

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessment of healthcare delivery in the early management of bacterial meningitis in UK young infants: An observational study
AUTHORS	Okike, Ifeanyichukwu; Ladhani, Shamez N.; Anthony, Mark; Ninis, Nelly; Heath, Paul

VERSION 1 - REVIEW

REVIEWER	M. Douglas Baker, MD Johns Hopkins University, School of Medicine Baltimore, MD, USA
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	<p>This is an interesting study of the common clinical presentation(s) of meningitis in young infants in England. The epidemiological information provided is additive, though not surprising. Perhaps one unexpected finding is the lack of reported fever in many infants affected with this disease. Although the study sample represents less than half of all eligible subjects, and a portion of the data is retrospectively reported following self-recollection, the data are nonetheless important to distribute to those engaged in clinical practice.</p> <p>I find the manuscript to be generally well written and complete. I do think that the authors missed an opportunity to make an additional comment of importance, however. It is remarkable that the data presented seem to indicate that hours of delay between onset of first symptoms and administration of antibiotics did not influence subsequent morbidity. In the US, there is great importance placed upon rapid administration of antibiotics in the instance of suspected serious bacterial illness. Perhaps this aspect of care should be further studied, so that a more informed approach to this step of management can emerge. I would suggest that in the "What this paper adds" section (page 21 of 43), the authors consider adding a second bullet statement in Section 2 that addresses this issue.</p> <p>One additional comment is regarding the importance of analysis of CSF in infants with fever or other unusual clinical behaviors. Both the Philadelphia Protocol for management of fever in young infants, and the Boston Protocol for management of fever in young infants call for lumbar puncture and CSF analysis in all febrile infants of young age. The Rochester Protocol makes that assessment optional. The data presented here support the approach recommended by both the Philadelphia and Boston investigators. As many clinicians choose to opt out of CSF analysis in febrile young infants, this point might warrant additional comment.</p>
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REVIEWER	Borja Gomez Cruces University Hospital, Pediatric Emergency Department. Spain
REVIEW RETURNED	24-Jan-2017

GENERAL COMMENTS	<p>I read with interest the manuscript by Dr Okike et al about the early management of young infants finally diagnosed with bacterial meningitis. The authors conclude that most of the symptoms presented when evaluated were already at the beginning of the illness. On the other hand, almost 40% of the infants had neurological consequences and estimated that for instance 30% of those admitted from home received inappropriate pre-hospital management, suggesting that this step could be an area of improvement.</p> <p>I have some questions and suggestions:</p> <ul style="list-style-type: none"> - one of my main concerns, already stated by the Authors as a limitation, is the method used to analyze the evolution of the symptoms in the recruited cases. <p>It was obtained using a questionnaire filled by the parents, probably being affected by several memory biases. The cases were diagnosed between September 2010 and July 2013. When was the questionnaire filled? Was it sent in a concrete date to all of them (for instance July 2014) or did each case receive the questionnaire after a specific period (for instance 1 month after the discharge)?</p> <p>For those infants already admitted at the onset of the illness (“in-patients”) was the evolution of symptoms obtained also from parental reports or from the patients’ medical records?</p> <p>According to the results, the median time from onset of symptoms to receipt of first antibiotic dose was 7 hours (5 hours to fist help + 2 hours to antibiotic). This fact also limits the obtained results because maybe there was no significative progression of symptoms because they receive the antibiotic treatment in the first hours of their illness.</p> <p>The graphics used to show the progression of symptoms (mainly 2A, 2B, 3A and 3B) are a bit confused. There are too may lines on each one and since all of them are gray it is quite difficult to identify which one belongs to each symptom. Probably, showing the accumulated percentage of patients who presents each symptom in specific moments (for instance at the beginning, 3 hours, 6 hours, 12 hours, 24 hours,...) would be enough to prove that the symptoms did not vary much as time passed.</p> <ul style="list-style-type: none"> - Abstract: the authors state in the conclusion that the patients have non-specific symptoms and signs. This conclusion, although probably true, is not supported by the Results shown in the abstract, and probably is not one of the most important facts identified in the study. I will add some data about the number of patients who do not receive an adequate management and whether it affected or not their outcome. - Introduction; page 5: “we hypothesised that earlier recognition may lead to earlier health intervention which in turn might improve the outcomes”. It is not well described throughout the manuscript whether the authors found or not data supporting this hypothesis.
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- Methods; page 6: since the surveillance database used in the study is “voluntarily” used to report infection. Did the authors have any estimation of its use and whether the number of bacterial meningitis reported reflects a reasonable percentage of the bacterial meningitis

really diagnosed in the study period? Similarly, how many pediatricians participate in the network used as an alternative method used to identify bacterial meningitis?

