Reviewer’s report

Title: Clinical Implications and Characterization of Group A Streptococcus Infections in Adults with Cystic Fibrosis

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Reviewer: Robert Whiley

Reviewer's report:

The high degree of complexity of the CF lung flora is now well recognised although the clinical significance of most taxa present is not yet understood. These authors have focussed their attention on Streptococcus pyogenes (the group A Streptococcus - GAS), a significant pathogen and potential cause of community acquired pneumonia, in order to determine the incidence, natural history and clinical impact of GAS infections in CF and to characterize the isolates both phenotypically and genotypically. The authors have at their disposal the considerable resource of the Southern Alberta Adult CF Clinic Biobank which allows retrospective evaluation of longitudinal microbiological and clinical data on adult CF patients between 1978 and 2013 and to further examine GAS isolates that had been obtained.

This study determines that GAS infection in CF lower airways is relatively rare (15/318 individuals = 4.7%) with the majority (13/15) having single isolations (transient GAS infection) that do not impact lung function, long term disease status nor disease progress. Despite the low numbers of GAS positive patients the authors were able to conclude that identification of GAS in CF sputa correlated with pulmonary exacerbation (PEx), especially when the GAS were numerically dominant. The latter finding was highlighted as potentially informing treatment strategies taking GAS into account in order to reduce the risk of PEx. No association between expression of specific virulence factors and PEx were determined.

Although many of the findings here are negative I am of the opinion that this paper contributes to the increasing understanding of the complex variations and dynamics inherent to CF lung infections. Members of this group have previously published seminal papers that focus on the complexity of the polymicrobial nature of the infected CF lung. In contrast this paper does not (and presumably cannot) include much in the way of microbiological context; on page 14 line 9 they state that risk of PEx was not affected by the presence of specific chronic cultured microorganisms - can this be expanded to describe exactly what is meant here? I would like to see some qualitative comment at least on the possibility (probability) of other members of the flora impinging on these data.
On page 15 line 44 the authors state that there was no association between production of particular virulence factors and the occurrence of PEx at isolation (data not shown) - in the abstract they state that GAS isolates produced variable levels of protease...etc; the data are shown in the Table as 'yes' or 'No' for expression - how is this 'variable levels' and was there any variation in the zone sizes between isolates? I think this should be made clearer.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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I am able to assess the statistics

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