

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality of newborn care: Adherence to guidelines for parenteral nutrition in preterm infants in in Four European Countries
AUTHORS	Lapillonne, Alexandre; Carnielli, Virgilio; Embleton, Nicholas; Mihatsch, Walter

VERSION 1 - REVIEW

REVIEWER	Dr Mark Johnson BM BSc MRCPCH NIHR Doctoral Research Fellow National Institute for Health Research Southampton Biomedical Research Centre University Hospital Southampton NHS Foundation Trust and Univeristy of Southampton, Southampton, UK I have no competing interests to declare.
REVIEW RETURNED	24-Jul-2013

RESULTS & CONCLUSIONS	<p>Given the multiple elements involved in PN prescription that must be surveyed in this kind of study, presenting the results in a clear and coherent fashion is always going to be challenge. Largely, the authors have succeeded in using tables to give a clear presentation of the results, though there are a few additions which might make things clearer for the reader. It is not clear until the discussion which of the ESPGHAN or Tsang guidelines the authors have chosen to use as their 'standard' to which the results are being compared (the first paragraph of the discussion states that the ESPGHAN one was 'mainly used'). I feel the choice needs to be stated earlier in the results. Also, the chosen standard range/target for each PN component should be given on table 4 so it is clear to the reader which specific recommendation the units are compliant with. Whilst the issues regarding compliance with guidelines are brought out nicely in the discussion, highlighting them in the result section would make it clearer for the reader, and also help reinforce the message that a significant number of units are failing to meet recommendations.</p> <p>The element of the study which was concerned with the factors influencing compliance to guidelines, potentially offers interesting insight into this important area, but currently the results are not clear and could be stronger, perhaps with some additional analyses. Firstly, it is not clear whether respondents were asked whether or not they agreed with the content of recommendations in isolation, or in relation to their compliance. Similarly, the potential barriers to compliance are presented in figure 2 as 'Justification for non-implementation of international clinical practice guidelines'- does this mean only the results for those who were not compliant are being presented (hence 'justifying' their reason for non compliance), or is this actually what all respondents said when asked which factors</p>
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	would affect their compliance (I suspect the latter but it is not clear). These things need to be made clearer in the text. In addition, it would be of interest, particularly in terms of addressing the issues of poor compliance highlighted by this study, to split these responses (perhaps using a cut off based on the guidelines), into 'compliers' and 'non-compliers', to see if the reasons for non-compliance are different between the two (statistics comparing these two groups could also be presented). Furthermore, It may also be appropriate to look at these reasons for poor compliance in relation to which guidelines respondents claimed to be aware of/using - for instance, it may be that some of the respondents who disagreed with the content of guidelines are referring to an 'in-house' or 'other' guideline and not the ESPGHAN one.
GENERAL COMMENTS	<p>This is an interesting, concise and well written paper which presents a timely and large scale update to previous work in this field. The high survey response rate achieved in this study is impressive and a testament to the amount of work done by the authors on this project. It will be of interest to both clinicians and policy makers, as it presents interesting findings regarding uptake of and adherence to internationally recognised guidelines.</p> <p>The introduction and methods are clear and well written, though there are a few elements of the results that would benefit from some clarification and changes as described above. Regarding the discussion, it is noteworthy that there was a significant amount of unanalysable surveys in Italy, with only 19 able to used- do the authors have any feel for why this was the case, and how does it affect the generalisability of the results? This is mentioned briefly in the discussion but perhaps needs elaborating a little. Overall, the discussion is good and the overall message of the paper is clear, calling for improved dissemination of guidelines and translation into practice, together with the use of standardised reporting to allow better monitoring, which is important</p>

REVIEWER	<p>Dr Alison Leaf, Academic Consultant Neonatologist, NIHR Nutrition Biomedical Research Centre, University Hospitals Southampton NHS Foundation Trust, Tremona Road, Southampton,</p> <p>I have no competing interests with regard to this manuscript.</p>
REVIEW RETURNED	27-Jul-2013

THE STUDY	No Consort check list in document - not relevant
RESULTS & CONCLUSIONS	<p>Mostly well presented. Table 4 is a very long table summarising the nutrient intakes prescribed by guidelines in the 4 different countries, however in the 'Results' section of the manuscript, it appears under the heading 'Factors that influence adherence to guidelines'. I think it might be clearer to have a separate section in the Results summarising these nutrient intakes and their variability. The 'Factors that influence....' seem to be more related to Figure 2. The value of Table 4 for readers will be partly to understand the variability in practice, but also to ascertain the position of their own unit within the spectrum. Would it be possible to highlight the recommended values within this table?</p>
REPORTING & ETHICS	No mention is made of ethical application or informed consent.

