Author's response to reviews

Title: Cardiopulmonary involvement in Puumala hantavirus infection

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Author's response to reviews: see over
To the Editor, 19 September, 2013

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Dear Sir/Madame,

Thank you for handling our manuscript “Cardiopulmonary involvement in Puumala hantavirus infection”. We would like to thank reviewers for their valuable comments and suggestions. As reviewer 1 and 4 had no direct questions, we focus on answering comments from reviewer 2 and 3. See our response point-by-point below.

Yours sincerely,

Johan Rasmuson, MD

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Reviewer 2 (PW):

Q 1: The authors report symptoms, blood biomarkers, lung function tests, echocardiography and computed tomography in the manuscript. A lot of information needed to appreciate the results is missing. Assessment of symptoms is not described at all. In a prospective study, one would expect standardised questionnaires to be used. Subjects are grouped as having or not having “impaired condition” at follow-up. What does this mean? Subjects are also grouped according to needing or not needing oxygen therapy. We are not told what indications were used for oxygen therapy. Oxygen saturation on breathing air is reported to be 92-96 %, figures hardly making oxygen therapy necessary. “Respiratory tract symptoms” are reported to occur in 67 % of the subjects. What were the specific symptoms and how were they assessed? Lung function is said to have been measured according to “clinical praxis”. What does that mean? Were current guidelines followed or not? Similarly, blood biomarkers are said to have been measured according to “hospital routine”. What does this mean?

Response: According to the ethical approval, patients included in the study should be treated according to standard clinical practise. During hospitalisation, patient-care including clinical decisions regarding medical care was provided by doctors not involved in the study. Study doctors working at the Department of Infectious Diseases (Rasmuson and Ahlm) enrolled patients to the study and saw them at the 3-month follow-up. A simple form of questionnaire, however non-validated, was given to the patients during hospitalisation and at follow-up. Only 63% of the patients returned the questionnaires. Due to the high non-response, we instead chose to rely on data regarding symptoms from the patients’ medical charts. The specific respiratory symptoms were dyspnoea or dry cough, mentioned in the text on page 10 and in Table 1. At clinical follow-up, we asked the patients if he or she felt fully recovered, and if not, if there were any residual symptoms. Half of the studied patients reported to not feel fully recovered and generally described tiredness or fatigue, something we chose to call impaired general condition. We have clarified this by expanding the subject method section (page 6) including the sentence: ‘Clinical data was retrieved from the patients’ medical charts’ and by explaining the term impaired general condition by adding ‘described as tiredness or fatigue’

Need of oxygen treatment was judged by the clinician responsible for the patient care, generally indicated by a combination of low oxygenation and symptoms (tachypnoea and/or dyspnoea). One-fourth of the patients had oxygen saturations at or below 92% as oxygen saturation is given as 25th-75th percentile. At our clinic it is common practise to provide oxygen treatment if saturation is below 94%, especially in combination with dyspnoea, giving an explanation why one-third was deemed to need oxygen therapy.

Lung function was performed at the Department of Clinical Physiology at Umeå University hospital, according to clinical routine. Current ATS/ERS guidelines (Miller 2005 and
MacIntyre 2005) were followed. We have revised the method section regarding measurements of lung function to describe this more clearly and included references to these guidelines.

Cardiac biomarkers and routine laboratory analyses were all performed by an accredited laboratory at the Department of Clinical Chemistry at Umeå University hospital. In cardiac biomarkers and routine laboratory analyses method section (page 9), we have changed the sentence ‘N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were analysed in plasma according to hospital routine’ to ‘...analysed in plasma according to clinical routine at the accredited laboratory at the Department of Clinical Chemistry at Umeå University hospital’.

Q 2: The authors draw very far-reaching conclusions from their echocardiography studies. Pulmonary vascular resistance is estimated by echocardiographic estimation of pulmonary arterial pressure and cardiac output together with a mere assumption of a left atrial pressure of 10 mmHg. I am not sure this assumption is necessarily valid in subjects with abnormal left ventricular function and pulmonary oedema detected by computed tomography. Considering the uncertainties involved, I find the conclusions overstated.

