Peer Review File

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Reviewer A

This paper reported a case of severe psittaci with copious watery sputum that was successfully treated with rapid diagnosis by mNGS and the use of effective antibiotics. The course and diagnosis of the atypical case of massive watery sputum are generally well written. However, I think the content of the discussion needs to be improved. The same content as the introduction is repeated, and there is a paragraph that only describe CT findings.

Response:
We thank dear professor for the support and agree with the review's insightful comment. We have revised the content of the discussion and introduction as the suggestions.

1.In introduction, it is repeatedly written in two paragraphs that psittaci is a systemic disease, caused by the zoonic bacterium. Furthermore, the first paragraph of discussion is almost the same as the first two paragraphs of introduction, so I think this paragraph could be omitted.

Response:
Thanks for the helpful comment. We integrate the contents of the first and second paragraphs in introduction into one paragraph, and the first paragraph of discussion, which is almost the same as the first two paragraphs of introduction, is omitted.

The revised paragraph in introduction is as following: "Psittacosis, also known as avian chlamydiosis, ornithosis, and parrot fever, is caused by the zoonotic bacterium *Chlamydia psittaci* (*C. psittaci*), which can be transmitted to humans primarily from birds (1). Psittacosis is a systemic disease, and the spectrum of the disease is highly variable, ranging from subclinical infection to less commonly reported severe pneumonia requiring mechanical ventilation or multi-organ failure. *C. psittaci* pneumonia comprises approximately 1% of all community acquired pneumonia (CAP) cases (2). However, based on metagenomic next-generation sequencing (mNGS), it accounts for 8% of severe CAP (SCAP) cases, who are immunocompetent and admitted to the intensive care unit (ICU) (3), and can be life-threatening in severe cases due to failure to diagnose or identify the pathogen in time and delayed treatment with targeted antibiotics. Therefore, it is necessary to highlight the optimal management of severe *C. psittaci* pneumonia to improve patient outcomes." **(See Line 9-20/Page 3).**

2. In case presentation, it was written that "when he was admitted to ICU (Day 1, D1), his vital signs were normal". His body temperature was 40 ℃ on admission, but did you use antipyretics afterwards?

Response:
Yes. His temperature was 40℃ when he was in emergency department, and use

antipyretics afterwards, then the temperature was 36.5℃ when he was admitted to ICU. We mentioned it in the case presentation that "treated with febrifuge, imipenem/cilastatin sodium". **(See Line 21/Page 4).**

3. In page 5, line 25, I think it would be better to write "patency of lung" as "patency of air way".

Response:
Thanks for the good advice. We revised "patency of lung" to be "patency of air way". **(See Line 27/Page 5).**

4. From page 5, line 31 to page 6, line 4, "We could not perform chest CT scan … with bilateral pleural effusion (Figure 2B).", I feel that one sentence is too long and difficult to understand.

Response:
Thanks for the comment, we revised the long sentence to be as following:
"While the CT scan on D1 revealed a large air-space consolidation of left lower lung(Figure 2A), the chest CT on D9 showed the new onset ground-glass opacities and inflammatory exudates of the right lung and left upper lobe (Figure 2B)." **(See Line 33/Page 5~Line 2/Page 6).**

5. Do you think that psittaci of this case was resistant to azithromycin, as his condition worsened during the first 3 days of azithromycin administration?

Response:
No, we don't think so. Firstly, the short time administration of azithromycin(3 days) may be insufficient for his worsening condition. Moreover, the target antibiotic treatment (azithromycin and doxycycline) was subsequently initiated on D7 for about 1 month and his pneumonia was recovered. As there is not any antibiotic sensitivity results for *C. psittaci* due to the negative result of BALF/sputum culture, we cannot proposed that psittaci of this case was resistant to azithromycin. Above all, we don't think that psittaci of this case was resistant to azithromycin.

6. Regarding the CT findings of D15, it appears that there is still some residual shadowing. Would it be appropriate to describe it as "resolved" at this point?

Response:
Thanks for the rigorous recommendation. We are sorry for the mistake, as the CT findings of D15 is still some residual shadowing. We changed the word "resolution" to be "absorption" in case presentation and figure legend. **(See Line 8/Page 6 and Line 9/Page 15).**

7. In page 6, line 17, could the description of improvement in blood findings be included

in t the flow of treatment progress up to the previous paragraph?