-Results (page 9, first line): how many infants were identified by each of the methods described (surveillance database, parents or network)?

- Table 2A: the first parameters could be obviated, since the second one also refer to the parental age and includes the median and the IQR.

- Results (page 9, second paragraph): it would be interesting to compare the symptoms at onset of the illness between those admitted from home and those in-patients. Table 4 includes fever and seizures but not those shown in the text (poor feeding, lethargy...).

- Results (page 10, second paragraph): “the majority of patients (47/62) presented to hospital within 24 hours of onset of symptoms, although 15 (24% parents presented to hospital after 24 hours”. This sentence duplicates information; delete one of the two parts.

- Results (page 10, third paragraph) and supplemental table 1: I think that it could be difficult to ensure that the management of some of these infants were as it appears if the data were obtained in a retrospective way. For instance, could the authors confirm that the doctor in charge blamed the fever on the umbilical hernia in patient 1 and on a change in milk formula in patient 68? Was it indicated in the medical report or that the fontanelle was not checked in patient 8 in his initial visit at the GP?

Probably it could be easier to present a table with the main reasons of inadequate management. For instance, according to the NICE guideline, any infant under 3 months of age with fever without source must be referred to be evaluated by a specialist and perform complementary tests, so all the febrile infants discharged to home received an inadequate management.

Overall, a table with all the reasons of inadequate management (pre-hospital and at-hospital, such as inadequate empiric antibiotic), depending on whether the infant was admitted from home or was an already in-patient, would summarize interesting information and show in how many patients the doctor in charge followed the recommendations included in the guidelines used by the authors to assess the management of the recruited patients. Moreover, it would mean a starting point to identify areas of improvement. It would

- Table 2B: the parameter “region of England” could be deleted if published in an international journal, or replaced by something like “rural/urban region”.

	<ul style="list-style-type: none"> - Results (page 14, second paragraph): a denominator is missed (inadequate empiric antibiotic in infants admitted from home) - Discussion (page 16, last paragraph): the authors indicate several reasons for the delay to first antibiotic dose. As happens with other data, unless this reasons are specifically indicated in the medical report (waiting for urine samples before giving antibiotics, waiting for handover between shifts...), it could be difficult to ensure whether they were only hypothesis. - Table 2: this table shows the value of different items in patients with or without complications; for instance % of patients with and without complications that had seizures. I think that it could be more useful to identify risk factors presenting the data on the contrary: % of patients with or without seizures that had any complication. - Study protocol (page 36): the authors propose as an objective the evaluation of the neurodevelopmental outcome of meningitis when the patients reach 2 years of each, but they do not include any specific result about it in the manuscript.
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

 Reviewer: 1
 Baker, MD
 Pediatric Emergency Medicine, Johns Hopkins Children's Center

Please leave your comments for the authors below

This is an interesting study of the common clinical presentation(s) of meningitis in young infants in England. The epidemiological information provided is additive, though not surprising. Perhaps one unexpected finding is the lack of reported fever in many infants affected with this disease. Although the study sample represents less than half of all eligible subjects, and a portion of the data is retrospectively reported following self-recollection, the data are nonetheless important to distribute to those engaged in clinical practice.

RESPONSE: THANK YOU.

I find the manuscript to be generally well written and complete. I do think that the authors missed an opportunity to make an additional comment of importance, however. It is remarkable that the data presented seem to indicate that hours of delay between onset of first symptoms and administration of antibiotics did not influence subsequent morbidity. In the US, there is great importance placed upon rapid administration of antibiotics in the instance of suspected serious bacterial illness. Perhaps this aspect of care should be further studied, so that a more informed approach to this step of management can emerge. I would suggest that in the "What this paper adds" section (page 21 of 43), the authors consider adding a second bullet statement in Section 2 that addresses this issue.

RESPONSE: IT IS TRUE THAT WE DID NOT FIND A SIGNIFICANT EFFECT OF DELAY IN ANTIBIOTICS AND OUTCOME. THIS HAS NOT BEEN SHOWN IN ANY PAEDIATRIC STUDY, ALTHOUGH IT HAS BEEN WIDELY PUBLISHED IN ADULT STUDIES. IT MAY WELL BE THAT WE DID NOT HAVE SUFFICIENT NUMBERS OF INFANTS IN THE STUDY (AND, MORE IMPORTANTLY, SUFFICIENT NUMBERS OF INFANTS WITH ADVERSE OUTCOMES, PARTICULARLY DEATH) TO BE STATISTICALLY CONFIDENT OF THE LACK OF ANY ASSOCIATION WITH ANTIBIOTIC TREATMENT. WHILST WE WERE UNABLE TO SHOW BETTER

