragraph 1: Not sure what is being quoted here as no reference. The paragraph has been modified and the phrase has been omitted.

Page 13, paragraph 1: Lines 4-5 are repeated but the sentence does not make sense anyway. The paragraph has been modified and the phrase has been omitted.

I think more should be written on the apparent indifference or diffidence of Respondents. We are not sure what is meant by this and cannot address the comment.

I do agree with the conclusions’ main points that there is great variability in practice that requires the drawing up and dissemination of proper guidelines.

On the whole I think there are a number of positive attributes to this manuscript but there are also several weaknesses which would need to be addressed.

Brian McCrossan
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.