Author's response to reviews

Title: Factors Determining Outcome of Children Hospitalized with Severe Pneumonia

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Pointwise explanation to Reviewer's report

Reviewer: Cristiana Nascimento-Carvalho

Reviewer's report:
The manuscript reports the results of an interesting research project. Nonetheless, several methodological issues must be revised and the manuscript must receive a major compulsory revision:

1) The study included children with congenital heart disease (24) and this is a confounding variable for outcome. Therefore, it will be better to exclude those children; the authors also can describe the specific congenital heart disease and exclude only those with cardiovascular consequences (increased pulmonary blood volume, for example); actually, all children with immunodeficiency or any other condition that could influence on the treatment's response should be excluded.

Response: Primary aim of study was to see the factors that may adversely affect the outcome of community acquired pneumonia. That's why we included all children who had not received prior antibiotics and were not in the hospital before enrolment in the study. We feel that important findings of our study is that none of the factors that are expected to change the outcome were found significant, suggesting that even with underlying diseases children can be managed like normal children. This we have included in the discussion. However as suggested we analyzed data after excluding children with underlying heart diseases and normal radiographs. The results are included in the results and discussed separately.

2) the study included children that had community-acquired pneumonia diagnosed on clinical grounds, according to WHO recommendation; out of 200 children, 146 had abnormal chest x-ray. We must consider that 146 had pneumonia and 54 had possibly any other lower respiratory tract disease, like bronchiolitis, wheezing, etc. The use of the WHO recommendation on clinical grounds is absolutely acceptable in order to include children with pneumonia rather than exclude them, especially at primary health care setting. Taking into account that the study was conducted at a tertiary hospital, only those with radiological diagnosed pneumonia should be included. This is a very important issue when change of antibiotics is a dependent variable (outcome variable) because bronchiolitis or wheezing do not need antibiotics as treatment.

Response: We agree with the reviewer and now included separate analysis of our data after excluding children with heart diseases and those with normal radiographs. Results are shown in table 7-11. However we would like to retain the analysis based on WHO define pneumonia.

3) I understood that the variable described in the second paragraph of the Introduction is "inability to drink" and not "inability to feed".
4) In the Methods, the authors informed that the antibiotics were changed if the patient did not improve after 48 hours of initiation of treatment or deteriorated in form of increasing chest indrawing or worsening hypoxemia. Therefore, in the Results, the frequency of the worsening or not improvement criteria should be presented.
Response: All the 113 patients that required change in antibiotics had worsening of hypoxia and chest indrawing. No antibiotic changes were needed for ‘no improvement’ in clinical features at 48 hours. Similarly in group with radiographically confirmed pneumonia all the 84 children needed change in antibiotics because of worsening chest indrawing and hypoxia. This has been included in the text.

5) When did the children who died, that is, during hospitalization (first 24h, 48h, etc)? This must be informed and discussed.
Response: There were total of 21 deaths (10.5%). Ten children died within 24 hours of admission, one patient died between 24-48 hours and 7 died after 48 hours.
In radiographically confirmed pneumonia a total of 13 patients died (10%). Nine died within 24 hours of admission, 1 died in 24-48 hours and 3 died after 48 hours.
Included in results as well as discussion.

6) Which were the frequencies of the radiographic alterations (consolidation, infiltrate, pleural effusion)? The presence of pleural effusion is a known associated factor with change of antibiotics as well as prolonged hospital stay.
Response: X ray findings were consolidation/ infiltration. None of the X rays showed pleural effusion.
Reviewer: Matti Korppi

Reviewer’s report:
This is a well-written paper on the risk factors of pneumonia in <5 years old children in a setting of a developing country. The outcome measures were the need of a change of antibiotics, the need of hospitalization for more than 5 days, the need of mechanical ventilation and mortality. The diagnosis of pneumonia was clinical according to WHO guidelines. A large number of risk factors were prospectively collected. The primary outcome measure was the need to change antibiotics, and the sample size calculation was based on this outcome. Overcrowding at home, lack of breast feeding and an abnormal chest radiograph finding were the most important risk factors for the complicated course of pneumonia.

There are some aspects which the authors should clarify.

1. First, the first line antibiotics and their alternatives were rather broad-spectrum drugs, chloramphenicol, ampicillin-gentamycin, cefuroxime and amoxicillin clavulanic acid were all accepted. So, the rationale of the change of antibiotics as an outcome measure is a little bit difficult to understand, since the second line antibiotics were not substantially better, not very much broader nor more specifically directed. Perhaps the rationale is that these children were not improved within 48 hours, which is an important matter. This 48-hour rule should be discussed.

Response: We agree with the comments. The primary antibiotics in all our patients were ampicillin-gentamycin, or amoxicillin clavulanic acid. None of the patients received cefuroxime or chloramphenicol. However all our patients required change in antibiotics because of worsening (chest indrawing or hypoxia) during the course of illness. None of the patient required antibiotic change due to no improvement at 48 hours. Suggesting that they had possibly infection due to drug resistant organisms and responded to change of antibiotics. We have discussed the same in section on discussion.