OUTCOMES WITH MORE TIMELY ANTIBIOTIC ADMINISTRATION, WE WOULD ADVOCATE TIMELY ANTIBIOTICS FOR ALL CHILDREN WITH SUSPECTED SERIOUS BACTERIAL INFECTIONS AND, THEREFORE, AVOID CONFLICTING MESSAGES TO THE READERS IN OUR MANUSCRIPT WE MADE THE POINT THAT THE MEDIAN TIME IN HOURS (IQR) FROM ONSET OF ILLNESS TO FIRST HELP IN INFANTS WITH POOR OUTCOMES 6.25 [1-24] HOURS WAS LONGER THAN IN THOSE WHO RECOVERED WITHOUT SEQUELAE (4.75 [2-10] HOURS, P=0.8) BUT THIS WAS NOT STATISTICALLY SIGNIFICANT. SIMILARLY THE RATE OF POOR OUTCOME WAS HIGHER IN 15 INFANTS WHO PRESENTED TO HOSPITAL >24 HOURS AFTER ONSET OF SYMPTOMS 8/15 [53%] COMPARED TO THOSE WHO PRESENTED <24HRS 18/47 [38%]; P=0.3, BUT AGAIN THIS WAS NOT STATISTICALLY SIGNIFICANT, POTENTIALLY BECAUSE OF SMALL NUMBERS OF CASES FOR THIS RELATIVELY UNCOMMON ILLNESS.

One additional comment is regarding the importance of analysis of CSF in infants with fever or other unusual clinical behaviors. Both the Philadelphia Protocol for management of fever in young infants, and the Boston Protocol for management of fever in young infants call for lumbar puncture and CSF analysis in all febrile infants of young age. The Rochester Protocol makes that assessment optional. The data presented here support the approach recommended by both the Philadelphia and Boston investigators. As many clinicians choose to opt out of CSF analysis in febrile young infants, this point might warrant additional comment.

RESPONSE: WE AGREE WITH THE REVIEWER AND, USING THE RESULTS OF OUR OWN STUDY, WE HAVE STRONGLY ADVOCATED THE IMPORTANCE OF PERFORMING A LUMBAR PUNCTURE AS PART OF THE NEONATAL SEPTIC SCREEN IN THE DISCUSSION SECTION

Reviewer 2

I read with interest the manuscript by Dr Okike et al about the early management of young infants finally diagnosed with bacterial meningitis. The authors conclude that most of the symptoms presented when evaluated were already at the beginning of the illness. On the other hand, almost 40% of the infants had neurological consequences and estimated that for instance 30% of those admitted from home received inappropriate pre-hospital management, suggesting that this step could be an area of improvement.

RESPONSE: THANK YOU

I have some questions and suggestions:

- one of my main concerns, already stated by the Authors as a limitation, is the method used to analyze the evolution of the symptoms in the recruited cases. It was obtained using a questionnaire filled by the parents, probably being affected by several memory biases. The cases were diagnosed between September 2010 and July 2013. When was the questionnaire filled? Was it sent in a concrete date to all of them (for instance, July 2014) or did each case receive the questionnaire after a specific period (for instance 1 month after the discharge)?

RESPONSE: WE ACCEPT THE POSSIBILITY OF MEMORY BIAS. HOWEVER, WE KNOW THAT MENINGITIS IS SUCH A FEARED INFECTION AND HAS A HUGE IMPACT ON FAMILIES. FOR THIS REASON WE THINK THAT PARENTS WILL RECALL THE EVENTS LEADING UP TO THE ILLNESS. THIS METHODOLOGY HAS BEEN USED BEFORE BY NINIS ET AL IN THE EARLY 2000s (WHEN ELECTRONIC COMMUNICATION THROUGH MOBILE PHONES AND OTHER HAND HELD DEVICES WERE NOT COMMON) AND, WHEN TALKING TO PARENTS, WE – LIKE NINIS'S GROUP - FOUND THAT PARENTAL RECALL WAS EXCELLENT. MOST PARENTS RECORDED MAJOR EVENTS ON THEIR MOBILES OR HANDHELD DEVICES, BUT WE CLEARLY ACCEPT THAT THERE MAY BE SOME ELEMENT OF RECALL BIAS. WHEREVER POSSIBLE, WE

TRIED TO MINIMISE THIS BY CORROBORATING PARENTAL REPORTING WITH MEDICAL NOTES ENTRIES.

