Author’s response to reviews

Title: Prognostic Factors Related to Sequelae in Childhood Bacterial Meningitis: Data from the Meningitis Registry

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Author’s response to reviews: see over
To the Editor in Chief
Melissa Norton, MD
BMC Infectious Diseases

Dear Editor,

RE: re-submission of revised manuscript [MS: 1070601284411904]

We would like to thank you for the opportunity to consider a revised version of our manuscript entitled “Prognostic Factors for the Determination of Sequelae in Childhood Bacterial Meningitis: Data from a Greek Meningitis Registry” in response to comments made by both reviewers for publication in BMC Infectious Disease.

We have taken into account comments made reviewer Mariel Mckenzie Finucane and have incorporated these changes into the revised manuscript accordingly. Please find attached point by point answers to the reviewer’s comments. We hope that the reviewer finds the responses adequate.

Please do not hesitate to contact me for any further clarifications that may be required.

Yours Sincerely

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Authors’ responses to reviewers: Allan Tunkel and Mariel Mckenzie Finucane.

“Prognostic Factors for the Determination of Sequelae in Childhood Bacterial Meningitis: Data from a Greek Meningitis Registry”

Reviewer #1: Allan Tunkel
We would like to thank the reviewer for his attention.

Reviewer #2: Mariel Mckenzie Finucane
We would like to thank the reviewer for the opportunity to improve our manuscript.

Major Compulsory Revisions:

1. I agree with comments #6 and #7 from Allan Tunkel. When rates of non-response are high, inference based on the subset of subjects with completed data registries may be misleading. Please note that neither large denominators nor small p-values alleviate this concern (as suggested in the authors’ response).

We would like to thank the reviewer for giving us the opportunity to improve the manuscript.

1a. At a minimum, please include a “percent missing” column in Tables 1a, 1b, 2, 3, 4, and 5 so that readers can easily identify those predictors for which results are based on a small subset of the study population. (As currently written, since the authors do not report how many subjects fall into each age group, an interested reader would not be able to calculate these percentages for Table 2 nor for those rows of Table 1a with an “a”, “b”, or “c” subscript.)

We included in the table 1a the column with the missing values as you can see most of the indicators have missing values between 0.4% (Haemorrhagic rash) and 35% (Poor feeding). We have excluded from table 1a, the analysis CRP which had a high rate of missing values (about 93%). With respect to this we have also deleted the following comment from Laboratory Findings (page 10):

“The median C-reactive protein (CRP) on admission was estimated at 123.5 (IQR=40.0-192.0).”

The percentage of lymphocytes in CSF and fever had also high rate of missing values (about 50%) as shown in Table1a. However, we do not have any indication that systematically some indicators were not collected in the Registry. Thus, we believe that the results are representative of the study population. The majority of results of the analysis of predictors are not based on a small subset of the study population. Eighty or ninety percent response rate could not be considered as a small subset of the study population. However,
acknowledging the possible problems with the missing values which are expected in a Registry we included in the last paragraph of the discussion section, the following comment:

“Moreover, a possible limitation of the study is the percentage of missing values ranging from 0.4% to 35% in different variables. However, since we believe the missing values were not systematically created, the subset of data without missing values could be considered representative of the study population.”

1b. Was the multivariate regression reported in Table 6 restricted to the <50% of subjects who had complete registries? If so, unless the authors can convincingly argue that these subjects represent a random subset of the total study population, I do not find this analysis informative and suggest that it be removed.

We appreciate the reviewer’s concern, however we consider that the subset of the total study population is a random subset as missing values were random and we do not have any identification that they were systematically created. To verify the representativeness of the proportion of subjects who had complete registries and were included in the logistic regression analysis we compared them with the subset of participants with missing values. We did not find any statistically significant difference on demographics factors sex (P=0.612), age (P=0.199), also in sequelae (P=0.673) and Period (P=0.755). Thus, we fully support that the subset is representative of the study population.

