

**Reply to Peer Review Report RE ESPS Manuscript No 26015 : The Role of
Inflammation and Infection in the Pathogenesis of Human Acute Liver Failure:
Clinical Implications for Monitoring and Therapy**

Dear Reviewers and Editor,

Thank you for your comments regarding our above manuscript, and for giving us the opportunity to resubmit the manuscript in response to the comments. Please find attached two versions of the updated manuscript; one with tracked changes and one with the changes accepted. Below is a point by point response to the reviewers' comments.

1. The only area I would recommend for revision is Table 1, which is rather selective and does not effectively summarise the wealth of studies on cellular immune dysfunction in ALF. This should be expanded to be more comprehensive or could legitimately be omitted due to this being an overview for a more general readership.

Thank you for this comment. As suggested, we have expanded Table 1 to be more comprehensive.

2. TLR-9 and neutrophilic involvement is poorly explained and needs to be expanded.

Thank you. The aim of this review was to outline the clinical aspects of inflammation and infection in ALF, rather than provide detailed reviews of basic science and pathophysiological mechanisms. We acknowledge this in the manuscript and provide references for relevant basic science papers for the interested reader.

3. A figure with drawing of the NLRP3 inflammasome cascade should be added.

A figure has been added as suggested.

4. The authors should address the influence of calcium flux, mtROS, mitochondrial membrane potential dysregulation, autophagic dysfunction and TXNIP with more clarity.

Thank you for raising this issue. When writing this review, we set out to write a very clinical paper, detailing a practical approach to the role of inflammation and infection in ALF. We had made a conscious effort to exclude human basic science and animal work, and had explained this in the main text of the manuscript. As such, we have not extensively discussed the factors described above, but acknowledged their importance in the development of ALF, and have provided references to direct the interested reader to the relevant literature.

5. Please explain in more detail the concept of the so called inflammasome- The article would strongly benefit from a figure explaining the immunological processes including immunological mediators in ALF.

Thank for this comment, and we agree that the article benefits from the above.

In response to this comment, we have added a section in the text explaining the activation of and formation of the inflammasome. In addition, as per the other reviewers' comment, we have added a figure detailing inflammasome activation.

6. Spelling errors

Our apologies for the spelling errors and error in author names- these have all now been amended.

Once again, we thank you for the opportunity to resubmit our revised manuscript, and we look forward to your hopeful acceptance. Should you wish any further amendments or clarifications, then please do not hesitate to get in touch.

With kind regards,

Dr Mhairi Donnelly and co-authors