Author's response to reviews

Title: Effectiveness of azithromycin in aspiration pneumonia: a prospective observational study

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Author's response to reviews: see over
Effectiveness of azithromycin in aspiration pneumonia: a prospective cohort study
Satoshi Marumo, Takashi Teranishi, Yuichi Higami, Yoshihiko Koshimo, Hirofumi Kiyokawa, and Motokazu Kato

Dear Philippa Harris PhD
Executive Editor
BMC-series Journals

We are most grateful to you and the reviewers for the helpful comments on the original version of our manuscript. We have taken all these comments into account and submit revised version of our paper.

We have addressed all the comments by Referee 1 and Referee 2, as indicated on the attached pages, and we hope that explanations and revisions of our work are satisfactory.

We hope that the revised version of our paper is now suitable for publication in BMC Infectious Diseases and we look forward to hearing from you at your earliest convenience.

Sincerely,
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Responses to referee 1

Major compulsory revisions.

Comment 1:
-The conclusion should be changed to “in this small prospective non-randomized observational study, we found no statistically significant differences in mortality or antibiotic failure in patients receiving azithromycin compared to ampicillin/subactam.”

Answer 1:
We totally agree with the referee’s suggestion.

Change 1:
We modified the manuscript on line 1, 42-45, and 288-290.

Comment 2:
-The authors should state more clearly how “antibiotic success” was defined by the clinicians.

Answer 2:
Clinical efficacy was assessed mainly based on the evaluation of body temperature, WBC count, CRP, chest X-ray findings, signs and symptoms of pneumonia generally according to the criteria for the evaluation of effectiveness in clinical efficacy recommended by Japanese Respiratory Society.

Change 2:
We modified the manuscript on line 141-144.

Comment 3:
-The Figure demonstrating the differences in time to resolution of fever, which is a major component to the objective measurement of clinical stability, is interesting and should be highlighted more. This suggests that time to clinical stability was different for the two groups. This should be added as a measured clinical outcome.

Answer 3:
We totally agree with the referee’s suggestion. In the present study, we found no statistically significant differences in mortality or antibiotic failure in patients receiving AZM compared to ABPC/SBT. However, Kaplan–Meier analysis revealed that the ABPC/SBT group had a significantly shorter febrile period than that of the AZM group.

Change 3:
We added the result of febrile period to the main clinical outcomes, and modified the manuscript on
Comment 4:
-Were there any patients during the study period who received both azithromycin and ampicillin/sulbactam? If so, these patients should be included in the study. ATS/IDSA guidelines would recommend combination therapy with both an anti-streptococcal beta-lactam and a macrolide for any patients with community-onset pneumonia, regardless of aspiration risk.

Answer 4:
There were no patients administrated with both AZM (i.v.) and ABPC/SBT in the present study. 12 patients treated with combination of CAM (oral) plus ABPC/SBT (n=7) or LVFX (i.v.) plus ABPC/SBT (n=5) were excluded in the present study (mentioned on line  of the manuscript). Indeed, ATS/IDSA guidelines would recommend combination therapy with both a beta-lactam and a macrolide for any patients with community-onset pneumonia, but Japanese guideline for aspiration pneumonia (NHCAP guideline; reference 2) would not recommend combination therapy. This might be the reason why combination therapy was not performed in our hospital. The similar results were shown in the previous report at another hospital in Japan (J Infect Chemother. 19(4):719-26, 2013 Aug.).

Change 4:
We did not change the manuscript.

Comment 5:
- State more clearly the inclusion criteria, ie, how “aspiration pneumonia” was defined. Was this based upon a reported history of aspiration by the patient? Actual documentation of oropharyngeal dysfunction? If the latter, were these test performed prior to the hospitalization or after the initial presentation?

Answer 5:
There are few guidelines which clearly define the criteria of aspiration pneumonia. In the present study, according to the NHCAP guideline (reference 2), aspiration pneumonia was defined as being pneumonia that develops in patients in whom dysphagia and aspiration is known to occur (or is strongly suspected). The diagnosis of aspiration pneumonia was categorized into three groups; definitive cases (direct observation of aspiration by videofluoroscopic (VF) examination of swallowing), probable cases (presence of functional dysphagia examined by bedside assessment of swallowing function, arterial oxygen saturation monitoring during swallowing, repetitive saliva swallowing test, water swallowing test, simple swallowing provocation test), and possible cases
(presence of risk factors for oropharyngeal aspiration but without direct observation of aspiration nor functional dysphagia). Swallowing function tests (VF and bedside examinations) were conducted when the pneumonia of the patient had been improved and started their meal according to the physician’s decision (not to the documented criteria). In the present study, there were 10 definitive cases, 99 probable cases, and 8 possible cases. There was no significant difference of the distribution of the diagnostic category between the two groups (definitive cases; n=2 vs n=8, probable cases; n=30 vs n=69, and possible cases; n=4 vs n=4: AZM group vs ABPC/SBT group, respectively).