	However as this was a questionnaire study, undertaken by practicing clinicians, and involved no direct patient data, it is likely that ethical approval was not required.
GENERAL COMMENTS	In several places within the manuscript the term 'Day of life' is used. 'Day of birth' and 'days after birth' may be preferable. It would be useful to include some discussion of how the International Guidelines were disseminated - part of the reason for lack of awareness, particularly in small or non-university teaching hospital units may be lack of access to specialist scientific journals. It is good that emphasis is given to the 'intention to treat' response to surveys, as actual practice may differ considerably. Perhaps in the 'Results' section of abstract statements could be modified to highlight this - eg '63% of the respondents AIM TO initiate AA....' etc.

REVIEWER	Hans van Goudoever/Marita de Waard Emma Children's Hospital AMC Amsterdam and Dept Pediatrics VU University Center, Amsterdam The Netherlands No competing interest.
REVIEW RETURNED	01-Aug-2013

THE STUDY	<p>\ The inclusion of hospitals seems to depend on the admission of > 5 infants needing TPN per week. However, from the description of the statistical analyses it seems that the survey only covers infants with a birth weight less than 1500 g. This addition can be easily inserted in the aim, in that the authors primary target was VLBW infants.</p> <p>\ From each hospital a senior physician was contacted for completion of the survey, which could also be delegated to a colleague devoting $\geq 20\%$ of their time to patient care and with > 3 years of clinical experience in neonatal intensive care. However, when no response was obtained, it seems that any other physician from the same unit could be approached, without taking experience into account anymore.</p> <p>\ The authors mentioned that invalid responses were mainly given in smaller units and than they conclude: 1. that these units are less likely to prescribe PN and 2. that this is in line with the observation that larger units prescribe PN and therefore are more likely compliant with guidelines. The first conclusion seems odd while only hospitals that admit >5 infants per weeks needing TPN were included. The second conclusion can not be concluded from the fact that smaller hospitals did not give valid answers to the questionnaire.</p> <p>\ Adding the survey questions (as supplemental material) would give a better idea of the quality of the questions. Certainly while 20% contained invalid responses.</p>
RESULTS & CONCLUSIONS	<p>\ For the sentence 'despite demonstrating apparent improvement in PN practices, the results presented here show that 37% of neonatal units in Europe initiate amino acid feeding on D1 or later and not on D0 as recommended' (page 9, line 34-38) I feel that the authors are jumping to conclusions, while they only have information on 4 countries while in addition practice differed significantly from each other.</p>

	<p>\ For the sentence 'This may be of relevance when the 40% of respondents who do not provide amino acids on the 1st day of life are considered' (page 10, line 12-14): did the authors assess whether the respondents who had no knowledge of international guidelines were the ones who started amino acid administration on D1 instead of D0?</p> <p>\ In the discussion and conclusion, the authors are making a comparison with historical data. The authors should mention this in the methods as well.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr Mark Johnson BM BSc MRCPCH
NIHR Doctoral Research Fellow
National Institute for Health Research
Southampton Biomedical Research Centre
University Hospital Southampton NHS Foundation Trust and Univeristy of Southampton,
Southampton, UK

'I have no competing interests to declare.

Given the multiple elements involved in PN prescription that must be surveyed in this kind of study, presenting the results in a clear and coherent fashion is always going to be challenge. Largely, the authors have succeeded in using tables to give a clear presentation of the results, though there are a few additions which might make things clearer for the reader. It is not clear until the discussion which of the ESPGHAN or Tsang guidelines the authors have chosen to use as their 'standard' to which the results are being compared (the first paragraph of the discussion states that the ESPGHAN one was 'mainly used'). I feel the choice needs to be stated earlier in the results.'

Response: It is now indicated in the Material and Methods section which 'standard' has been used.

'Also, the chosen standard range/target for each PN component should be given on table 4 so it is clear to the reader which specific recommendation the units are compliant with. Whilst the issues regarding compliance with guidelines are brought out nicely in the discussion, highlighting them in the result section would make it clearer for the reader, and also help reinforce the message that a significant number of units are failing to meet recommendations.'

