Author’s response to reviews

Title: The clinical features of respiratory infections caused by the Streptococcus anginosus group

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Author’s response to reviews:

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Editorial Office
BMC Pulmonary Medicine
Section Editors of Infectious, Rare and Idiopathic Pulmonary Diseases
Professors Sanjay Chotirmall and Giovanni Sotgiu,

Thank you very much for your letter dated Aug 14, 2015, about our manuscript entitled, “The clinical features of respiratory infections caused by the Streptococcus anginosus group” (PULM-D-15-00001). We deeply appreciate your interest in our manuscript and your courteous reply.
We have read the informative comments from the two reviewers very carefully, and have rewritten our manuscript accordingly. We are hereby sending a revised version of our manuscript, together with our point-by-point responses to the reviewers’ comments.

We hope that our responses are satisfactory, and that our manuscript is now acceptable for publication in BMC Pulmonary Medicine. We are looking forward to your favorable consideration.

Respectfully yours,

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Reviewer #1:

Mayor revision

1- You should be more clear in the description of the methods, mainly in the statistical and microbiological evaluation.

(Response)

Thank you very much for your important comments. In relation to microbiological evaluation in this study, we evaluated bacterial cultivation using a semi-quantitative method. We also thought that quantitative methods were more suitable for evaluating the etiology of the lower respiratory tract infection. Unfortunately, this was not possible in our respective institutions. We agree that we need to describe the microbiological evaluation in greater detail. We therefore added the sentences below, and also revised the statistical analysis section.

Before

Page 8, line 14-16:

in the present study by a bacterial volume of “1+ or greater” in bronchoalveolar lavage fluid (BALF) or “2+ or greater” in sputum samples [16].

After

Page 9, line 16- page 10, line 2:

in the present study by a bacterial volume of “1+ (≥103-105 colony-forming units (CFU)/ml)” in bronchoalveolar lavage fluid (BALF) or “2+ (≥106 CFU/ml)” in sputum samples by reference to the results of quantitative culture, the findings of which included ≥106 CFU/ml in sputum and 104 CFU/ml in BALF [16-18].
Added references


Before

Page 9, line 5-8:

All statistical analyses were performed using the SPSS software package (version 19), and a value of p<0.05 was considered to be statistically significant. Fisher’s exact test for tables (2×2) and the Mann-Whitney (non-parametric) test were used for the statistical analyses.

After

Page 10, line 15- page 11, line 2:

All statistical analyses were performed using the SPSS software package (version 19), and a value of p<0.05 was considered to be statistically significant. Continuous variables were compared using the Mann-Whitney (non-parametric) U-test, while categorical variables were compared using Fisher’s exact test (2×2), as appropriate.

2-You need to improve the grammar and spelling. Many mistakes were found.

<Response>

We greatly appreciate your comment. The revised manuscript has been reviewed by a professional editor who is a native speaker of English.

3-Why did you exclude 79 patients with positive culture to SAG? You should be more explicit with inclusion and exclusion criteria.

<Response>
Thank you for this helpful comment. We have explained the inclusion and exclusion criteria, as below.

Before
Page 8, line 7-9:

Empyema thoracis was defined by the existence of macroscopically observable purulent pleural fluid [15].

After
Page 9, line 7-11:

Empyema thoracis was defined by the existence of macroscopically observable purulent pleural fluid [15]. Patients who did not fulfill the above-described diagnostic criteria (pneumonia, lung abscess, and bacterial pleurisy only) were excluded from the study.

Before
Page 9, line 1-2:

VITEK 2 system (bio-Mérieux) with or without an API 20 STREP system (bio-Mérieux) [17].

After
Page 10, line 5-10:

VITEK 2 system (bio-Mérieux) with or without an API 20 STREP system (bio-Mérieux) [19]. Patients who did not fulfill the following criteria were excluded to avoid bacterial contamination to the extent that was possible, even when one of the above diagnostic criteria for pneumonia, lung abscess and bacterial pleurisy was fulfilled: a bacterial volume of “≥1+” in BALF or “≥2+” in sputum samples.