THE NINIS STUDY HAD A MEDIAN OF 140 DAYS INTERVAL BETWEEN ILLNESS AND QUESTIONNAIRE COMPLETION, WHILE WE HAD A 280 DAY INTERVAL. THIS WAS UNAVOIDABLE BECAUSE OF THE NATURE OF THE STUDY METHODOLOGY. THE STUDY BEGAN AFTER COMPLETION OF THE BPSU EPIDEMIOLOGICAL STUDY AND REQUIRED AN ENTIRELY NEW ETHICS PROPOSAL, ALONG WITH COMPLEX AND TIME-CONSUMING INTERNAL RESEARCH APPROVALS WITHIN INDIVIDUAL NATIONAL HEALTH SERVICE TRUSTS, BEFORE THE PAEDIATRICIANS COULD BE ENGAGED TO CONTACT THE FAMILY IN QUESTION AND SEND THEM THE DETAILS OF THE STUDY.

For those infants already admitted at the onset of the illness (“in-patients”) was the evolution of symptoms obtained also from parental reports or from the patients’ medical records?

RESPONSE; PARENTS WERE ASKED TO COMPLETE THE SAME QUESTIONNAIRES AS THOSE WHOSE INFANTS WERE ADMITTED FROM HOME. AMONG IN-PATIENTS, HOWEVER, WE HAD MORE DETAILED LONGITUDINAL MEDICAL RECORDS THAT WAS USED TO CORROBORATE THE PARENTS’ RECALL OF THE EVENTS

According to the results, the median time from onset of symptoms to receipt of first antibiotic dose was 7 hours (5 hours to first help + 2 hours to antibiotic). This fact also limits the obtained results because maybe there was no significative progression of symptoms because they receive the antibiotic treatment in the first hours of their illness.

RESPONSE: WE WOULD LIKE TO CLARIFY THAT THE MEDIAN TIME FROM ONSET TO FIRST HELP WAS 5 HOURS. THE FIRST HELP RANGED FROM TELEPHONE CALLS TO A NON-URGENT MEDICAL HELPLINE (111)/ NHS DIRECT/ THE COMMUNITY MIDWIFE, GP VISIT OR THE A&E VISIT. IT DOES NOT REFER TO THE TIME TO ILLNESS RECOGNITION. FOR EACH CASE, WE CALCULATED THE TIME FROM ONSET TO ILLNESS RECOGNITION, AND THEN CALCULATED THE TIME FROM ILLNESS RECOGNITION TO TREATMENT SEPARATELY.

The graphics used to show the progression of symptoms (mainly 2A, 2B, 3A and 3B) are a bit confused. There are too may lines on each one and since all of them are gray it is quite difficult to identify which one belongs to each symptom. Probably, showing the accumulated percentage of patients who presents each symptom in specific moments (for instance at the beginning, 3 hours, 6 hours, 12 hours, 24 hours,...) would be enough to prove that the symptoms did not vary much as time passed.

RESPONSE; WHEN IN COLOUR, FIGURE 2A SHOWS THAT MOST FEATURES ARE NOTED BY PARENTS AT TIME 0 WITH VERY FEW NEW FEATURES (OR NO AND THEREFORE PERCENTAGE OF INFANTS ACQUIRING ANY ADDITIONAL NEW FEATURES). WE WOULD LIKE TO EMPHASISE THAT THE INDIVIDUAL FEATURES ARE LESS IMPORTANT THAN THE OBSERVATION THAT NEARLY ALL THE SYMPTOMS OCCURRED AT PRESENTATION WITH VERY FEW ADDITIONAL SYMPTOMS AS THE ILLNESS PROGRESSED. FIGURE 2B SHOWS THE PERCENTAGE OF INFANTS WITH ANY FEATURES AT 1 HOURLY INTERVAL. THIS PROVIDES THE BREADTH OF THE FEATURES AS THEY OCCUR. FIGURE 2B SHOWS THE ACCUMULATED PERCENTAGE AS REQUESTED WHILE FIGURE 2C COMPARES ONSET FEATURES WITH ADMISSION FEATURES. FIGURES 3A TO 3C FOLLOW THE SAME PRINCIPLE.

- Abstract: the authors state in the conclusion that the patients have non-specific symptoms

and signs. This conclusion, although probably true, is not supported by the Results shown in the abstract, and probably is not one of the most important facts identified in the study. I will add some data about the number of patients who do not receive an adequate management and whether it affected or not their outcome.

RESPONSE; WE AGREE. WE HAVE HIGHLIGHTED THE ACUTUAL DIFFERENCES BETWEEN THE NON-SPECIFIC AND THE SPECIFIC FEATURES AT ONSET AND AT ADMISSION. THE SENTENCE SHOULD NOW READ:

“In young infants, the non-specific features associated with bacterial meningitis appear to show no progression from onset to admission whereas there were small but significant differences in the proportion of infants with more specific symptoms at hospital admission compared with at the onset of the illness.”