Response: In order to make clearer the adherence to guidelines, a specific graph has been made in the Results section and we have drawn a specific figure (Figure 1). We have chosen not reporting the guidelines in table 4 since the table is already very long but we have highlighted in bold the recommended intakes as defined in the methods section.

'The element of the study which was concerned with the factors influencing compliance to guidelines, potentially offers interesting insight into this important area, but currently the results are not clear and could be stronger, perhaps with some additional analyses. Firstly, it is not clear whether respondents were asked whether or not they agreed with the content of recommendations in isolation, or in relation to their compliance.'

Response: They were asked if they agree with guidelines, independently of their compliance. Change has been made in the result section

'Similarly, the potential barriers to compliance are presented in figure 2 as 'Justification for non-implementation of international clinical practice guidelines'- does this mean only the results for those

who were not compliant are being presented (hence 'justifying' their reason for non compliance), or is this actually what all respondents said when asked which factors would affect their compliance (I suspect the latter but it is not clear). These things need to be made clearer in the text. In addition, it would be of interest, particularly in terms of addressing the issues of poor compliance highlighted by this study, to split these responses (perhaps using a cut off based on the guidelines), into 'compliers' and 'non-compliers', to see if the reasons for non-compliance are different between the two (statistics comparing these two groups could also be presented). Furthermore, It may also be appropriate to look at these reasons for poor compliance in relation to which guidelines respondents claimed to be aware of/using - for instance, it may be that some of the respondents who disagreed with the content of guidelines are referring to an 'in-house' or 'other' guideline and not the ESPGHAN one.'

Response: As suggested by the reviewer we have indicated in the Results section the compliance to guidelines of the respondents. We also further explored the reasons for non-compliance by analyzing the association between being aware of guidelines for use of neonatal / pediatric PN and being compliant with guidelines. However there was no significant association for all nutrients; there was only a trend for an association between being aware of guidelines and being compliant for the lipid target dose ($p=0.054$) and for the initiation of amino acids ($p=0.070$).

'This is an interesting, concise and well written paper which presents a timely and large scale update to previous work in this field. The high survey response rate achieved in this study is impressive and a testament to the amount of work done by the authors on this project. It will be of interest to both clinicians and policy makers, as it presents interesting findings regarding uptake of and adherence to internationally recognised guidelines.

The introduction and methods are clear and well written, though there are a few elements of the results that would benefit from some clarification and changes as described above. Regarding the discussion, it is noteworthy that there was a significant amount of unanalysable surveys in Italy, with only 19 able to be used- do the authors have any feel for why this was the case, and how does it affect the generalisability of the results? This is mentioned briefly in the discussion but perhaps needs elaborating a little.'

Response: We do not have specific explanation except that most of the smallest units were found in Italy and therefore, were less likely prescribing PN as already indicated in the Discussion section.

'Overall, the discussion is good and the overall message of the paper is clear, calling for improved dissemination of guidelines and translation into practice, together with the use of standardised reporting to allow better monitoring, which is important'

Reviewer: Dr Alison Leaf,
Academic Consultant Neonatologist,
NIHR Nutrition Biomedical Research Centre,
University Hospitals Southampton NHS Foundation Trust,
Tremona Road,
Southampton,
SO16 6YD.

'I have no competing interests with regard to this manuscript.

Mostly well presented. Table 4 is a very long table summarising the nutrient intakes prescribed by guidelines in the 4 different countries, however in the 'Results' section of the manuscript, it appears under the heading 'Factors that influence adherence to guidelines'. I think it might be clearer to have a separate section in the Results summarising these nutrient intakes and their variability. The 'Factors that influence....' seem to be more related to Figure 2. The value of Table 4 for readers will be partly to understand the variability in practice, but also to ascertain the position of their own unit within the

spectrum. Would it be possible to highlight the recommended values within this table?'

Response: The Results section has been reorganized and partially rewritten. In order to make clearer the adherence to guidelines, a specific graph has been made in the Results section and we have drawn a specific figure (Figure 1). We have chosen not reporting the guidelines in table 4 since the table is already very long but we have highlighted in bold the recommended intakes as defined in the methods section.

'No mention is made of ethical application or informed consent. However as this was a questionnaire study, undertaken by practicing clinicians, and involved no direct patient data, it is likely that ethical approval was not required.'