Response:
Yes, the description of improvement in blood findings was included in the flow of treatment progress up to the previous paragraph, and we have included the description of improvement in blood findings in the previous paragraph. **(See Line 16-20/Page 6).**

8. At the end of the case presentation, it is suddenly mentioned that the treatment for ARDS was successful. However, it is not clear whether the shadows observed in this case were solely due to psittaci pneumonia or if ARDS was also present. If so, I would like to see the details of when and on what basis this diagnosis of ARDS was made during the course.

Response:
Thank you for the insightful comment. It is difficult to verify that the shadows observed in this case were solely due to psittaci pneumonia or if ARDS was also present. The pathological hallmark of the ARDS acute phase is diffuse alveolar damage, which should be confirmed by lung biopsy and it is unusual to perform in clinical practice. However, we hold the opinion that ARDS should be diagnosed on D3 according to the 2012 Berlin definition, as the progressively severe hypoxemia with PaO2/FiO2 52 mmHg (PEEP≥5 cm H_2O) with the repeat chest X-ray showed progressive multiple patchy shadows on bilateral lungs that excluding cardiac failure or fluid overload. Moreover, pneumonia can cause direct pulmonary injury and is the most common risk factor for ARDS (59.4%)(4)，and there are studies report about the severe C. psittaci-induced ARDS(5-8).
We added the details about the diagnosis of ARDS in case presentation: “He was suffering progressively severe hypoxemia (PEEP≥5 cm H_2O) with bilateral opacities in chest x-ray that excluding cardiac failure or fluid overload, acute respiratory distress syndrome (ARDS) was diagnosed according to Berlin definition(9).” **(See Line 22-25 /Page 5)**.

9. Regarding the description of the image starting from the 19th line on page 8, if there is nothing specific about the imaging findings in this case, it might be unnecessary since it only states the imaging observations.

Response:
We agree with the comment. We delete the description of the image. **(See Line 23-32 /Page 8)**.

10. Kurahara's paper on page 9 reported a case of tuberculosis, which typically presents with productive cough. However, it is unclear what the purpose is of comparing the sputum progression in this case of psittaci with that of tuberculosis.

Response:
It is just an example for infectious diseases that cause excessive watery sputum, and there is no comparison between psittaci and tuberculosis. We deleted the content about Kurahara's report of tuberculosis. **(See Line 8-12 /Page 9)**.

11. In psittaci, are there any clinical symptoms that have been identified to differ based on the genotype at this point?

Response:
Yes. According to the reports(10,11), when infected with genotype A strains, which are thought to be highly virulent to both birds and men, the symptoms included non-productive cough, fever, myalgia, generalized skin rash, acral edema, headache, weakness muscle ache, and chills. While when infected with genotype E/B(12), may caused shortness of breath and often no severe clinical symptoms in humans.

12. It appears that there is no evident improvement in the oxygenation index in Figure 3 before the administration of effective antibiotics on D3-7. Do you believe that steroids had a therapeutic effect?

Response:
Before the administration of effective antibiotics on D3-7, the oxygenation index was elevated from 52 mmHg to 145 mmHg, which maybe due to the effective intratracheal suction of yellow watery sputum, intravenous methylprednisolone, and mechanical ventilation with high PEEP. With the dyspnea was relieved, and the sputum became viscous, along with a reduction in the volume of sputum on D5, we supposed that glucocorticoids may have powerful anti-inflammatory activities that mitigate the consequences of pneumonia. However, it is difficult to confirm the corticosteroids' therapy effect, as this study is a case report and not an RCT. But there are many studies on the roles of the corticosteroids on the SCAP. Besides several case reports (5-7) highlight the important roles of corticosteroids in severe C. psittaci-induced ARDS or organizing pneumonia, the recent RCT study(13) publicated in *The New England Journal Of Medicine* indicates that among patients with severe community-acquired pneumonia being treated in the ICU, those who received hydrocortisone had a lower risk of death by day 28 than those who received placebo. Above all, we believe that glucocorticoids had a therapeutic effect.

We revised the content about steroids: "Treatment options to reduce the volume of water in the sputum include corticosteroids, macrolide antibiotics, and other medications (14,15). Given *C. psittaci* causing a more severe inflammatory reaction than other chlamydia species(16), corticosteroids may help reduce lung inflammation caused by *C. psittaci*. Previous studies(5-7) have shown the benefits of corticosteroids in severe *C. psittaci*-induced ARDS or organizing pneumonia. A recent randomized controlled trial (13) also indicates that hydrocortisone improves mortality in SCAP cases in ICU. In this report, we combined methylprednisolone with antibiotics to treat the hyper-inflammatory response caused by *C. psittaci* infection and improve the patient's outcome." **(See Line 13-30 /Page 10)**.