Before
Page 9, line 12-15:

From the 944 patients in whom SAG bacteria were cultured during the study period, a total of 30 patients were diagnosed with a respiratory infection (pneumonia, lung abscess, bacterial pleurisy only) due to S. intermedius, or S. constellatus, or S. anginosus (Figure 1).

After
Page 11, line 6-15:
Among the 944 patients in whom SAG bacteria were cultured during the study period, 109 patients showed cultures that were positive for SAG bacteria from lower respiratory tract, pleural effusion or blood samples. In these 109 patients with pneumonia, 74 patients were excluded because they did not fulfill the diagnostic criteria of pneumonia, lung abscess or bacterial pleurisy only, and 5 patients were excluded because their bacterial volume, which was calculated semi-quantitatively, did not fulfill the diagnostic criteria. Finally, a total of 30 patients were diagnosed with a respiratory infection (pneumonia, lung abscess, bacterial pleurisy only) due to S. intermedius, or S. constellatus, or S. anginosus (Figure 1).

4- You included six patients with mixed infections, you should excluded the patients with common pathogens for respiratory infections such as H influenzae, E coli, K pneumoniae or at least make a separately analysis.

<Response>

Thank you very much for this important comment. Based on your suggestion, we excluded the six cases of mixed infection, and reanalyzed the 24 remaining patients. We have revised the sentences, table and figure as follows.

Before
Page 3, line 17- page4, line 5:

Pus formation occurred in half of the 22 patients with pleural effusion. The average age of patients who were diagnosed with “pneumonia with pleural effusion” was significantly higher than that of patients with “bacterial pleurisy only”. S. intermedius was identified significantly more frequently in patients with “pneumonia with pleural effusion” than in patients with “bacterial pleurisy only.”

After
Page 3, line 17- page 4, line 12:

Empyema was observed in half of the 22 patients with pleural effusion. S. intermedius, S. constellatus and S. anginosus were detected in 16 (53.3%), 11 (36.7%) and 3 (10.0%) patients, respectively. Six patients had mixed-infections. The duration from the onset of symptoms to the hospital visit was significantly longer in “lung abscess” patients than in “pneumonia” patients among the 24 patients with single infections, but not among the 6 patients with mixed-infection. The peripheral white blood cell counts of the “pneumonia” patients were higher than those of the “lung abscess” patients and S. intermedius was identified significantly more frequently in patients with pulmonary and pleural infections (pneumonia and lung abscess) than in patients with bacterial pleurisy only. In addition, the patients in whom S. intermedius was cultured were significantly older than those in whom S. constellatus was cultured.
Before

Page 9, line 5-7:

All statistical analyses were performed using the SPSS software package (version 19), and a value of p<0.05 was considered to be statistically significant.

After

Page 10, line 13-17:

After excluding the 6 patients with mixed infection to clarify the characteristics of SAG respiratory infection, we analyzed the results of 24 patients. All statistical analyses were performed using the SPSS software package (version 19), and a value of p<0.05 was considered to be statistically significant.

We revised the tables of the characteristics of a total of 30 patients of “clinical and laboratory features of Table 1” and “the treatment outcomes of Table 3” as “Table1” in the revised manuscript, as follows.

Before

Table 1. The clinical and laboratory features of 30 patients with a Streptococcus anginosus group infections

Table 3. The treatments and outcomes of 30 patients with Streptococcus anginosus group infections

After

(In the revised manuscript) Table 1. The clinical and laboratory features of 30 patients with a Streptococcus anginosus group infections

No statistically significant differences among the three diseases were observed in relation to the patients’ age and C-reactive protein levels in a statistical reanalysis of the 24 remaining patients (after the exclusion of the 6 cases with mixed infection). Based on this finding, we deleted the following sentences. In addition, we added the differences in the clinical features, laboratory features, treatments and outcomes of 24 patients (after the exclusion of the 6 cases with mixed infection) with the three diseases as a new paragraph in the Results session as follows.

Deleted sentences

Page 10, line 2-3:
The average age of the pneumonia patients was higher than that of patients with bacterial pleurisy only.

Page 10, line 4-7:

The laboratory findings of patients diagnosed with “pneumonia” and “bacterial pleurisy only” showed higher values of inflammatory markers (WBC, CRP) in comparison with patients who were diagnosed with “lung abscess”.

