Reviewer's report

Title: Common TNF-alpha, IL-1beta, PAI-1, uPA, CD14 and TLR4 polymorphisms are not associated with disease severity or outcome from Gram negative sepsis

Version: 1 Date: 18 May 2007

Reviewer: Charles J. Hinds

Reviewer's report:

General
Many studies have investigated the influence of polymorphisms of genes involved in innate immunity and coagulation on disease severity and outcome in sepsis. To date results have often been conflicting, failure to replicate positive findings has been common and many studies (often unpublished) have been negative. Imprecise definition of phenotype and small sample sizes have contributed to these inconsistent findings. The study described in this manuscript is also underpowered but the phenotype (gram negative sepsis) is well defined, consecutive patients were recruited and rather than studying just one candidate the authors have investigated the role of several genes. Although the findings are negative the importance of avoiding publication bias is widely acknowledged.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. My main concern is that the study is underpowered both for disease severity (given that the subgroups with severe sepsis and septic shock are very small) and for outcome (given that mortality is only 19% and that the TLR4 SNP is extremely rare). Thus for example the doubling of mortality in those with the TNF -308 homozygous SNP and the higher mortality in the TLR4 SNP heterozygotes do not reach significance, perhaps because of the small numbers. The authors must justify and discuss analysing such a small patient population.

2. The authors must explain more clearly the basis on which they selected the genes and SNPs to be included in their analysis. Why did they select only one SNP for each gene?

3. The authors should include a description of the procedures they used for the quality control of genotyping.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Table 2, column 4 should be headed "septic shock".

2. The authors might like to cite another negative TNF/LTA SNP association study (Gordon et al. Genes and Immunity 2004).

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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 I have no competing interests