WE INCLUDED THE NUMBER WITH INAPPROPRIATE MANAGEMENT IN THE ABSTRACT: 20/66 (30%) infants were assessed to have received inappropriate pre-hospital management. WE HAVE PROVIDED A TABLE OF RESULTS THAT SUMMARISED FACTORS THAT INDEPENDENTLY AFFECTED SHORT-TERMS OUTCOMES AND ONLY SEIZURES WAS SIGNIFICANT. WE ARE CURRENTLY IN THE MIDDLE OF THE NEXT PHASE OF THE STUDY ASSESSING LONGER-TERM OUTCOMES.

- Introduction; page 5: “we hypothesised that earlier recognition may lead to earlier health intervention which in turn might improve the outcomes”. It is not well described throughout the manuscript whether the authors found or not data supporting this hypothesis.

RESPONSE: WE WERE UNABLE TO IDENTIFY ANY FEATURES THAT MIGHT HAVE LED TO EARLIER RECOGNITION AND WE WERE UNABLE TO DEMONSTRATE ANY ASSOCIATION BETWEEN EARLY TREATMENT AND BETTER OUTCOME. THESE ARE DESCRIBED IN THE RESULTS AND HIGHLIGHTED IN THE DISCUSSION. WE HOPE THAT THE ONGOING FOLLOW-UP STUDY MAY IDENTIFY FACTORS ASSOCIATED WITH LONG-TERM OUTCOMES

- Methods; page 6: since the surveillance database used in the study is “voluntarily” used to report infection. Did the authors have any estimation of its use and whether the number of bacterial meningitis reported reflects a reasonable percentage of the bacterial meningitis really diagnosed in the study period? Similarly, how many pediatricians participate in the network used as an alternative method used to identify bacterial meningitis?

RESPONSE: THE SURVEILLANCE DATABASE CAPTURES NEARLY 90% OF SIGNIFICANT REPORTS ACROSS ENGLAND AND WALES. THEREFORE, THIS DATABASE WOULD IDENTIFY NEARLY ALL INFANTS WITH CONFIRMED BACTERIAL MENINGITIS. OUR METHODOLOGY, HOWEVER, ADDITIONALLY REQUIRED LOCAL PAEDIATRICIANS ACROSS THE COUNTRY TO CONFIRM THAT THE CHILD DID SUFFER FROM BACTERIAL MENINGITIS AND THEN FORWARD THE STUDY INFORMATION TO THE FAMILIES. IF THE FAMILY CONSENTED TO PARTICIPATE, THEN THEY WERE ASKED TO COMPLETE THE DETAILED QUESTIONNAIRE. THEREFORE, OUR OVERALL RESPONSE RATE WAS LOWER FOR THESE LOGISTICAL REASONS. OUR METHODOLOGY, HOWEVER, MADE IT DIFFICULT TO CONTACT FAMILIES OF INFANTS WHO DIED OF THEIR ILLNESS, USUALLY BECAUSE THE PAEDIATRICIAN FELT THAT IT WOULD BE INAPPROPRIATE TO CONTACT THE FAMILY. OVERALL, HOWEVER, OUR COHORT OF INFANTS WAS RECRUITED FROM 48 DIFFERENT HOSPITALS ACROSS THE COUNTRY AND SHOULD PROVIDE A TRUE REPRESENTATION OF OVERALL CASES.

-Results (page 9, first line): how many infants were identified by each of the methods described (surveillance database, parents or network)?

RESPONSE: WE WOULD LIKE TO CLARIFY THE METHODOLOGY AS FOLLOWS: NEARLY ALL CASES WERE IDENTIFIED FROM THE NATIONAL SURVEILLANCE DATABASE. FOR EACH CASE, THE PAEDIATRICIAN WAS CONTACTED TO CONFIRM THE CASE AND, IF THEY FELT IT APPROPRIATE, TO FORWARD THE RELEVANT INFORMATION TO THE FAMILIES. ALSO, MANY OF THE CASES WERE IDENTIFIED THROUGH MULTIPLE SOURCES. FOR EXAMPLES, PARENTS WHO LEARNT OF THE STUDY THROUGH THE MENINGITIS CHARITIES WERE ASKED TO CONTACT THEIR PAEDIATRICIAN TO TAKE PART IN THE STUDY

AS PER OUR RESPONSE TO THE PREVIOUS QUESTION, WE CONTACTED THE PAEDIATRICIANS OF ALL THE CASES WE IDENTIFIED THROUGH ALL SOURCES AND WE CONTINUED TO RECRUIT UNTIL WE REACHED OUR TARGET NUMBER OF CASES. FOR THE PURPOSES OF THIS STUDY, THE SOURCE OF THE REPORTING IS NOT IMPORTANT.

