Author's response to reviews

Title: Causative Agent Distribution and Antibiotic Therapy Assessment among Adult Patients with Community Acquired Pneumonia in Chinese Urban population

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Author's response to reviews: see over
**Answer to the reviewer Patrick GP Charles**

**Major compulsory revisions:**

1. The number of patients who had viral testing was small, because of charges were expensive for all serums being tested. Blood samples were taken if patients had a fever of \(>38.5^\circ\) C, because it is not been accepted by patients to take blood culture if they had not fever in China. Urinary antigen testing was not performed because detection kit had not been supplied in 2004 year in China. We agree with you that over half the patients were pre-treated before enrollment, the rate of pneumococcal infections may be grossly underestimated.

2. For viral testing, we use diagnosis criteria of Roux (Roux, A, Marcos MA, Garcia E, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. Chest, 2004; 125:1343-1352), in his paper, the diagnosis of definite infection was made if seroconversion was measured. In our research from 2001 to 2001 year (Chin J Tuberc Respir Dis,2004,27:27-30), the seroconversion and PCR both performed to detect *C. pneumoniae*, in a total 103 patients, 2 patients had seroconversion and PCR positive, 2 patients had not seroconversion but PCR positive, 99 patients had not seroconversion and PCR negative, so we think seroconversion is in accordance with PCR. On the other hand, we think if PCR positive, the colonization of pathogens in upper respiratory tract is not been excluded. Thus we only chose seroconversion as diagnosis criteria for chlamydial infections, and we not chose a single high titres of antibodies.

3. For serological testing, we chose 2-4 weeks, because some patients in the out-patient clinic, return visit was difficult if the time is longer than 4 weeks (We added it in the discussion (page 16)).

   Urinary antigen testing for Legionella only serotype 1, but in China serotype 12 of *L. pneumophilla* was the predominant one (Chin J nosocomiol, 2007,17:743-745), so we not use Urinary antigen testing.

4. This break points for penicillin is used since 2008 year, because our research was performed in 2003 and 2004, so we use original break point. In the discussion, we added some contents (page 18) about this.
5. Sputum samples were taken at day of their admission. 56.1% of patients received antibiotics before enrolling (added in the page 13). In China, empirical choice of antibiotics may be second or third cephalosporins, some of these had effectivity to *K. pneumoniae* or *E.coli*, so we think the influence was not greater. Sputum was Gram-stained mainly to see if it was representative sputum originated from the lower respiratory tract. So we had not correlation data between sputum Gram stain and culture results. We agree with you that sputum which shows mixed flora on Gram stain but cultures a Gram-negative organism is likely to be indicative of a misleading culture result.

6. On page 13, paragraph 3, line 2, is “In patients with Class *V* disease …”

**Discretionary revisions:**

1. We agree with your viewpoint, fluoroquinolone resistance in China is increasing, but macrolide resistance of *Streptococcus pneumoniae* is too high in China, so for patients has comorbidities, fluoroquinolone may be a good choice.

2. Table 2 and 3 have been simplified.

**Thank you very much!**

**Answer to the reviewer Stephen Baum**

1. Atypical pathogens had been defined in the article (page 8).

2. Chlamydia had been changed to Chlamyphila.

3. Percentage of the number in which pathogens were identified was noted in the note of the table 2 and table 3.

4. For atypical pathogens, we do not cultured, only detected by serology, so do not have data of the percentage of serology vs culture. And for atypical pathogens, the diagnosis criteria were serologic conversion (≥ 4-fold increase in titers of antibodies), so it can be acute infection.

5. For important pathogens, such as *H. influenzae* and *S. pneumoniae*, had been correlated with previous antibiotics (page 13), but for other pathogens, we had
not Statistic data.

6. In our study years 2003-2004, there was no high influenza prevalence in China, so we think our results may not be influenced by high influenza prevalence.

7. In China, the resistance rate of S. pneumoniae to macrolide is high, but to fluoroquinolones is relatively low.

8. Table 2 title had been corrected.

Thank you very much!

Answer to the reviewer grant waterer:

1. We think that the title should not be changed, because our patients were consecutively enrolled, and according to PORT classification, high risk Class V was determined in 1.0%. In our study, severe patients were less, we think it was because at enrollment about half of patients had antibiotics.

2. In the article, page 13, we wrote that “56.1% of patients received antibiotics before enrolling. H. influenzae was 6-fold more frequently isolated from patients who had not received antibiotics before enrolling than those who had been treated with antibiotics (17.2% (46/268) vs. 2.9% (10/342), p<0.05). Prior antibiotic therapy did not significantly reduce the frequency of S. pneumoniae isolation.” For patients who had received antibiotics before enrolling, 40.95% had been detected bacteria, and for had not received antibiotics before enrolling, 51.23% had been detected bacteria. For blood culture, as sputum culture, 51% of patients had received antibiotics before obtained samples, only one was S. pneumoniae.

3. We agree with you that blood culture was small, in our study blood samples were taken if patients had a fever of >38.5°C, because it is not been accepted by patients to take blood culture if they had not fever in China. As bacteria were cultured less from blood, only in 5 patients, S. pneumoniae only in one patient, and M. pneumoniae was in 27 patients (same as the in total patients, it was 20.7%), so we did not presented it in the article.
4. We agree with you, we chose 2-4 weeks, because some patients in the out-patient clinic, return visit is difficult if the time was longer than 4 weeks. We added it in the discussion (page 16).
5. The discussion had been cut shorter.
6. On page 18, the paragraph that states pneumococcal infection was less common in patients receiving antibiotics ..... was deleted.
7. Table 4 had been deleted.

Thank you very much!