Reviewer B

This case report about Chlamydia psittaci causing severe pneumonia with an initial complaint of massive watery sputum is very interesting and relevant and should be recommended for publication. The paper is an important addition to the literature. However, my one comment would be that the Discussion is a drop long and needs to be focused and re-edited.

Response:
Thanks for the approvement for publication and the helpful advice. Based on your suggestions, we removed repetitive or irrelevant content in Discussion. We have also re-edited and polished the text to make it more focused and clear. As a result, the Discussion section has been reduced about from 1480 words to 860 words.
After our modifications, the discussion section now consists of five paragraphs: Paragraph 1: The differentiation of typical and atypical pneumonia, and as an atypical severe pneumonia caused by C. psittaci may involve in multiple lung lobes and organs. Paragraph 2: We emphasize the advantages and limitation of BALF mNGS for identification of atypical pathogens. Paragraph 3: We discussed the pathogens causing the patient's lung infection and the possibility of intra-pulmonary transmission in this case. Paragraph 4: We discussed that excessive watery sputum in various diseases, including infection disease, and raised that the initial watery sputum may be a characteristic of *C. psittaci* pneumonia in our case. Paragraph 5: We discussed the possible mechanism of watery sputum in *C. psittaci* pneumonia and its treatment options, particularly the corticosteroids. We also made minor correction in Conclusion: We highlight the importance of early detection by mNGS, as well as timely and comprehensive treatment in severe C. psittaci pneumonia.

The revised Discussion and Conclusion is as following:
"**#Discussion**
Cunha (17) stated that differentiating atypical from typical CAP pathogens lies in the presence or absence of extra-pulmonary findings. Typical CAPs caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* are characterized by clinical and laboratory findings limited to the lungs. In our cases, the patient presented with severe pneumonia and concurrent extra-pulmonary injuries. Hence, we initiated short-term treatment (3 days) with azithromycin to cover atypical pathogens, and subsequently added doxycycline (plus azithromycin) upon diagnosis of psittacosis on D7. Fulminant psittacosis can lead to multi-organ dysfunction, as observed in our patient who experienced acute hepatic and kidney injury. Fortunately, targeted antibiotics treatment resulted in their recovery within 1 week. Additionally, Li et al.(18) demonstrated that patients with severe *C. psittaci* pneumonia exhibited abnormal CK and brain natriuretic peptide (BNP) levels, and were more likely to develop dyspnea and progress to respiratory failure with involvement of multiple lung lobes. This finding aligns with our case.

Psittacosis can be diagnosed by real-time polymerase chain reaction (RT-PCR) or serology based on clinical suspicions. Recent studies (19-23) have reported the

successful use of mNGS for diagnosing psittacosis. The mNGS of BALF (3)has the potential to improve pathogen identification in cases of severe pneumonia. The advantages of mNGS in detecting lung disease pathogens include its unbiased comprehensive profiling of microbial genomes, high throughput sequence, rapid results, and high sensitivity, even in patients previously treated with antibiotics. Additionally, BALF meets the requirements for accurate diagnosis of lung infections(24) and is feasible and accurate for patients undergoing mechanical ventilation. However, there are limitations to using mNGS, including (1) limited access to NGS platform due to technical requirement and high cost; (2) the challenge of obtaining qualified samples; (3) the potential detection of both pathogens and the airway microbiome;(4) the need for a specific method for fungi DNA extraction when fungal infection is suspected based on clinical evidence. In our patient, mNGS successfully identified an atypical pathogen that was not detected in sputum/BALF cultures.

It is stated that co-infections are extremely rare, and it is unnecessary to use diagnostic resources to search for co-pathogens in patients with CAP (17). However, in our patient, it was important to distinguish between *C. psittaci* pneumonia and nosocomial infection due to the rapid progression of inflammation in other lobes after the left lower lobe. Despite the absence of other pathogens (including bacteria and fungi) in BALF or sputum cultures, the rapid new onset of exudation in the right lobe and left upper lobe (2 days after ICU admission), as well as the improvement of left lower lobe consolidation after targeted antimicrobial therapy against *C. psittaci*, clinically supported the diagnosis of *C. psittaci* infection. We believe that the worsening condition of the patient was a result of the infection spreading from left lower lobe to the right lung and left upper lobe.