Response: The approval of an ethic committee was indeed not required for such study. To make this point clear, we have added a paragraph in the Method section.

'In several places within the manuscript the term 'Day of life' is used. 'Day of birth' and 'days after birth' may be preferable.'

Response: Changes have been made accordingly to the reviewer's suggestion.

'It would be useful to include some discussion of how the International Guidelines were disseminated - part of the reason for lack of awareness, particularly in small or non-university teaching hospital units may be lack of access to specialist scientific journals. It is good that emphasis is given to the 'intention to treat' response to surveys, as actual practice may differ considerably. Perhaps in the 'Results' section of abstract statements could be modified to highlight this - eg '63% of the respondents AIM TO initiate AA....' etc.'

Response: It is now indicated in the text how the European Guidelines were disseminated. We made the editorial changes in the abstract as recommended.

Reviewer: No competing interest.
Hans van Goudoever/Marita de Waard
Emma Children's Hospital AMC Amsterdam and
Dept Pediatrics
VU University Center, Amsterdam
The Netherlands

'The inclusion of hospitals seems to depend on the admission of > 5 infants needing TPN per week. However, from the description of the statistical analyses it seems that the survey only covers infants with a birth weight less than 1500 g. This addition can be easily inserted in the aim, in that the authors primary target was VLBW infants.'

Response: The use of a threshold of 1500 g had been used only for the statistical analysis. Since infants with a birth weight below 1500g are those more likely receiving PN, splitting the data using this parameter was consider to better reflect the experience in prescribing PN than using the whole population of newborn admitted in a NICU. This is now indicated in the Methods section.

'From each hospital a senior physician was contacted for completion of the survey, which could also be delegated to a colleague devoting $\geq 20\%$ of their time to patient care and with > 3 years of clinical experience in neonatal intensive care. However, when no response was obtained, it seems that any other physician from the same unit could be approached, without taking experience into account anymore.'

Response: We thank the reviewers to have pointed out that the physicians who responded to the questionnaire may not be as experienced as requested. In fact, this is not the case since only one respondent had less than 3 years of experience. This is now indicated in the Results section.

'The authors mentioned that invalid responses were mainly given in smaller units and than they conclude: 1. that these units are less likely to prescribe PN and 2. that this is in line with the observation that larger units prescribe PN and therefore are more likely compliant with guidelines. The first conclusion seems odd while only hospitals that admit >5 infants per weeks needing TPN were included. The second conclusion cannot be concluded from the fact that smaller hospitals did not give valid answers to the questionnaire.'

Response: To emphasize the point that invalid responses were mainly given by smaller units, we have provided a statistical analysis showing that 50% of the units that have given invalid surveys had less than 5 high acuity care beds vs. 12% ($p < 0.001$). We have removed the second conclusion since the supplement table #2 supports but only partially, this statement.

'Adding the survey questions (as supplemental material) would give a better idea of the quality of the questions. Certainly while 20% contained invalid responses.'

Response: The questions of the survey questionnaire that have been used in this report are now reported in the Supplemental files (table 3)

'For the sentence 'despite demonstrating apparent improvement in PN practices, the results presented here show that 37% of neonatal units in Europe initiate amino acid feeding on D1 or later and not on D0 as recommended' (page 9, line 34-38) I feel that the authors are jumping to conclusions, while they only have information on 4 countries while in addition practice differed significantly from each other.'

Response: Changes have been made accordingly to the reviewer's suggestion.

'For the sentence 'This may be of relevance when the 40% of respondents who do not provide amino acids on the 1st day of life are considered' (page 10, line 12-14): did the authors assess whether the respondents who had no knowledge of international guidelines were the ones who started amino acid administration on D1 instead of D0?'

Response: As suggested by the reviewer and reviewer #1, we have further explored the reasons for non-compliance by analyzing the association between being aware of guidelines for use of neonatal / pediatric PN and being compliant with guidelines. However there was no significant association for all nutrients; there was only a trend for an association between being aware of guidelines and being compliant for the lipid target dose ($p = 0.054$) and for the initiation of amino acids ($p = 0.070$).

'In the discussion and conclusion, the authors are making a comparison with historical data. The authors should mention this in the methods as well.'

Response: The comparison with historical data was not an objective of the study but was only a section of the discussion. We have modified the abstract and the text to make this point clearer.