Author's response to reviews

Title: Management of Neonatal Hyperbilirubinemia: Pediatricians' Practices and Educational Needs

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Author's response to reviews: see over
Dear Sir/Madam,

We are in receipt of your letter regarding revisions required to the above-mentioned manuscript and the enclosed comments from the experts in the field who evaluated the manuscript. Please thank the reviewers on our behalf for their vigorous analysis and very valuable suggestions.

Response to Drs. Valerie Flaherman and Thomas B. Newman

Major compulsory revisions:
1. Dates of the survey should be provided. The objective is to examine current practices, and yet the survey is in reference to the 1994 guidelines. The authors should explicitly state that they are comparing responses to the 1994 AAP hyperbilirubinemia guidelines, not the 2004 guidelines.

Answer:
The dates (month and year) of the survey have been included in the manuscript (see Methods para 1, line 4). In the revised version, the exact dates of mailing have been added.

We agree that the survey analyzed the pediatricians’ practices in accordance with the 1994 AAP guidelines with respect to the recommended TSB levels for phototherapy and exchange transfusion. We asked about the hour-specific bilirubin levels used for the initiation of treatment (see Q#13 and Q#14). We have clearly stated that the comparison of the TSB levels in our study was based on the 1994 guidelines and in accordance with your recommendations emphasized this in the revised manuscript.

Q13. At what bilirubin level at a particular age do you order phototherapy?
<=24 hours_______
25-48 hours_______
49-72 hours_______
>72 hours_______

Q14. At what bilirubin level at a particular age do you request exchange transfusion?
<=24 hours_______
25-48 hours_______
49-72 hours_______
>72 hours_______
However, because we asked questions regarding risk factors that have also been included in the 2004 guidelines for neonatal hyperbilirubinemia management (treatment, pre-discharge assessment, and follow-up), we believe that this study also evaluated the several aspects of the 2004 guidelines. In Q #17 of our survey we asked “Do you believe that the following factors are associated with severe hyperbilirubinemia in term neonates (Check all that apply)”. The risk factors we listed were jaundice presenting in the first 24 hours, jaundice noted after discharge from the hospital, previous siblings with jaundice, breastfeeding, bruising/cephalohematoma, Rh/ABO incompatibility, gestational age between 37-38 weeks, and glucose-6-phosphate dehydrogenase deficiency. We used a scale (hardly at all, to a small degree, to a moderate degree, to a very high degree, not applicable) to assess the level of the pediatrician’s belief regarding the importance of these factors in the development severe hyperbilirubinemia. All these risk factors are listed in Table 2 of the practice parameters published in 2004 by the AAP (Pediatrics 2004;114:page 301) and the 2004 guidelines addressed management for specific risk groups. Moreover, we asked questions regarding the use of transcutaneous bilirubinometry for the assessment of neonatal jaundice and the pediatricians’ practices regarding the post-discharge management of infants with jaundice. The transcutaneous bilirubin measurement and the post-discharge algorithm, visual and laboratory assessment have been also discussed by the 2004 AAP guidelines.

Dear Drs. Flaherman and Newman, because your review question #2 included several separate questions, we have provided separate answer for each of them.

2.1 The authors should include more of the details of the survey instrument in the paper.
Answer: We are not sure as to what details you were suggesting, however, we have provided additional information (see Material…)

2.2 Regarding follow-up for infants whose TSBs were not is treatment range, did the survey questions include specific values for TSB? Did respondents have a way to identify whether the TSB was close to the treatment threshold or not? If these questions were not asked clearly in the survey, then the data from these questions may be of little value and should be omitted.
Answer: This question (Q#16) did not include the values because the previous Q#13 and Q#14 asked about the hour-specific TSB value used for ordering phototherapy and exchange transfusion. We thought that providing information regarding recommended TSB values for treatment in Q#16 would bias the response for Q#13 and Q#14. However, we agree that absence of the recommended TSB values in Q#16 may affect the response. Therefore, this question has been omitted from the “Results and Discussion” parts of the revised manuscript in accordance with your recommendation.

