Author’s response to reviews

Title: Assessment of the association between increasing membrane pore size and endotoxin permeability using a novel experimental dialysis simulation set-up

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Author’s response to reviews:

Dear Editor, dear professor Santoro

Please find enclosed the second revised version of our manuscript (BNEP-D-17-00385R1) entitled: “Assessment of the association between increasing membrane pore size and endotoxin permeability using a novel experimental dialysis simulation set-up” by Eva Schepers, Griet Glorieux, Sunny Eloot, Michael Hulko, Adriana Boschetti-de-Fierro, Werner Beck, Bernd Krause and Wim Van Biesen, that we submitted on-line for publication in BMC Nephrology.

This paper was adjusted and declarations were added as suggested.

In attach you find a point-to-point answer.

We hope the manuscript can be accepted.
1. We note that your abstract was published in Nephrology Dialysis Transplantation as part of the 53th ERA-EDTA Congress. Please can you clarify whether you have permission to publish your abstract under Open Access and if not your abstract will need to be reformulated.

Please also provide a statement in the Declarations stating that your abstract has been presented at a conference.

The abstract included in the manuscript is already a reformulated version compared to the abstract published in NDT. However, as suggested, we added a sentence to declare this in the “Acknowledgements” section:

“Data presented here were partially published in abstract format in Nephrology Dialysis Transplantation as part of the 53th ERA-EDTA Congress Supplement (Nephrol Dial Tranpl 2017; 32(suppl 3):iii625–iii626)”

2. The Availability of data and materials section refers to the raw data used in your study and presenting tables and figures is not sufficient to state that all data is contained within the manuscript and additional files. Please only use this statement if you have indeed provided all raw data on which your study is based. We strongly encourage all authors to share their raw data, either by providing it in a supplementary file or depositing it in a public repository and providing the details on how to access it in this section. If you do not wish to share your data, please clearly state this in this section along with a justification. Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):
• The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS] • The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
• All data generated or analysed during this study are included in this published article [and its supplementary information files].
• The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
• Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
• The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
• Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

Please note that if you include your raw data as a supplementary file you will need to provide, after the References, a section titled “Additional files” where you list the following information about each of your supplementary files: * File name (e.g. Additional file 1), * Title of data, * Description of data. All additional files will also need to have been cited in the main manuscript.

In the “Declarations” section, there is already a statement on “Availability of data and materials” claiming all data generated or analysed during this study are included in this published article. This mainly refers to the data presented in Table 3. The raw data of the other tables are available upon request. Therefore the statement was changed accordingly:

“Part of the data generated and/or analysed during this study are included in this publication. The other datasets are available from the corresponding author upon request.”

3. Thank you for providing a competing interests statement. We note that Baxter also provided some of the materials used in this study, please declare this in the Competing interests section. If
any of the authors received fees, funding, salary from or hold stocks/shares in any other organization that provided materials in this study this should also be declared in this section.

Please note that financial competing interests include (but are not limited to):

- Receiving reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of the manuscript, either now or in the future.
- Holding stocks or shares in an organization that may in any way gain or lose financially from the publication of the manuscript, either now or in the future.
- Holding, or currently applying for, patents relating to the content of the manuscript.
- Receiving reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript.

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Baxter provided the dialysis membranes, therefore the following sentence was added to the “Competing interests and funding” section:

“The dialysis membranes (Polyflux® 17L, Revaclear 400, Theranova 400 and Theralite™ 2100) were provided by Baxter, Hechingen, Germany.”

4. We note that you have not included a ‘Funding’ section in the Declarations. All sources of funding for the research reported should be declared in this section.

Please also clarify whether the funding body played a role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript and if so please clearly state what role the funding body played in this section.
We put “Funding” in the same section of the competing interest, as we believe there is an overlap here. The contributions of the funding body Baxter are stated for each co-author employed by the company separately in the “Authors’ contribution” section in detail.

5. Please upload all figures as separate figure files and remove them from the main manuscript. Please note, however, that all figure titles/legends should be placed at the end of the main manuscript, after the References, and not within any of the figure files.

A separate file is uploaded for Figure 1.

6. Thank you for providing your point-by-point response to the reviewers’ comments. We are satisfied with your responses overall however, we note that you have not addressed points 3 and 4 of reviewer 2 in your manuscript. Please can you either address these points in your manuscript or provide a justification as to why these do not need to be included in the manuscript.

For point 3 of reviewer 2 the following paragraph was added to the discussion section:

“It was chosen to give the individual data from all experiments as this is the most exact way to present the data and to give the reader full visibility of the data. The PVP solutions in many cases had a measured LAL activity below the LOD and the individual numbers give a better impression of the limited degree of contamination in case values were above LOD in the blood compartment. It might be speculated that increasing the number of experimental repeats could lead to statistical significance in the differences between the membranes, however this will not change the clinical relevance of the low degree of contamination.

For the question (point 4) on the high standard deviations of the endotoxin load, some additions were made in the manuscript accordingly:

“Although dialysate-endotoxin concentration varied between 3.2 and 33.7 EU/ml in the individual experiments, mainly due to the difficulty of filtrate preparation and complexity of the experimental set-up, the mean exposure to endotoxins through the contaminated dialysate was above the intended minimum 4 EU/ml for each of the different experiments and did not differ
between the different membranes. No correlation was found between endotoxin load and permeability.”

7. Please upload your revised manuscript as a clean copy and remove the manuscript with tracked changes from the additional files as it is no longer required at this stage of the editorial process.

This is done accordingly