While hyper-concentrated, dehydrated environments are typically associated with muco-obstructive diseases(25-27), some cases have reported excessive watery sputum in conditions such as bronchoalveolar carcinoma (BAC) or adenocarcinoma (14,28-30), infectious diseases (including TB, Aspergillosis) (31-33), poisoning (34,35), and bronchobiliary fistula (36). In the case of *C. psittaci* pneumonia, non-productive cough has often been reported (8,10,37,38). However, the patient in this report had been expectorating for 1 month, with initially watery sputum that subsequently became yellow and thick, this patten was similar to the characteristics of sputum in the ICU where a large volume of golden-yellow watery secretion exudated from the right and left upper lobar/segmental bronchi before becoming viscous. Hence, the initial watery sputum may be a characteristic of *C. psittaci* pneumonia that has not been previously reported.

The cause of watery sputum in *C. psittaci* pneumonia is not clear. Studies (39,40) have shown that the hydration of airway mucus is controlled by the active ion transport and water permeability of airway epithelia. We found that the ionic composition of watery sputum was similar to plasma, suggesting a leakage from plasma. Genotyping of *C. psittaci* is important for understanding its impact in humans (1). There are 10 genotypes (designated A to G, WC, E/B, and M56) of *C. psittaci* (12,16,41-44), with some found in humans (10-12,43). Our hypothesis is that severe epithelial inflammatory damage caused by *C. psittaci* may lead to watery sputum. Different genotypes of *C. psittaci* may cause different clinical symptoms. The production of a massive volume of watery sputum is uncommon in *C. psittaci* pneumonia, but can be serious to cause airway obstruction and severe respiratory distress. When the watery sputum become thick, it can cause lung consolidation, which may explain the consolidation of left lower lobe on the first chest CT on D1 in our patient. Treatment options to reduce the volume of water in the sputum include corticosteroids, macrolide

antibiotics, and other medications (14,15). Given *C. psittaci* causing a more severe inflammatory reaction than other chlamydia species(16), corticosteroids may help reduce lung inflammation caused by *C. psittaci*. Previous studies(5-7) have shown the benefits of corticosteroids in severe *C. psittaci*-induced ARDS or organizing pneumonia. A recent randomized controlled trial (13) also indicates that hydrocortisone improves mortality in SCAP cases in ICU. In this report, we combined methylprednisolone with antibiotics to treat the hyper-inflammatory response caused by *C. psittaci* infection and improve the patient's outcome.

#Conclusions

In summary, in severe *C. psittaci* pneumonia, which often affects multiple lung lobes and organs, the prompt identification of the atypical pathogen through BALF mNGS may facilitate early use of effective antibiotics. The presentation of our patient underscores that the significance of timely and comprehensive treatment for severe cases of *C. psittaci* pneumonia and ARDS in ICU, as it can improve survival rates." **(See Line 28/Page 6~Line 11/Page 11)**

We hope that the major corrections resolve your concerns about the Discussion section.

Reference

1. Balsamo G, Maxted AM, Midla JW, et al. Compendium of Measures to Control Chlamydia psittaci Infection Among Humans (Psittacosis) and Pet Birds (Avian Chlamydiosis), 2017. J Avian Med Surg 2017; 31 (3):262-82.
2. Hogerwerf L, B DEG, Baan B, et al. Chlamydia psittaci (psittacosis) as a cause of community-acquired pneumonia: a systematic review and meta-analysis. Epidemiol Infect 2017; 145 (15):3096-105.
3. Wu X, Li Y, Zhang M, et al. Etiology of Severe Community-Acquired Pneumonia in Adults Based on Metagenomic Next-Generation Sequencing: A Prospective Multicenter Study. Infect Dis Ther 2020; 9 (4):1003-15.
4. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Jama 2016; 315 (8):788-800.
5. Zuzek R, Green M, May S. Severe psittacosis progressing to suspected organizing pneumonia and the role of corticosteroids. Respir Med Case Rep 2021; 34:101486.
6. Price ME, Harrison BD. Restrictive pattern of lung function following psittacosis treated with corticosteroids. Br J Dis Chest 1982; 76 (2):199-201.
7. Hirata M, Noto M, Oda K, et al. [A case of psittacosis presenting as adult respiratory distress syndrome and successfully treated with steroid pulse therapy]. Kokyu To Junkan 1988; 36 (8):893-7.
8. Shi Y, Chen J, Shi X, et al. A case of chlamydia psittaci caused severe pneumonia and meningitis diagnosed by metagenome next-generation sequencing and clinical analysis: a case report and literature review. BMC Infect Dis 2021; 21 (1):621.
9. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama 2012; 307 (23):2526-33.