1c. By the same token, I would recommend removing those sentences from the text that describe results based on a small subset of the study population. I disagree with the authors’ claim that response rates of 66-87% are “high” for the purposes of making valid statistical inference.

As it has already mentioned, we removed CRP from the Table 1a, whilst the indicators percent of lymphocytes in CSF and fever are presented in the Table 1a, however it is noted that both have high rate of missing values (about 50%).

2. The authors report more than 100 p-values in Tables 2-6 without correcting for multiple comparisons. The probability of a false positive result is thus substantial. I suggest that the authors use a more stringent criteria for statistical significance than p=0.05 or, at a minimum, report the number of “significant” tests that would be expected to occur by pure chance.

We would like to thank the reviewer for their comment. In tables with univariate analysis (Table 3, 4 and 5) we considered an indicator statistically significant having a P-value less than or equal to 0.01. The following has been added to the Data analysis (page 6) section:
“P-values less than or equal to 0.01 were considered statistically significant in the univariate analysis, whilst in multivariate analysis when P-values less than 0.05 were considered statistically significant.”

Minor Essential Revisions:

1. I believe there is an inconsistency between the second paragraph of “Clinical data” and the second paragraph of “Discussion”. Were seizures more or less common in children under one year of age?

We agree with the reviewer and appreciate the opportunity to clarify this. The discussion (page 14) now reads as follows:

“Infants less than one years of age presented more commonly with seizures, bulging fontanelle, grunting and poor feeding as expected for such an age group. However this age group presented less commonly with coma.”

2. Please clarify the third sentence in the second paragraph of “Data analysis”. Is this how candidate predictors were chosen for the backward selection?

The second paragraph of “Data analysis” (page 6) has been modified and was replaced by the following paragraph:

“Two multiple logistic regression analyses were performed for sequelae in survivors related to risk factors on admission and risk factors during hospitalization. Multiple logistic regression analysis was performed using the backward conditional method to identify predictors of sequelae. Sequelae were used as dependent variables and candidate predictors selected when P-values were less than 0.05 in the univariate analysis. Moreover, we included in the logistic regression models variables which have been reported in the literature to be related with the prognosis of BM.”

3. I believe there is an inconsistency in the sixth sentence of “Sequelae and complications”. Were there 152 or 153 episodes of complications?

We apologise for the misunderstanding. In order to clarify this, we have modified the section of Sequelae and complication section (sixth sentence, page 11) with the following:

“The rate of acute complications was estimated 6.8% (152/2,251 BM cases, 95% CI 5.8-7.9) with a total of 153 episodes of complications in 152 meningitis cases.”
Discretionary Revisions:

1. In the abstract, it might be helpful to let readers know that these data come from a single hospital in Athens, Greece. Similarly, perhaps the title should be “Prognostic Factors Related to Sequelae in Childhood Bacterial Meningitis: Data from a Greek Meningitis Registry”.

We have changed the title and abstract according to reviewer’s proposal. Please note that the amendment made in the Abstract section (page 2) has been highlighted and reads as follows:

“A total of 2,477 ……old hospitalized in a Children’s Hospital in Greece ……. a Meningitis Registry, from 1974 to 2005.”

Minor issues not for publication:

1. The second sentence in the second paragraph of “Clinical data” is tautological: “The most common findings in infants included… as these are the most likely clinical features in infants.”

We agree with reviewer’s remark, thus we deleted the last part of this sentence in the text. The paragraph now reads as follows:

“Clinical manifestations of bacterial meningitis were found to be dependent on the age of the patient, as shown in Table 2. The most common findings in infants included grunting (57.6%, RR 1.64, 95%CI 1.38-1.97), poor feeding (54.7%, RR 4.93, 95%CI 4.06-5.97) and bulging fontanelle (58.2%, RR 3.70, 95%CI 2.73-5.01). Seizures were more common in children under one year of age compared to older children (RR 1.70, 95%CI 1.40-2.06), while infants presented less frequently with coma (RR 0.49, 95%CI 0.33-0.73). Fever however, was found to be independent of age with frequencies of fever >90% throughout all ages as seen in Table 2.”