Added sentences

Page 13, line 13- page 14, line 7:

The clinical features, laboratory features, treatment, and outcomes among the patients with single infections (pneumonia, lung abscess or bacterial pleurisy only)

After excluding the 6 patients with mixed infections, 16, 5, and 3 patients were classified as having “pneumonia”, “lung abscess” and “bacterial pleurisy only”, respectively (Table 3). No significant differences were observed among three diseases with regard to age, gender, comorbid diseases and symptoms at presentation. The duration (in days) from the onset of symptoms to the patient’s hospital visit was significantly longer in the “lung abscess” patients than in the “pneumonia” patients. The “pneumonia” patients showed higher peripheral WBC counts than the “lung abscess” patients. No significant differences were observed in the numbers of detected bacteria, the treatments or the clinical outcomes of these three categories (Table 4).

(In the revised manuscript)

Table 3. The clinical and laboratory features of 24 patients who were classified in pneumonia, lung abscess and bacterial pleurisy only

(In the revised manuscript)

Table 4. The treatments and outcomes of 24 patients who were classified in pneumonia, lung abscess and bacterial pleurisy only

Before

Page 12, line 5- 15:

The number of patients with pleural effusion in “pneumonia” and “lung abscess” totaled 14 (73.7%) and 2 (40.0%), respectively (Table 1). The clinical characteristics and laboratory findings of patients with pneumonia complicating pleural effusion and “bacterial pleurisy only” are shown in Table 4. There were no significant differences in gender, comorbid diseases,
symptoms at presentation, or clinical and laboratory parameters between these two categories. Whereas the average age of patients who were diagnosed with “pneumonia with pleural effusion” was significantly higher than that of patients with “bacterial pleurisy only”, and S. intermedius identified significantly more frequently in patients with “pneumonia with pleural effusion” than in patients with “bacterial pleurisy only”.

After

Page 14, line 10- page 14, line 17:

The clinical characteristics and laboratory findings of the “pneumonia” or “lung abscess” patients that were complicated with pleural effusion and the “bacterial pleurisy only” patients are shown in Additional Table S1. There were no significant differences in age, gender, comorbid diseases, symptoms at presentation, and clinical and laboratory parameters between these two categories. Whereas, S. intermedius was significantly more frequently identified in “pneumonia” and “lung abscess” patients with “pleural effusion” than in patients with “bacterial pleurisy only” (Figure 2).

(In the revised manuscript)

Figure 2

The differences of detected rate of three bacterial species between patients with pneumonia or lung abscess with pleural effusion (n=16) and those with bacterial pleurisy only (n=3).

A) Streptococcus intermedius, B) Streptococcus constellatus, C) Streptococcus anginosus.

(In the revised manuscript)

Additional Table S1. The clinical and laboratory features of patients with pneumonia or lung abscess with pleural effusion and bacterial pleurisy only

Before

Page 11, line 15- page 12, line 2:

There were no significant differences in the comorbid diseases, symptoms at presentation, laboratory findings, treatments or outcomes among three SAG bacterial species (Additional Tables S1 and S2). All of the eleven patients in whom S. constellatus was identified were males, and significantly more males were infected with S. constellatus in comparison to S. intermedius and S. anginosus (Figure 2).

After
There were no significant differences in the comorbid diseases, symptoms at presentation, laboratory findings, treatments or outcomes among three SAG bacterial species (Additional Table S2). The patients with positive S. intermedius cultures were significantly older than those with positive S. constellatus cultures (Figure 3A). All of the eight patients in whom S. constellatus was identified were males, and significantly more male patients were included among the patients with S. constellatus than those with S. anginosus (Figure 3B).

(In the revised manuscript)

Figure 3
Age and gender-based comparison of each bacterial member of the Streptococcus anginosus group
A) age, B) gender.

(In the revised manuscript)

Additional Table S2

Before

Page 14, line 13-17:
In this study, patients with pneumonia, with or without pleural effusion, or those with bacterial pleurisy tended to show a shorter period from the onset of symptoms to the diagnosis and more elevated levels of inflammatory reactions (such as WBC and serum CRP) than patients with lung abscess.

