Reviewer's report

Title: Moraxella catarrhalis acquisition, airway inflammation and protease-antiprotease balance in chronic obstructive pulmonary disease

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Reviewer: Hortense Slevogt

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' Moraxella catarrhalis acquisition, airway inflammation and protease-antiprotease balance in chronic obstructive pulmonary disease'

Ganapathi I Parameswaran, Catherine T Wrona, Timothy F Murphy and Sanjay Sethi BMC Infectious Diseases Research article

Overall an interesting study focussing on the influence of Moraxella catarrhalis colonization and infection for the protease-antiprotease balance in patients with COPD. The manuscript is well written and in general, data are sound and the manuscript adhere to the relevant standards for reporting and data deposition.

However. The study has some weaknesses mentioned in the following:

Major compulsory revisions:

1.) Page 6 Line 5: The authors should specify: what criteria determined “baseline” and what criteria does imply the increase of respiratory symptoms from baseline (eg. Dypnea to what extent, cough etc.) Was a score system used for the severity of signs and symptoms demonstrated by the patients?

2.) Fig 2: Is the increase in TNF a significant? The authors should include this in the figure and the figure legend (p19)

3.) Fig.3 and 4 and result part of these figures on page 10:

In Figure 3 the authors are demonstrating that the neutrophil elastase (NE) is increased in COPD patients with an exacerbation compared to "colonized" patients.

However, as shown in Fig. 4 there is no difference in the SLPI between these groups.

This should more precisely described in the result part (page 10).

Moreover on page 10 line 8 the authors are stating: “Colonisation, as well as exacerbation was associated with reciprocal changes in NE and SLP”. This sentence is misleading.

It would be clearer to say that as shown in Table 2 M. catarrhalis acquisition was
leading to an inverse relationship between NE and SLPI triggered by an increase of NE and a decrease of SLPI.

However the increase of NE was dependent on whether patients were “colonized” or had an exacerbation (fig 3). Regarding SLPI there was no difference in the decrease of SLPI in colonized patients when compared to exacerbated patients (Fig 4). Thus, the decrease in SLPI shown in Tabl. 2 seemed to be dependent on the acquisition of M. catarrhalis and seemed to be independent from colonization vs exacerbation as shown in fig 4. The authors should more precisely describe and discuss these results.

In the discussion part the authors should add an assessment of how M. catarrhalis-induced inflammation might be or is related to the protease-antiprotease imbalance since they show in Tabl. 2, in Fig 1-2 as well as in Fig 3 that the M. catarrhalis-related increase of NE can be related to the concomitant increase of M. catarrhalis-induced IL-8 and TNF.

4.) (Fig 5) To distinguish between the protease:antiprotease balance in patients without vs with M. catarhalis infection and colonized with or having an exacerbation due to M. catarrhalis the linear regression for the relationship between SLPI and NE should also be differentially provided for

# Samples from patients in the preacquisition state alone ,
# The acquisition state and with the additional differentiation between a.) with M. catarrhalis colonization and b.) exacerbation.

Furthermore a correlation coefficient for each of the correlations should be provided

Minor compulsory revisions:

1.) Page 5: In the introduction it is important to specifically introduce active neutrophil elastase (NE) and secretory leukocyte protease inhibitor (SLPI) for there potential role in the course of COPD alone as well as for emphysema development.

The authors should introduce to what extent measurement of the SLPI and NE is representative for assessing the protease-antiprotease balance in the airways.

2) In figure 2 and 4 a p value should be provided demonstrating that data are not significant

3.) The data presented in Fig 3 and 4 demonstrate that M. catarrhalis exacerbation is associated with an increase in NE when compared to “colonized” patients, whereas no difference is seen between those two groups for the decline in SLPI.

Activation of neutrophils with IL-8 and other chemoattractants has previously been shown to result in an increased expression of NE (Nadel, Chest 2000).

Fig 1-3: Thus, it would also be interesting to correlate the NE data with the IL-8 and TNFα in colonized vs exacerbated patients by linear regression to point out this relationship. The authors should state if the increase in NE seems to be
associated with M. catarrhalis-induced inflammation since they can be linked with the increase in IL-8 (and TNF α, if significant)

In addition the authors should add to the discussion part a statement whether they interpretate the data as M. catarrhalis-specific effect or as an unspecific effect due to the M.catarrhalis-induced inflammation

4) Page 5 line 14 as well as later on in the manuscript: acquisition of a new strain of M. catarrhalis implicates a differentiation of different M. catarrhalis strains. In this work only the presence of M. catarrhalis is documented. Therefore it would be more concise to just say “acquisition of M. catarrhalis”.

5.) Page 11 line 11: Previous studies… This statement should be accompanied by appropriate citations.

Discretionary Revisions

2.) Page 11 and 12: Downregulation of SLPI was also described to e.g. be due to overexpression of TGF beta (Jaumann et al. Eur Res J 2000; 15: 1052-1057). The authors did not mention the possibility of downregulation in their discussion part (page 11).

Are there other mechanisms/bacteria known to downregulate SLPI?

If so its seems possible and therefore might be an interesting point to discuss that M. catarrhalis could also be directly involved in downregulation of SLPI since it is not related to the extent of airway inflammation (colonization vs exacerbation)

4.) Page 12 Line 14: A further limitation is and could be stated is that only one protease and antiprotease was investigated despite the fact that more proteases and antiproteases are involved in the imbalance hypothesis.

Minor comments:

The authors should use the abbreviation M. catarrhalis instead of M catarrhalis
Page 4 line 10: in the lower airways
Page 4 line 20: bacteria-associated
Page 12: line 8: NF-#B

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'