10. Vande Weygaerde Y, Versteele C, Thijs E, et al. An unusual presentation of a case of human psittacosis. Respir Med Case Rep 2018; 23:138-42.
11. Heddema ER, van Hannen EJ, Duim B, et al. An outbreak of psittacosis due to Chlamydophila psittaci genotype A in a veterinary teaching hospital. J Med Microbiol 2006; 55 (Pt 11):1571-75.
12. Harkinezhad T, Verminnen K, Van Droogenbroeck C, et al. Chlamydophila psittaci genotype E/B transmission from African grey parrots to humans. J Med Microbiol 2007; 56 (Pt 8):1097-100.
13. Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med 2023; 388 (21):1931-41.
14. Rémi C, Rémi J, Bausewein C. Pharmacological Management of Bronchorrhea in Malignant Disease: A Systematic Literature Review. J Pain Symptom Manage 2016; 51 (5):916-25.
15. Suga T, Sugiyama Y, Fujii T, et al. Bronchioloalveolar carcinoma with bronchorrhoea treated with erythromycin. Eur Respir J 1994; 7 (12):2249-51.
16. Knittler MR, Sachse K. Chlamydia psittaci: update on an underestimated zoonotic agent. Pathog Dis 2015; 73 (1):1-15.
17. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect 2006; 12 Suppl 3:12-24.
18. Su S, Su X, Zhou L, et al. Severe Chlamydia psittaci pneumonia: clinical characteristics and risk factors. Ann Palliat Med 2021; 10 (7):8051-60.
19. Yuan Y, Zhang X, Gui C. Detection of Chlamydia psittaci in both blood and bronchoalveolar lavage fluid using metagenomic next-generation sequencing: A case report. Medicine (Baltimore) 2021; 100 (27):e26514.
20. Yang F, Li J, Qi B, et al. Clinical Symptoms and Outcomes of Severe Pneumonia Caused by Chlamydia psittaci in Southwest China. Front Cell Infect Microbiol 2021; 11:727594.
21. Xiao Q, Shen W, Zou Y, et al. Sixteen cases of severe pneumonia caused by Chlamydia psittaci in South China investigated via metagenomic next-generation sequencing. J Med Microbiol 2021; 70 (11).
22. Chen X, Cao K, Wei Y, et al. Metagenomic next-generation sequencing in the diagnosis of severe pneumonias caused by Chlamydia psittaci. Infection 2020; 48 (4):535-42.
23. Zhang H, Zhan D, Chen D, et al. Next-generation sequencing diagnosis of severe pneumonia from fulminant psittacosis with multiple organ failure: a case report and literature review. Ann Transl Med 2020; 8 (6):401.
24. Liu BB, Tian Q, Wang P, et al. Evaluating the diagnostic value of using metagenomic next-generation sequencing on bronchoalveolar lavage fluid and tissue in infectious pathogens located in the peripheral lung field. Ann Palliat Med 2022; 11 (5):1725-35.
25. Hill DB, Button B, Rubinstein M, et al. Physiology and pathophysiology of human airway mucus. Physiol Rev 2022; 102 (4):1757-836.
26. Atanasova KR, Reznikov LR. Strategies for measuring airway mucus and mucins. Respir Res 2019; 20 (1):261.

27. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med 2010; 363 (23):2233-47.
28. Arriero JM, Chiner E, Signes-Costa J, et al. Chronic alveolar consolidation and watery sputum in an elderly woman. Respiration 2000; 67 (6):693-5.
29. Hidaka N, Nagao K. Bronchioloalveolar carcinoma accompanied by severe bronchorrhea. Chest 1996; 110 (1):281-2.
30. Roeder NL, Marshall JD, Britto CJ. A Woman in Her 60s With Lung Adenocarcinoma Presents With Copious Watery Sputum and Respiratory Failure. Chest 2017; 152 (6):e143-e46.
31. Romero-Palacios A, Mera Gallardo O, Jiménez Aguilar P, et al. [Obstructive tracheobronchitis due to Aspergillus fumigatus in an immunocompetent patient]. Rev Iberoam Micol 2019; 36 (1):34-36.
32. Kurahara Y. Massive Bronchorrhea. Intern Med 2021; 60 (13):2155-56.
33. Olum R, Osaigbovo, II, Baluku JB, et al. Mapping of Chronic Pulmonary Aspergillosis in Africa. J Fungi (Basel) 2021; 7 (10).
34. Slavica V, Dubravko B, Milan J. Acute organophosphate poisoning: 17 years of experience of the National Poison Control Center in Serbia. Toxicology 2018; 409:73-79.
35. Weir AGA, Makin S, Breeze J. Nerve agents: emergency preparedness. BMJ Mil Health 2020; 166 (1):42-46.
36. Cheng AC, Chen HW, Chen PJ, et al. Bronchobiliary Fistula. Intern Emerg Med 2021; 16 (4):1093-94.
37. Ojeda Rodriguez JA, Modi P, Brady MF. Psittacosis Pneumonia. StatPearls. Treasure Island (FL): StatPearls Publishing

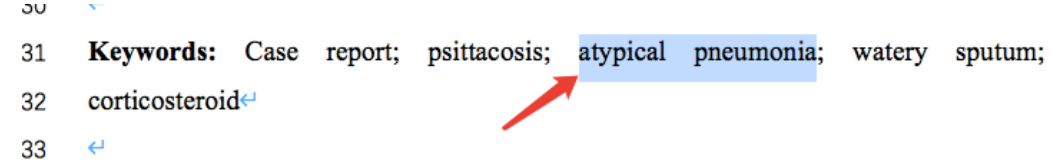
38. Compendium of measures to control Chlamydia psittaci infection among humans (psittacosis) and pet birds (avian chlamydiosis), 2000. Centers for Disease Control and Prevention. MMWR Recomm Rep 2000; 49 (Rr-8):3-17.
39. Jayaraman S, Song Y, Vetrivel L, et al. Noninvasive in vivo fluorescence measurement of airway-surface liquid depth, salt concentration, and pH. J Clin Invest 2001; 107 (3):317-24.
40. Schmidt H, Michel C, Braubach P, et al. Water Permeability Adjusts Resorption in Lung Epithelia to Increased Apical Surface Liquid Volumes. Am J Respir Cell Mol Biol 2017; 56 (3):372-82.
41. Radomski N, Einenkel R, Müller A, et al. Chlamydia-host cell interaction not only from a bird's eye view: some lessons from Chlamydia psittaci. FEBS Lett 2016; 590 (21):3920-40.
42. Geens T, Desplanques A, Van Loock M, et al. Sequencing of the Chlamydophila psittaci ompA gene reveals a new genotype, E/B, and the need for a rapid discriminatory genotyping method. J Clin Microbiol 2005; 43 (5):2456-61.
43. Van Lent S, Piet JR, Beeckman D, et al. Full genome sequences of all nine Chlamydia psittaci genotype reference strains. J Bacteriol 2012; 194 (24):6930-1.
44. Read TD, Joseph SJ, Didelot X, et al. Comparative analysis of Chlamydia psittaci genomes reveals the recent emergence of a pathogenic lineage with a broad host range.

mBio 2013; 4 (2).

Reviewer C

1. **This keyword "atypical pneumonia" is not appeared in abstract or main text. Please check.**

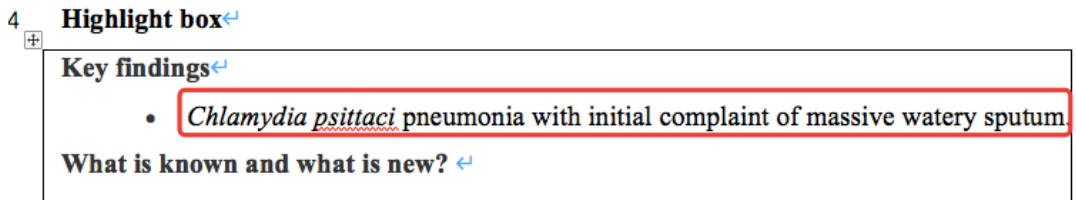
Note: The number of Keywords should be 3-5.