- Table 2A: the first parameters could be obviated, since the second one also refer to the parental age and includes the median and the IQR.

RESPONSE: DONE

- Results (page 9, second paragraph): it would be interesting to compare the symptoms at onset of the illness between those admitted from home and those in-patients. Table 4 includes fever and seizures but not those shown in the text (poor feeding, lethargy...).

RESPONSE; THE TWO FEATURES (FEVER AND SEIZURES) WERE THE MOST PREVALENT. WE DID NOT INCLUDE THE LESS COMMON SYMPTOMS AND SIGNS IN ORDER TO AVOID OVER-ANALYSING OUR DATA AND HAVING TO CORRECT FOR MULTIPLE ANALYSES. MOREOVER, MANY OF THE SYMPTOMS WERE NOT COMPARABLE BETWEEN THE TWO GROUPS – FOR EXAMPLE, THE INPATIENT INFANTS WERE OFTEN PREMATURE AND ON NASOGASTRIC FEEDS – THEREFORE, POOR FEEDING WOULD NOT BE APPROPRIATE WITH A SIMILAR ARGUMENT FOR LETHARGY IN VENTILATED INFANTS, FOR EXAMPLE

within 24 hours of onset of symptoms, although 15 (24% parents presented to hospital after 24 hours”. This sentence duplicates information; delete one of the two parts.

RESPONSE; THE SECOND SENTENCE DELETED.

- Results (page 10, third paragraph) and supplemental table 1: I think that it could be difficult to ensure that the management of some of these infants were as it appears if the data were obtained in a retrospective way. For instance, could the authors confirm that the doctor in charge blamed the fever on the umbilical hernia in patient 1 and on a change in milk formula in patient 68? Was it indicated in the medical report or that the fontanelle was not checked in patient 8 in his initial visit at the GP?

Probably it could be easier to present a table with the main reasons of inadequate management. For instance, according to the NICE guideline, any infant under 3 months of age with fever without source must be referred to be evaluated by a specialist and perform complementary tests, so all the febrile infants discharged to home received an inadequate management.

Overall, a table with all the reasons of inadequate management (pre-hospital and at-hospital, such as inadequate empiric antibiotic), depending on whether the infant was admitted from home or was an already in-patient, would summarize interesting information and show in how many

patients the doctor in charge followed the recommendations included in the guidelines used by the authors to assess the management of the recruited patients. Moreover, it would mean a starting point to identify areas of improvement. It would

RESPONSE

WE WISH TO EMPHASISE HERE THAT THERE WAS INAPPROPRIATE MANAGEMENT FOR THE 20 INFANTS, INCLUDING 12 WHO PRESENTED WITH FEVER AND WARRANTED HOSPITAL INVESTIGATIONS AS PER THE NATIONAL (NICE) GUIDELINES. THE OTHER 8 WHO WERE AFEBRILE HAD OTHER WORRYING FEATURES INCLUDING NEUROLOGICAL FEATURES OR BREATHING DIFFICULTIES. TAKEN TOGETHER, WE WOULD LIKE TO MAKE THE POINT THERE WAS EITHER POOR MANAGEMENT OF FEBRILE YOUNG INFANTS OR NON-RECOGNITION OF OTHER WORRYING FEATURES WHICH WARRANT HOSPITAL INVESTIGATIONS.

- Table 2B: the parameter "region of England" could be deleted if published in an international journal, or replaced by something like "rural/urban region".

RESPONSE: THE INCLUSION OF REGIONS WAS IN OUR A PRIORI ANALYSIS TO DEMONSTRATE BROAD RECRUITMENT ACROSS THE COUNTRY. THE REGIONS CANNOT BE DIVIDED INTO RURAL/UNBAN AREAS BECAUSE THEY ENCOMPASS LARGE AREAS OF BOTH. WE BELIEVE IT IS USEFUL TO INCLUDE THIS INFORMATION IN THE TABLE, BUT WOULD BE HAPPY TO REMOVE IF THE EDITORIAL TEAM WISHES US TO DO SO)

- Results (page 14, second paragraph): a denominator is missed (inadequate empiric antibiotic in infants admitted from home)

RESPONSE: DENOMINATOR NOW ADDED

- Discussion (page 16, last paragraph): the authors indicate several reasons for the delay to first antibiotic dose. As happens with other data, unless these reasons are specifically indicated in the medical report (waiting for urine samples before giving antibiotics, waiting for handover between shifts...), it could be difficult to ensure whether they were only hypothesis.