After

Page 17, line 7-10:
In this study, patients with pneumonia, with or without pleural effusion, tended to show a shorter period from the onset of symptoms to the diagnosis and more elevated levels of peripheral WBC counts than patients with lung abscess.

Before

Page 17, line 6-7:
S. constellatus was more frequently detected in male patients than the two other members of the SAG in this study.

After

Page 19, line 15- page 20, line 1:

In comparison with the two other SAG members, S. constellatus tended to be more frequently detected in male patients in this study, although there were no significant differences in the gender of patients whose cultures were positive for S. intermedius or S. constellatus.

5- You should describe more clinical outcomes such as mortality, UCI admission, etc. What is "Improvement by treatment"?

<Response>

Thank you very much for this comment. We have added the mortality rate and the intensive care unit (ICU) admission rate in Tables 1, 3 and 5 as follows. We also evaluated the improvement of treatment according to The Japanese Respiratory Society guidelines for respiratory infections.

Treatment was considered to be “clinically effective” in cases which more than three of the following criteria were satisfied: (1) an improvement or the complete resolution of clinical symptoms; (2) an improvement in the body temperature to ≤37°C; (3) a chest radiography score of ≤70% of the previous value; (4) a WBC count ≤9,000/mm3; and (5) a CRP level of ≤30% of the previous value. The clinical efficacy of each treatment for lung abscess and bacterial pleurisy was assessed by the chief physician based on the above criteria.

We deleted the initial definition of “improvement of treatment” because, as you pointed out, it was not common.

Before

Page 11, line 10-12:

There were no significant differences in the lengths of stay or the treatment responses among the patients diagnosed with any of the three diseases.

After

Page 12, line 18- page 13, line 3:

There were no significant differences in the lengths of stay or the treatment responses among the patients diagnosed with any of the three diseases. Six patients (20.0%) were admitted to the intensive care unit (ICU) and there were 2 cases (6.7%) of in-hospital mortality
Table 1 (in the revised manuscript)

Total (n=30)

- ICU admission 6 (20.0)
- In-hospital mortality 2 (6.7)

Table 4 (in the revised manuscript)

<table>
<thead>
<tr>
<th></th>
<th>Total (n=24)</th>
<th>Pneumonia (n=16)</th>
<th>Lung abscess (n=5)</th>
<th>Bacterial pleurisy only (n=3)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>6 (25.0)</td>
<td>6 (37.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>2 (8.3)</td>
<td>2 (12.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

6- Why most of the patients received carbapenem?

<Response>

Thank you very much for your comments. This study was retrospective in nature, and the attending physicians at each hospital could freely administer any antimicrobial agent. Gram positive bacteria, including obligate anaerobes and Gram negative bacteria are known as causative pathogens in patients with pleurisy associated with respiratory infection and empyema is a relatively severe infectious condition. The attending physicians might prefer to use carbapenems because assume that the above-mentioned bacteria are causative pathogens. We have added the fact that many of the patients in the present study had previously received carbapenems.

Before

Page 11, line 5-6:

Antibiotic monotherapy was administered to 25 of 30 (83.3%) patients,

After

Page 12, line 12-13:
Antibiotic monotherapy was administered to 25 of 30 (83.3%) patients, and 19 of 25 (63.3%) patients were treated with carbapenems.

Reviewer #2

As the authors explain in the abstract/introduction, streptococci are frequently cited as contaminants. The method used to define infection here is a bacterial volume of 1+ or greater in BAL or 2+ or greater in sputum - I am not aware of any data supporting the validity of this definition. How do you know this does not simply represent contamination?

<Response>

Thank you very much for your important comments. In relation to microbiological evaluation in this study, we evaluated bacterial cultivation using a semi-quantitative method. We think that quantitative methods are superior for evaluating the etiology of lower respiratory infections; unfortunately, we lacked the facilities to employ such methods at the institutions that were involved in this study. We agree that there are no obvious reports to show the usefulness of the semi-quantitative cultivation methods; however, the semi-quantitative drip slide method has been shown to be yield comparable results to conventional quantitative culture techniques (Chest 1996;109(6):1423-9). There are several reports detailing the etiological evaluation in patients with pneumonia by semi-quantitative methods, we believe that our results, which used a semi-quantitative method are reliable and that the data are interesting. However, we agree that we need to describe the methods of the microbiological evaluation in greater detail, to allow the readers to better understand the procedures of the experiments. We therefore added the following sentences.