2. Second, an abnormal chest radiograph was an independent risk factor. In western countries, an abnormal radiograph is the criterion of pneumonia, and cases with no radiological infiltration are not considered as pneumonia at all. The authors should refer to the new papers from Pakistan, which have presented, that the WHO criteria select a large number children into the pneumonia group, though they don’t have pneumonia at all. In addition, radiological pneumonia was present in the small minority of the cases. In western countries, bronchiolitis and wheezy bronchitis are more common than pneumonia, also more common causing hospitalization. This may be true also in developing countries.
Response: Now we have provided data after excluding children with normal chest radiographs and those with congenital heart diseases. Paper from Pakistan is included in the discussion. However we would like to retain the original findings based on WHO defined pneumonia.

3. The authors say in the material part that they measured serum electrolytes, but the results are not presented. Hyponatremia is often considered as a significant risk factor for a complicated course of invasive infections like pneumonia.

Response: Hyponatremia was present only in one patient. The mean serum sodium was 142 ± 5.8 mEq/l. This has been included in the result section.

The discussion part should not include statistical details from other studies, such as odds ratios or risk ratios by two decimals and their confidence intervals. E.g. the expression 3-fould is enough, not OR 3.23, 95%CI 1.66-6.28.

Response: Necessary changes have been made in the text.
Pointwise explanation to Reviewer's report
Reviewer: Yhu-Chering Huang

Dr Tiewsoh et al enrolled 200 children aged 2 to 60 months with the diagnosis of severe pneumonia to study risk factors for change of antibiotics, prolonged hospital stay and mortality.

Major comments:
1. The conclusion that abnormal chest x-ray were associated with the need for change of antibiotics is quite strange. In my point of view, children with the diagnosis of severe pneumonia should have abnormal chest x-ray. What kinds of children with the diagnosis of severe pneumonia have normal chest x-ray?

Response: We included children diagnosed by WHO case definition. WHO case definition is based on clinical features (Respiratory rates, difficulty in respiration, cyanosis, and inability to drink). Now we have provided separate data on children with radiographically confirmed pneumonia. However we would like to retain the original results and analysis based on WHO defined severe pneumonia.

2. The authors should describe the total number of children with the diagnosis of pneumonia during the study period. In what percentage the case of severe pneumonia was. The definition of severe pneumonia should be described clearly in the manuscript.
Response: Definition of severe pneumonia has been included in the text. In this study we included children admitted in the pediatric wards with severe pneumonia. All children who were eligible for enrolment were included in the study. (mentioned in the text). Children with pneumonia (only with rapid respiration) are treated on ambulatory basis. We do not have data on number of children treated on ambulatory basis during study period. Therefore may not be able to provide number of all the children diagnosed as pneumonia during study period.

3. In the study, there were 200 children. Only 30 patients had evidences of bacterial infection based on the findings of blood culture. In this situation, whether changing antimicrobial agents is important for patients. Is there any other data that support most of these children in the study got bacterial infections.

Response: We agree with the reviewers comment. Our aim was to see if we can identify children with WHO defined severe pneumonia that require change of antibiotics or prolong hospital stay. WHO case definition is for countries with infant mortality of > 40/1000 live birth. The guideline suggests administration of antibiotics to all pneumonia. It does not differentiate between bacterial and viral pneumonia as it is not possible to differentiate by clinical features alone.
The yield of blood culture positive in pneumonia is very poor 5-15% and is not the method for identification of bacterial agents. We did not perform CRP or PCT (surrogate markers of bacterial infections) to suggest proportion of true bacterial infection. That is limitation of the study and mentioned in the text..

Minor comments
1. What is “head nodding”, more description of the definition of severe pneumonia, altered sensorium
Response: Details of these terms included in text.
Pointwise explanation to Reviewer’s report

Reviewer: Girdhar Agarwal

I have some basic questions about the present study.

1. I am bewildered about the first paragraph in the Statistical Analysis Section about sample size calculation.
2. The authors are not clear about the objective for which they are calculating the sample size.
3. They have mixed up the problem of (i) Estimation and (ii) testing of hypothesis. These are two separate branches of statistical inference and need different methods of sample size calculations.
4. They are talking about both confidence as well as power. Confidence interval is required for estimation, whereas the power is required for testing.
5. The sample size calculation is based on two cohorts (breast fed children and non-breast fed children). This is a testing of hypothesis problem.
6. I don’t think the sample size is calculated for testing of hypothesis problem here, as is evident from the reference given by them.
7. Since sample size is the basis of any study, I would like to see the sample size calculation and formula used.
8. In the study, they are trying to find risk factors for outcomes (i) change in antibiotics (primary objective), (ii) prolonged hospital stay (secondary), (iii) need for mechanical ventilation (secondary), and (iv) mortality (secondary).
9. For obtaining the risk factors, they need to identify two cohorts, which, in my view, could be (a) breast fed children and (b) non-breast children. Instead, they are trying to show breast feeding as a risk factor. Actually, in sample size calculation, they have considered these two groups as exposed and unexposed group. But then why they want to show this as a risk factor, is unclear.

Response:
We thank the reviewer for the comments. We have improved the language in the section on Statistics including the sample size calculation. The sample size was calculated for the primary objective to estimate the rate of need for change of antibiotic using Epi-info software. Thereafter, we have shown the sample size calculations for analysis of risk factors.