RESPONSE; THESE REASONS FOR DELAY WERE BASED ON ENTRIES IN THE MEDICAL NOTES. FOR EXAMPLE, "WAIT FOR THE URINE AND THEN START ANTIBIOTICS" OR "WILL HANDOVER TO THE NIGHT TEAM" ARE ALL DOCUMENTED IN THE MEDICAL NOTES.

- Table 2: this table shows the value of different items in patients with or without complications; for instance % of patients with and without complications that had seizures. I think that it could be more useful to identify risk factors presenting the data on the contrary: % of patients with or without seizures that had any complication.

RESPONSE: THE QUESTION HERE IS "DOES HAVING SEIZURE INFLUENCE THE RISK OF DEVELOPING COMPLICATIONS". THE OUTCOME UNDER REVIEW IS COMPLICATION OR NO COMPLICATION. THE DATA ARE PRESENTED IN A FORMAT THAT MAKES THE TABLE EASY TO UNDERSTAND AS IT CLEARLY SHOWS THE PROPORTION OF INFANTS WITH SEIZURES WHO HAD COMPLICATIONS AND THOSE WHO DIDN'T. WE ARE HAPPY TO TAKE ADVICE FROM THE EDITORIAL TEAM AND REVISE THE TABLE IN ANY FORMAT.

- Study protocol (page 36): the authors propose as an objective the evaluation of the neurodevelopmental outcome of meningitis when the patients reach 2 years of age, but they do not include any specific result about it in the manuscript.

RESPONSE: WE PROPOSED TO DO THIS AS A FOLLOW-ON STUDY. THE FOLLOW-ON STUDY IS NOW UNDERWAY. WE PLAN TO REPORT THE FINDINGS IN A SEPARATE PUBLICATION.

VERSION 2 – REVIEW

REVIEWER	M. Douglas Baker, MD Johns Hopkins University, school of Medicine
REVIEW RETURNED	20-Mar-2017

GENERAL COMMENTS	Thank you for addressing the issues raised in initial review.
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REVIEWER	Borja Gomez Cruces University Hospital, Pediatric Emergency Department. Spain
REVIEW RETURNED	24-Mar-2017

GENERAL COMMENTS	<p>I would like to thank the authors for the effort made in the revision of their manuscript and I hope our suggestions have been useful for them</p> <p>I have no additional comments besides those already made in the first revision and I think that those changes made by the authors have improved the quality of the paper. I only would like to mention that although the authors have properly answered to each comment made, I have missed the additional information provided in some of the answers to be included also in the manuscript, such as the interval between illness and questionnaire made to the parents, clarification made by the Authors about the different intervals calculated for the patients...</p> <p>In relation to the intervals calculated, I have still some doubts about them. In the response provided, the authors state that they calculated “for each patient the time from onset to illness recognition and then from illness recognition to treatment”. Throughout the text, we can find “time from onset of first features to first help”, “time from triage to receipt of the first antibiotic dose”, “Onset to hospital visit” and “Onset to first dose of antibiotics”, the last two ones in a table. So many intervals could make it difficult to understand the meaning of each one, unless summarized all of them on a table to read them altogether. On the other hand, I am not sure which of the intervals presented on the manuscript referred the Authors.</p> <p>They also state in their response that have modified the conclusion of the Abstract to “In young infants, the non-specific features associated with bacterial meningitis appear to show no progression from onset to admission whereas there were small but significant differences in the proportion of infants with more specific symptoms at hospital admission compared with at the onset of the illness”, but this sentence does not appear in the new version of the manuscript.</p> <p>Finally, in relation to their response about supplementary table 2 (now, supplementary table 1), they state that “THE DATA ARE PRESENTED IN A FORMAT THAT MAKES THE TABLE EASY TO UNDERSTAND AS IT CLEARLY SHOWS THE PROPORTION OF INFANTS WITH SEIZURES WHO HAD COMPLICATIONS AND</p>
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	<p>THOSE WHO DIDN'T". If I have understood the table, it is incorrect. The table shows the proportion of infants with complications who presented seizures (14/26; 56%) and those without complication who presented seizures (7/40; 18%). Inversely, "THE PROPORTION OF INFANTS WITH SEIZURES WHO HAD COMPLICATIONS" would be 66.6% (14/21) and in "THOSE WHO DIDN'T" would be 26.6% (12/45). Please, confirm that.</p>
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VERSION 2 – AUTHOR RESPONSE

REVIEWERS' COMMENTS April 2017

I would like to thank the authors for the effort made in the revision of their manuscript and I hope our suggestions have been useful for them.