Before

Page 8, line 14-16:

in the present study by a bacterial volume of “1+ or greater” in bronchoalveolar lavage fluid (BALF) or “2+ or greater” in sputum samples [16].

After

Page 9, line 16- page10, line 2:

in the present study by a bacterial volume of “1+ (≥103-105 colony-forming units (CFU)/ml)” in bronchoalveolar lavage fluid (BALF) or “2+ (≥106 CFU/ml)” in sputum samples by reference to the results of quantitative culture, the findings of which included ≥106 CFU/ml in sputum and 104 CFU/ml in BALF [16-18].
Added references


Before

Page 18, line 11-12:

Second, it was unclear whether the appropriate conditions were created for the detection of anaerobic cultures.

After

Page 21, line 5-9:

Second, it was unclear whether the appropriate conditions were created for the detection of anaerobic cultures. Third, although quantitative culture methods are desirable in the bacteriological and etiological evaluation of pneumonia, we were only able to evaluate the bacterial composition semi-quantitatively.

We know from the existing literature that strep milleri group are a frequent cause of pleural infection- what does this paper tell us that we did not already know?

<Response>

Thank you very much for this important comment. Despite the relatively small number of patients in this study, we think that our article highlights that there are significant differences in the clinical features of S. intermedius and the other two bacteria. This has been described in the revised conclusion. And we therefore changed Figures 2 and Figure 3 to make the figures easier to understand.

(In the revised manuscript)

Figure 2
The differences of detected rate of three bacterial species in Streptococcus anginosus group between patients with “pneumonia” or “lung abscess” with pleural effusion (n=16) and bacterial pleurisy only (n=3).

A) Streptococcus intermedius, B) Streptococcus constellatus, C) Streptococcus anginosus.

(In the revised manuscript)

Figure 3

A) Age and gender-based comparison of each bacterial member of the Streptococcus anginosus group.

B) Age, B) Gender.

Was pH or the presence of bacteria on Gram strain not included in the definitions of complicated effusion or empyema thoracis?

<Response>

Thank you very much for your comments. We had actually performed Gram staining in all patients but some of the pleural pH data, which is used in the definition of complicated pleural effusion, was missing. As a result, we did not use the pH data in the definition of the complicated case. We therefore added the following sentences.

Before

Page 8, line 5-7:

Complicated parapneumonic effusion was defined by a low glucose level (<40mg/dL) and high levels of lactate dehydrogenase (>1,000IU/L), or positive culture results.

After

Page 9, line 5-7:

Complicated parapneumonic effusion was defined by a low glucose level (<40mg/dL) and high levels of lactate dehydrogenase (>1,000IU/L), or positive gram staining or culture results.

What is "bacterial pleurisy" - I do not know this condition. Does this mean pleural infection? i.e complicated parapneumonic effusion or empyema?

<Response>
Thank you very much for your comments. We used the term “bacterial pleurisy” to describe bacterial pleural effusion (infection), including complicated parapneumonic effusion and empyema. Although this term may not be common, the usage is in line with our previous report (Chest 2011;139:600-608) – furthermore, the present study included some cases of simplified parapneumonic effusion that did not meet the diagnostic criteria of complicated parapneumonic effusion or empyema. We chose to keep the term in place; however, we have added an explanation to clarify this definition to the readers.

Before

Page 7, line 17-Page 8, line 1:

Bacterial pleurisy was macroscopically defined by the existence of purulent pleural fluid or inflammatory cells (predominantly neutrophils) in the pleural effusion in addition to (1) and (3) of the above criteria.

After

Page 8, line 16- page 9, line 1:

Bacterial pleurisy, which is defined as pleural infection due to bacteria, was macroscopically defined by the existence of purulent pleural fluid or inflammatory cells (predominantly neutrophils) in the pleural effusion in addition to (1) and (3) of the above criteria.

Abstract- Change pus formation to "empyema".

<Response>

Thank you very much for your comment. We have changed “pus formation” to “empyema” in the abstract.