Response: Thank you for the reasonable comment. We have revised the keywords "atypical pneumonia" to be "pneumonia". **(See Line 31/Page 2).**

2. **Highlight Box**

It seems that this sentence is incomplete. You should report the key findings of the study. Please check.

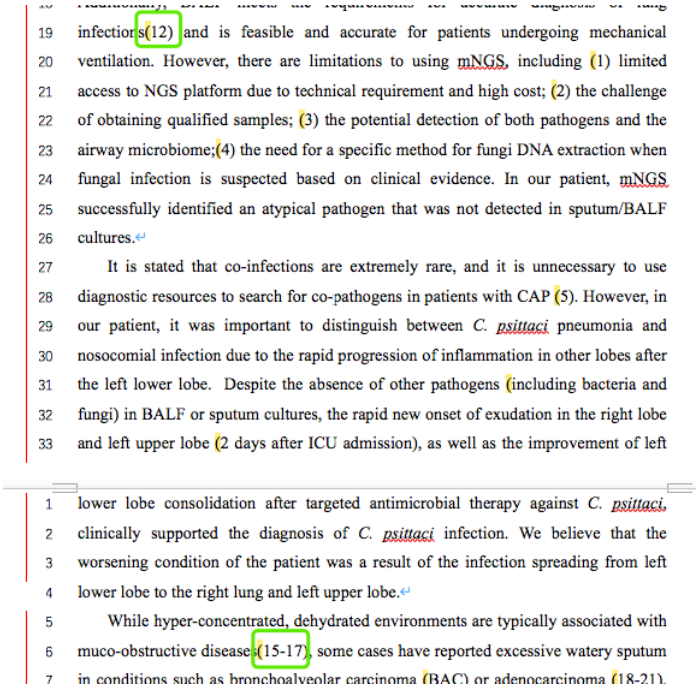


Response:

We have re-edited the key findings to be "It needs intensive treatment in severe *C. psittaci* pneumonia with initial complaint of massive watery sputum." **(See Line 4/Page 3).**

3. **Reference/citation**

a. The citation of ref. 13 and 14 should be cited consecutively between ref. 12 and ref. 15 in the main text. Please check and revise.

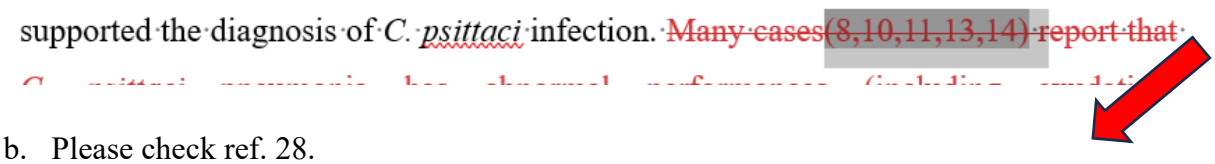

infections(12) and is feasible and accurate for patients undergoing mechanical ventilation. However, there are limitations to using mNGS, including (1) limited access to NGS platform due to technical requirement and high cost; (2) the challenge of obtaining qualified samples; (3) the potential detection of both pathogens and the airway microbiome;(4) the need for a specific method for fungi DNA extraction when fungal infection is suspected based on clinical evidence. In our patient, mNGS successfully identified an atypical pathogen that was not detected in sputum/BALF cultures.

It is stated that co-infections are extremely rare, and it is unnecessary to use diagnostic resources to search for co-pathogens in patients with CAP (5). However, in our patient, it was important to distinguish between *C. psittaci* pneumonia and nosocomial infection due to the rapid progression of inflammation in other lobes after the left lower lobe. Despite the absence of other pathogens (including bacteria and fungi) in BALF or sputum cultures, the rapid new onset of exudation in the right lobe and left upper lobe (2 days after ICU admission), as well as the improvement of left lower lobe consolidation after targeted antimicrobial therapy against *C. psittaci*, clinically supported the diagnosis of *C. psittaci* infection. We believe that the worsening condition of the patient was a result of the infection spreading from left lower lobe to the right lung and left upper lobe.

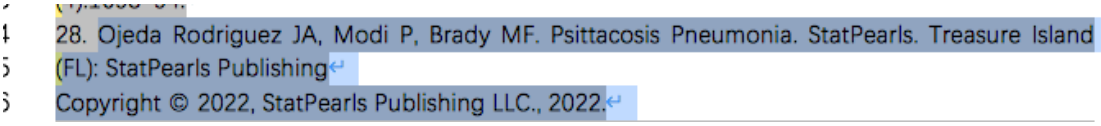
While hyper-concentrated, dehydrated environments are typically associated with muco-obstructive disease(15-17), some cases have reported excessive watery sputum in conditions such as bronchoalveolar carcinoma (BAC) or adenocarcinoma (18-21).