Q #16: What is your usual neonatal jaundice follow up practice if the initial bilirubin level is not in the treatment range?
See patient next day
Ask mother to call you if baby’s skin appears more yellow
Refer baby to the lab for total serum bilirubin measurement
Other
2.3 For the question in Table 2 under the label of TSB testing with clinical jaundice post-discharge, were respondents given any information about extent of jaundice and/or age of infants? Clearly a 50-hour-old infant jaundiced to the thighs will need different treatment that a 6-day-old jaundiced to the chest. If the question was not clear, the results may not be useful.

Answer: We did not include information about the extent of jaundice and the age of the infant because this question was supposedly about the pediatrician’s behavior regarding TSB testing of infants with “jaundice” but not the treatment of jaundiced infants. The 2004 AAP guidelines clearly stated (Pediatrics 2004; 114:300) that the “visual estimation of bilirubin levels from the degree of jaundice can lead to errors.” By asking this question, we tried to identify the pediatrician’s usual practice regarding TSB testing of infants after discharge who present at the first office visit with clinical jaundice.

3. Regarding the questions concerning risk factors for hyperbilirubinemia and kernicterus. I think it likely that respondents were describing a small or moderate significance of the risk factors discussed, rather than a small or moderate belief. If the authors want to sustain their conclusion that neonatal hyperbilirubinemia-related risk factors were underestimated by the majority of pediatricians, they should offer additional evidence in support of this conclusion.

Answer: Definitely, Q#17 (see below) asked about the pediatrician’s belief regarding each risk factor. Therefore, we would like to substantiate with our conclusion in the revised manuscript.

**Q17: Do you believe that the following factors are associated with severe hyperbilirubinemia in term neonates? (Check all that apply)**

<table>
<thead>
<tr>
<th>1. Hardly at all</th>
<th>2. To a small degree</th>
<th>3. To a moderate degree</th>
<th>4. To a very high degree</th>
<th>5. Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice presenting in the first 24 hours</td>
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<tr>
<td>Jaundice noted at discharge from the hospital</td>
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<td>Precious sibling with jaundice</td>
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<tr>
<td>Gestational age between 37 and 38 weeks</td>
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<td></td>
<td></td>
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<tr>
<td>Breast feeding</td>
<td></td>
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<tr>
<td>Bruising/cephalohematoma</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Rh incompatibility</td>
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<tr>
<td>ABO incompatibility</td>
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<tr>
<td>Glucose-6-phosphate dehydrogenase deficiency</td>
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</tbody>
</table>

4. Figure 2 is confusing and should be redone. For example, just looking at the black bars, it appears that 65% of pediatricians would do an exchange
transfusion TSB <20 mg/dL, and more than 50% at 20 mg/dL. This makes no sense. The problem is not just the numbers, this particular way of displaying the data would be confusion even if the numbers added up. One possibility for displaying the same data would be to use the same format as Figure 1, where at least the numbers appear to add to 100% in each panel. Another possibility would be to construct a graph with TSB on the x-axis, % of respondents on the y-axis, and three separate lines showing the relationship of TSB level to the cumulative % of respondents who recommend each treatment at 25-48 hours, 49-72 hours and >72 hours. If this second possibility id chosen, the authors should revise Figure 1 to present the information in a similar way.

Answer: Figure 2 is presented in the revised manuscript in the same fashion as Figure 1. Thanks for the suggestion.

* Some statements in the paper seem to contradict others. Information on the average length of practice described in section on Risk Factors for Hyperbilirubinemia and Kernicterus contradicts information in Table 1 and is not credible 6 years vs. 3 years? The last 2 sentences in the results portion of the abstract appear to contradict each other. The entire paper has typographical mistakes and grammatical errors that may cause erroneous understanding. This paper should be carefully proofread.

Answer: By mistake, we wrote “on average 6 years vs.3 years”. It supposed to be “on average 6 years and 3 years. To avoid any further misunderstanding, in the revised manuscript the mean and SD of ‘years in practice’ and ‘age’ has been included (see Results under “Risk Factor for Hyperbilirubinemia and Kernicterus”).

The correction regarding the last 2 sentences in the Abstract has been made. The last sentence should read “more than 72 hours”

Per your suggestions, the paper was reviewed and proofread (see manuscript).