THANK YOU

I have no additional comments besides those already made in the first revision and I think that those changes made by the authors have improved the quality of the paper. I only would like to mention that although the authors have properly answered to each comment made, I have missed the additional information provided in some of the answers to be included also in the manuscript, such as the interval between illness and questionnaire made to the parents, clarification made by the Authors about the different intervals calculated for the patients...

RESPONSE:

THE TIME INTERVAL TO COMPLETION OF QUESTIONNAIRE HAS BEEN ADDED IN THE TEXT (PAGE 9 LINE 7 AND 8 IN RESULTS SECTION).

In relation to the intervals calculated, I have still some doubts about them. In the response provided, the authors state that they calculated "for each patient the time from onset to illness recognition and then from illness recognition to treatment". Throughout the text, we can find "time from onset of first features to first help", "time from triage to receipt of the first antibiotic dose", "Onset to hospital visit" and "Onset to first dose of antibiotics", the last two ones in a table. So many intervals could make it difficult to understand the meaning of each one, unless summarized all of them on a table to read them altogether. On the other hand, I am not sure which of the intervals presented on the manuscript referred the Authors.

RESPONSE:

MUCH OF THE WORK PRESENTED IN THE MANUSCRIPT IS QUALITATIVE ANALYSIS. THE DIFFERENT INTERVALS OFTEN RELATE TO DIFFERENT GROUPS OF INFANTS, THEREFORE, MAKING IT DIFFICULT TO SUMMARISE FOR THE WHOLE INFANT COHORT. FOR EXAMPLE, SOME PARENTS TOOK THEIR INFANTS TO THE GP AND THEN TO THE HOSPITAL, WHILE OTHERS TOOK THEIR INFANTS DIRECTLY TO THE HOSPITAL – THE INTERVAL BETWEEN ONSET OF SYMPTOMS AND FIRST HELP, THEREFORE, WOULD BE COMPLETELY DIFFERENT AND, MOST PROBABLY, SHOULD NOT BE COMBINED BECAUSE ONE WOULD EXPECT THE MORE UNWELL INFANTS TO PRESENT DIRECTLY TO HOSPITAL. WE HAVE GONE THROUGH THE WHOLE MANUSCRIPT AGAIN AND, WHERE POSSIBLE, TRIED TO CLARIFY THE TIMINGS AS MUCH AS WE CAN. WE BELIEVE THAT TABLE 3 PROVIDES THE MOST ACCURATE REFLECTION OF THE DIFFERENT INTERVALS THAT ARE IMPORTANT IN THE CONTEXT OF THIS STUDY.

They also state in their response that they have modified the conclusion of the Abstract to "In young infants, the non-specific features associated with bacterial meningitis appear to show no progression from onset to admission whereas there were small but significant differences in the proportion of infants with more specific symptoms at hospital admission compared with at the onset of the illness",

but this sentence does not appear in the new version of the manuscript.

RESPONSE:

I HAVE ADDED THIS SENTENCE TO THE ABSTRACT. I HAVE DISCUSSED WITH THE ASSISTANT EDITOR WHO ACCEPTED THAT I CAN INCLUDE THIS STATEMENT EVEN THOUGH IT TAKES US OVER THE WORD LIMIT FOR THE ABSTRACT (PAGE 2, CONCLUSIONS SECTION OF THE ABSTRACT).

Finally, in relation to their response about supplementary table 2 (now, supplementary table 1), they state that "THE DATA ARE PRESENTED IN A FORMAT THAT MAKES THE TABLE EASY TO UNDERSTAND AS IT CLEARLY SHOWS THE PROPORTION OF INFANTS WITH SEIZURES WHO HAD COMPLICATIONS AND THOSE WHO DIDN'T". If I have understood the table, it is incorrect. The table shows the proportion of infants with complications who presented seizures (14/26; 56%) and those without complication who presented seizures (7/40; 18%). Inversely, "THE PROPORTION OF INFANTS WITH SEIZURES WHO HAD COMPLICATIONS" would be 66.6% (14/21) and in "THOSE WHO DIDN'T" would be 26.6% (12/45). Please, confirm that.

RESPONSE:

THAT IS CORRECT. IN ORDER TO IDENTIFY RISK FACTORS FOR COMPLICATIONS, WE ASSESSED THE PREVALENCE OF DIFFERENT VARIABLES IN THOSE WITH COMPLICATIONS COMPARED TO THOSE WHO HAD NO COMPLICATIONS. THE TABLE IS USEFUL BECAUSE IT IMMEDIATELY IDENTIFIES THOSE FACTORS THAT ARE MORE COMMON IN INFANTS WITH COMPLICATIONS, E.G. SEIZURE.