**Change 5:**
We added the definition of aspiration pneumonia in the methods and the category distribution in the results. We modified the manuscript on line 125-136, 165, and Table 1.

**Comment 6:**
- *Add a power analysis in the statistical methods for all primary outcomes of interest (mortality and antibiotic success).*

**Answer 6:**
The present study was an explorative observational study of pneumonia admitted to our hospital and not designed to prove non-inferiority of AZM to ABPC/SBT in patients with aspiration pneumonia. Therefore, we had not calculated the required sample size on the study protocol.

**Change 6:**
We modified the conclusion as follows: “In this small prospective non-randomized observational study, we found no statistically significant differences in mortality or antibiotic failure in patients receiving AZM compared to ABPC/SBT”.

**Minor, essential**

**Comment 7:**
- *Add a description of A-DROP and CURB-65. Were the data elements contributing to these severity measurements consistently collected? Was there any missing data? If so, how was this treated?*

**Answer 7:**
We totally agree with the referee’s suggestion. The data elements of A-DROP and CURB-65 could be obtained in all cases.

**Change 7:**
We added the description of A-DROP and CURB-65. We modified the manuscript on 91-97 line.
Minor, discretionary

Comment 8:
-It would be interesting to see a severity-adjusted comparison in clinical outcomes between the two groups using logistic regression and the two severity scores (A-DROP and CURB-65).

Answer 8:
A-DROP is a modified version of the CURB-65 score based on Japanese situations and gives similar results to CURB-65 (Respirology. 13(5), 731-5, 2008 July). Therefore, A-DROP and CURB-65 are not independent factor of clinical outcomes. We regret to inform the referee that we thought logistic regression analysis between the two severity scores wasn’t good for comparison in clinical outcomes.

Change 8:
We did not change manuscript.
Responses to referee 2

Major points

Comment 1:

1. Although I'm afraid I poorly understand the study, the study seems to be a case-control (observational) study. If so, the study requires more considerations about some biases including selection bias although the concern is partly described in discussion. Even if the cohort study, I wonder if the physicians’ decision can be strongly-affected by getting participation information. Did the authors blind the subjective person in any way? Anyway, the authors should describe more details about study protocols. For instance, when the patients were included in this study? /who decided the treatment strategy? /the drug selection was decided by physicians? ...

Answer 1:

I am very sorry not to describe the study protocols clearly. The subjects included into the present study were selected from the prospective cohort of pneumonia at our hospital. Therefore, the subjects provided written informed consent and were included into the present study on admission. The physicians decided the drug selection and did not blind the subjects. As the referee pointed out, many confounders might influence the clinical outcomes. We discussed this in the discussion.

Change 1:

We modified the title, method and discussion on line 1, 80-81, 84, and 273-276.

Comment 2:

2. Macrolide antibiotics have potent activities against atypical pathogens including Chlamyphila. How about possible involvements of atypical pathogens? In addition, were anaerobic cultures performed?

Answer 2:

Anaerobic cultures were not performed as a routine examination of sputum culture in our hospital. In the present study, serum Mycoplasma pneumoniae IgM antibody was examined for all the subjects, but serum Chlamydophila pneumoniae and Chlamydophila psittaci antibody were not examined. There are two patients with positive serum Mycoplasma Pneumoniae IgM antibody in the AZM group. On the other hand, there was no patient in the ABPC/EBT group. Excluding the two patients in the AZM group, we compared the clinical outcome again. There was no significant difference in the success rate of 1st-line antibiotics between the ABPC/EBT and AZM groups (74.1% vs. 74.3%, respectively, $P = 1.000$). Mortality and hospitalization periods did not differ significantly between groups (11.1% vs. 8.8%, $P = 1.00$; 22.3 ± 7.3 vs. 20.7 ± 8.0 days, $P = 0.674$, respectively). The total antibiotic costs were significantly lower in the AZM group than the ABPC/EBT group (2.13 ± 1.62...
×10,000 yen vs. 2.94 ± 1.67 ×10,000 yen, respectively, \( P = 0.024 \).

**Change 2:**
We modified the manuscript on line 104, 111-112, 187-195, and 278-280.

**Comment 3:**
3. *In table 1, MRSA and *P. aeruginosa* are listed as pathogens. These are causative bacteria or colonization?*

**Answer 3:**
In the present study, microbiological studies were defined to reflect causative pathogens, therefore the pathogens in the Table 1 mean causative bacteria. Indeed, AZM and ABPC/SSBT failed to improve in the patients with MRSA or *P. aeruginosa*.

**Change 3:**
We did not change the manuscript.

**Minor points**

**Comment 4:**
1. *PSI score can also serve for understanding of readers. Do the authors have data?*

**Answer 4:**
As the referee pointed out, PSI is the golden standard. But we do not have the data evaluating PSI.

**Change 4:**
We did not change the manuscript.

**Comment 5:**
2. *Table 1 H. influenza -> H. influenzae*

**Answer 5:**
We are so sorry for a simple mistake we made.

**Change 5:**
We corrected the spelling.