Minor compulsory revisions:
1. Given that the authors are using the 1994 AAP guidelines, they must explicitly state whether they are using the guidelines for consider phototherapy or the guidelines for recommend phototherapy.

Answer: Figure 1 provides comparison of the results of the survey with the TSB levels that recommend phototherapy (not considered) as per the 1994 AAP guidelines. TSB levels less than 15 mg/dL at 25-48 hours, <18 mg/dL at 49-72 hours, and < 20 mg/dL at >72 hours were identified as TSB levels for ‘consider’ phototherapy (AAP, 1994).

Discretionary revisions/suggestions:
Although commonly used, the term clinical jaundice is unclear or redundant.
Jaundice is visible by definition; it is not clear what nonclinical jaundice would be.

Answer: We agreed that this term “clinical jaundice” is redundant. The correction has been made over the manuscript.

Quality of written English:
Needs some language corrections before being published.
THERE ARE FOUR AUTHORS-IF EACH OF THEM PROOFREAD IT, IT WOULD PROBABLY BE OK.

Answer: Although one reviewer seemed satisfied with quality of language used in this manuscript, the editorial work has been done. Thanks for this suggestion.

Response to Dr. Claudio Tiribelli
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached).

The response rate was less than 50%, which invalidates the study. Also how the pediatricians were selected is less than clear. The authors indicate to have “randomly” selected 800 out of 1623 pediatric doctors of the NJC of AAP. Oft of 800, 430 returned the questionnaire of which 24 were incomplete and 51 (13+17+21) discarded. In spite of the fact that the final number equal to 355 and NOT 365 as reported, how was selection bias was ruled out? This needs to be clarified. Statistical analysis may help.

Answer: Typically, mail surveys of physicians are characterized by lower response rates than the general population (Asch DA, Jedrzejewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J Clin Epidemiol 1997;50:1129-1136) (Martin B. Don’t survey physicians! Chicago, III: American Medical Association; 1984). In 2002, I published a study “Obstetrician preferences for prenatal strategies to reduce early-onset group B streptococcal infection in neonates: A population-based survey” in the American Journal of Obstetrics and Gynecology that had a response rate of 44.9%. Therefore, it is not surprising that in most of the mailing surveys of physicians in the United States, the response rates are very low. Actually, the results of some of the published mailing surveys of pediatricians were even lower than in our study (41% in the Borowsky and Ireland study of pediatricians’ violence prevention counseling, published in the Arch Pediatr Adolesc Med 1999:153:1170-6). However, in our manuscript the low response rate has been discussed in the limitation portion of the “Discussion”. Moreover, the response in our study may possibly be representative of the pediatricians in the nation because no significant differences were identified in the demographic characteristics of the respondents as compared to other US pediatricians.

The random sampling technique was used to identify the sample of pediatricians from among the AAP Fellows in New Jersey. Random numbers were generated from the list of the AAP Fellows and survey questionnaire were mailed to the randomly selected pediatricians. A total number of 431 (not 430) surveys were returned. We apologize for this mistake and the required correction has been made (see Methods).

Minor Essential Revisions
The lack of experience and/or not following the guidelines is associated with over-treatment. This needs to be stressed.

Answer: The difference in using TSB levels recommended by AAP (1994) was mainly associated with the age of the infant. For example, less than one-third of the pediatricians reported using TSB levels lower than recommended for phototherapy in infants who were less than 72 hours old, but 57.3% preferred to initiate phototherapy at lower than
recommended levels for infants who were more than 72 hours old. Because most of the healthy term infants are discharged from hospital at age <72 hours, the “over treatment” is associated with the post-discharge status. It is not easy to explain why these pediatricians prefer lower TSB levels for treatment after hospital discharge. We think that it may be associated with the higher TSB levels recommended for initiation of phototherapy at age >72 hours (≥20 mg/dL) as compared with TSB ≥18 mg/dL for the initiation of phototherapy at age between 48-72 hours. Additionally, pediatricians may be concerned about not being able to monitor the infant while he/she was at home, and the possibility of rapid increase of TSB and risk of neurological complications. We would have to conduct an additional survey of the pediatricians in order to clarify this. Thanks for your question and excellent review.