Peer Review File

Article information: https://dx.doi.org/10.21037/atm-22-3437

Response to Reviewer A

General comment. In this nicely written review, the authors address one of the most important areas of bronchiectasis with high clinical relevance and many unanswered questions. I have two minor comments, but no others.

Response. Thank you for your positive feedback. We are submitting a revised manuscript to address these concerns. Detailed point-by-point responses to these concerns are provided hereinunder.

Specific Comments

Comment 1 (C1). Page 5 Line 117:

… when clinically stable and (?) during exacerbation…

Response 1 (R1). We appreciate the reviewer's careful review of our manuscript. We have corrected this as follows (page 9, line 158).

"…, sputum was collected from patients when they were clinically stable and during exacerbations."

C2. Page 5 paragraph 2:

Missing Citation (Line 138), probably

Mac Aogáin M, Narayana JK, Tiew PY, Ali NABM, Yong VFL, Jaggi TK, Lim AYH, Keir HR, Dicker AJ, Thng KX, Tsang A, Ivan FX, Poh ME, Oriano M, Aliberti S, Blasi F, Low TB, Ong TH, Oliver B, Giam YH, Tee A, Koh MS, Abisheganaden JA, Tsaneva-Atanasova K, Chalmers JD, Chotirmall SH. Integrative microbiomics in bronchiectasis exacerbations. Nat Med. 2021 Apr;27(4):688-699. doi: 10.1038/s41591-021-01289-7. Epub 2021 Apr 5. PMID: 33820995.

R2. We have added the reference to the revised manuscript (page 10, line 180).

“…between microbes during exacerbations that was partially reversed after antibiotic treatment (28)”

Response to Reviewer B

General comment. This is a narrative review of the definition, aetiology of exacerbations of bronchiectasis, coupled with the management including both medical, mucolytic therapy and physiotherapy management. A review of the literature has been undertaken, highlighting the key findings relevant to diagnosis and management of this clinical state. This is a well written and comprehensive overview, outlining the existing knowledge and relevance to current clinical practice and also highlights recent trials currently being undertaken. Some suggestions or queries to the authors are outlined below:

Response. We appreciate the reviewer’s encouragement and helpful comment. We are submitting a revised manuscript to address these concerns. Detailed point-by-point responses to these concerns are provided hereunder.

Specific Comments

C1. Introduction: Page 3, line 35: it would be useful to clarify if bronchiectasis is a cause or a type of suppurative lung disease. Can the authors provide some comment related to this?

R1. Bronchiectasis is a heterogeneous condition that may be a standalone suppurative pulmonary disease and can sometimes complicate other pulmonary diseases, including asthma and chronic obstructive pulmonary disease. Thus, physicians should recognise this heterogeneous lung condition to appropriately manage patients with bronchiectasis. In this context, we have modified the Introduction section of the revised manuscript (page 5, lines 58–63).

“…bronchiectasis is not rare and contributes to a considerable healthcare burden and increased mortality. Bronchiectasis is a heterogeneous condition that may be a standalone

suppurative pulmonary disease and can sometimes complicate other pulmonary diseases, including asthma and chronic obstructive pulmonary disease (COPD) (6). Thus, physicians should recognise this heterogeneous lung condition to appropriately manage patients with bronchiectasis."

C2. Page 4, the authors have outlined the current knowledge for definitions of exacerbations of bronchiectasis, including reference to the most recent consensus. They also demonstrated the disconnect between patients experiencing worsening of symptoms, which are not reported as an exacerbation. As this is a key point in clinical practice, particularly for those patients whose exacerbation severity is insufficient to warrant hospital admission, can the authors add a summary point at the end of this paragraph (page 4, line 88), regarding what this may mean for clinical practice?

R2. Thank you for pointing this out, which we had not fully acknowledged in our original manuscript. As recommended, we have added a summary at the end of the paragraph (page 8, lines 123–126).

"Considering the detrimental effect of exacerbations in patients with bronchiectasis (19), clinicians should educate their patients to recognise the worsening of symptoms, particularly for those whose exacerbation is insufficiently severe to warrant hospital admission."

C3. The information provided regarding causes of exacerbations is comprehensive and well written.

R3. Thank you for your positive feedback.

C4. Page 8, line 251 the authors comment that prevention of exacerbation is of paramount importance to management. Is there any additional information which could be included here from the patient's perspective?

R4. As recommended, we have included the patients' perspective in the revised manuscript (page 15, lines 301–303).

"Additionally, exacerbations are the second most concerning aspect of bronchiectasis from the

patient's perspective in a European survey (1). Exacerbations are also associated with poorer quality of life (QoL) (2)."

References

1. Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J 2016;48:632-47.
2. Guan WJ, Gao YH, Xu G, et al. Inflammatory Responses, Spirometry, and Quality of Life in Subjects With Bronchiectasis Exacerbations. Respir Care 2015;60:1180-9.

C5. Page 10, line 331 – while there has been demonstration of long term effects of airway clearance therapy, only a single study has covered a duration of 12 months, so it is would be useful to the reader to highlight that a single study has demonstrated these positive findings.

R5. We agree with the reviewer's comments. As recommended, we have highlighted this in the revised manuscript (page 19, lines 389–391).

"An RCT exploring the long-term benefits of airway clearance technique (ACT) in bronchiectasis identified its potential role in the management of acute exacerbation, although only one study covered a duration of 12 months."

C6. Page 10, line 336. While it is true that a second SR including 7 studies of 105 patients concluded the role of ACT was unknown, that was in reflection of the clinical effects. It would be useful if the authors can include this comment, to distinguish the difference between the 2 systematic reviews.

R6. Thank you for pointing this out, which we did not fully acknowledge in our original manuscript. We have added a comment regarding the systematic review to the revised manuscript (pages 19–20, lines 395–398).

"Another systematic review including seven studies with 105 patients concluded that the role of ACT in acute exacerbation of bronchiectasis is unknown in relation to its clinical effects;

however, in view of the chronic nature of bronchiectasis, additional data may be needed to accurately establish its effect."

C7. Figure 2 – there is a considerable amount of text included in the legend of Figure 2. It would be helpful for the authors to try to simplify the information outlined if possible.

R7. We agree with the reviewer's comments. Most of the details have been explained in the manuscript and we have retained the title of Figure 2 in the revised manuscript (page 39, line 781):

*"**Figure 2.** Management targeting treatable traits to prevent bronchiectasis exacerbations"*

C8. Overall, this is a well written review which includes narratives of all relevant key concepts in understanding exacerbations and management.

R8. Thank you for your positive feedback.