Response: Whilst we have not been able to verify (by invasive monitoring) whether the assumption of left atrial pressure of 10 mmHg is valid in this patient cohort, we believe that the resulting estimations of increased pulmonary vascular resistance is valid given that other indirect measures also indicate increased pulmonary vascular resistance (increased systolic pulmonary pressure, shortened pulmonary arterial acceleration time and borderline significantly longer IVRT for the right ventricle). Additionally, the normal left atrial size strongly indicates normal pulmonary capillary wedge pressure.

In the discussion section (page 18) of the previously submitted manuscript we have included a paragraph regarding the limitation of using echocardiographic estimations versus more exact invasive PA-catheter measurements.

Data from previous studies (Hallin 1996) supports that increased pulmonary vascular resistance is present in patients with hantavirus infection. American hantavirus-infected patients commonly suffer from cardiorespiratory failure including pulmonary oedema. PA-catheter measurements have displayed normal pulmonary capillary wedge pressures, indicative of non-cardiogenic pulmonary oedema, while elevated pulmonary pressure and increased pulmonary vascular resistance have been reported in those patients (see reference Duchin 1994 and Hallin 1996). These results are similar in nature, albeit of more severe magnitude, to what we report from non-invasive echocardiography estimates from PUUV-infected patients.
Q 3: The discussion is far too long and very speculative.

Response: We believe that the discussion is adequate in length considering that the study is relatively comprehensive and include data from echocardiography, lung function, computed tomography, biomarkers as well as clinical characteristics of the patients that requires to be discussed. Furthermore, the discussion includes a section regarding limitations of the study, please see response to Q2.

Q 4: Lung function variables are not abbreviated according to current standards. Please supply a reference to the predicted values.

Response: Thank you for noticing this. We realise that forced vital capacity should actually be vital capacity and DLCO should be ‘diffusing capacity of the lung for carbon monoxide’. Also, in Table 3 we have used the abbreviation FEV1% instead of writing FEV1/VC.

Changes made:
‘FVC’ has been changed to ‘VC’ and ‘FEV1/FVC’ to ‘FEV1/VC’ in the lung function method section on page 7 as well as in Table 3.
DLCO has been written out as ‘diffusing capacity of the lung for carbon monoxide’ instead of ‘diffusion capacity for carbon monoxide’ in lung function method section and Table 3.
Consequently, diffusion capacity has been changed to diffusing capacity throughout the manuscript.
In Table 3, ‘FEV1%’ has been changed to ‘FEV1/VC’.
References to predicted values (European Community for Steel and Coal) have been added to the lung function method section.

Reviewer 3 (DS)

Q1: In the methods section there is a statement that 21 patients were considered healthy. How can a patient who has been admitted to a hospital for an acute infection be considered healthy? I think what the authors are suggesting is that these 21 patients had no underlying health conditions. This should be clarified.

Response: We agree and have changed the sentence ‘Twenty-one patients were considered healthy’ to ‘Twenty-one patients were previously healthy’.
Q2: It seems that the one patient with hypertensive heart failure and chronic obstructive pulmonary disease was excluded from the many of the vital tests which this study was designed to utilize. To me, this patient should be screened out and lower the overall study size to 26.

Response: We have discussed this issue and decided to keep this patient in the study cohort. The reason for this is that even though the patient could not be compared to the healthy population it would be possible to compare data from acute phase and follow-up since the patients then acts as their own control. Both echocardiographic and blood biomarker investigations had been performed during hospitalisation and at follow-up and as we saw no statistical or methodological problems in using the data from this patient, we judged it unethical to not include the collected data in the analyses.

Q3: You should consider commenting on why only 26 patients received follow up evaluation. What happened to the other patient?

Response: One patient did not want to participate in follow-up investigations but allowed us to use already collected data. We have added the sentence ‘One patient declined follow-up investigation’ to the subject method section on page 6.

Q4: When reporting the results of lung function and high-resolution computed tomography, it would be helpful to indicate the number of patients evaluated by each test (similar to how the ECG data is presented). Although this information is provided in the table, it would be helpful to have it in the text as well.

Response: We previously decided to omit this information from the text to keep the manuscript shorter and easier to read, as it is presented in the tables. However, we are willing to include this information also in the text if preferred by the Journal Editorial Office.