Response:

The citations"(8,10,11,13,14)"is in deleted, and the document is in revision state, Endnote cannot update the citation number, so we will accept the revision of the content "Many cases (8,10,11,13,14)"to update the citation number. The citation and reference have been updated.


supported the diagnosis of *C. psittaci* infection. ~~Many cases(8,10,11,13,14) report that~~

b. Please check ref. 28.


28. Ojeda Rodriguez JA, Modi P, Brady MF. Psittacosis Pneumonia. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2022, StatPearls Publishing LLC., 2022.

Response:

We re-edited ref. 28 as following:

27. Ojeda Rodriguez JA, Modi P, Brady MF. Psittacosis Pneumonia. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC., 2022. **(See Line 24-25/Page 13).**

c. The author's name does not match the citation. Please check and revise.

"Li et al.(6) demonstrated that patients with severe C. psittaci pneumonia exhibited abnormal CK and brain natriuretic peptide (BNP) levels,"

6. Su S, Su X, Zhou L, et al. Severe Chlamydia psittaci pneumonia: clinical characteristics and risk factors. Ann Palliat Med 2021; 10 (7):8051-60.

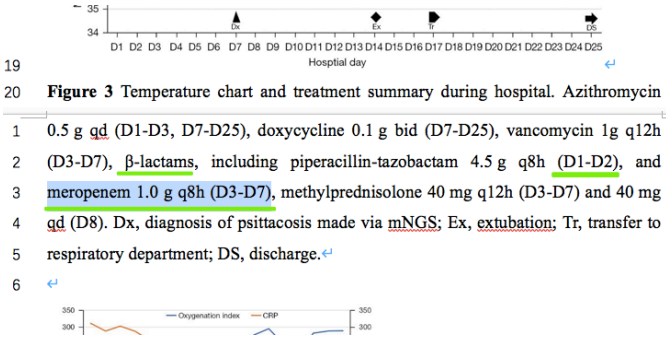
Response:

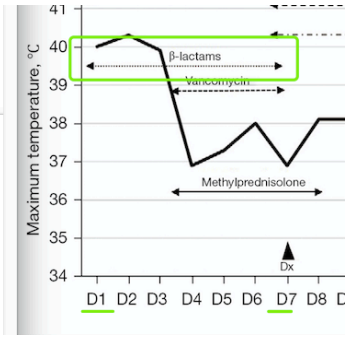
We used the correspondence author "Li". We have cited first author name and revised

it to be "Su et al." **(See Line 14/Page 7)**

4. Figure 3

The "meropenem" was not indicate in figure 3, and "β-lactams" was range from D1-D7". Please confirm if it is correct.



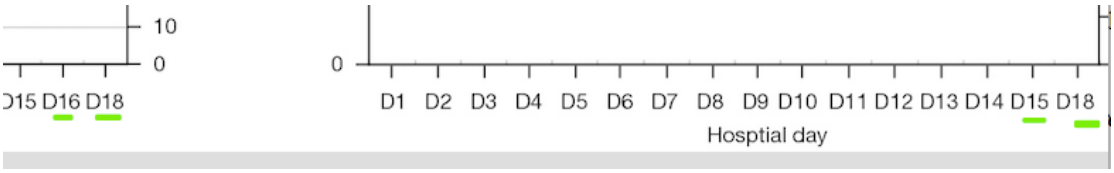


Response:

The figure is correct. β-lactams includes piperacillin-tazobactam and meropenem. To clearly stated it in the legend, we revised it to be "β-lactams (D1-D7) (piperacillin-tazobactam 4.5 g q8h (D1-D2) and meropenem 1.0 g q8h (D3-D7))". **(See Line 2-3/Page 16).**

5. Figure 5

Please check if D18 after D16 should be D17, and D18 after D15 should be D16.



Response:

As the data of blood biochemistry and blood routine are not available on D17 or D16, so the Day can not be continued day by day. And there is no need to modified the figures. We thanks for helpful suggestions, and have made corrections in this revised manuscript. We hope that the changes we have made resolve all your concerns about the article.