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**Response to Schöneweck et al.:
Common genomic variation
in the *FER* gene: useful
to stratify patients with sepsis
due to pneumonia?**

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Dear Editor,

We were interested to read the letter from Schöneweck et al. [1] in which they report that they were unable to replicate the primary finding of our recently published genome-wide association study (GWAS) [2]. In that study, we describe the association between a common genetic variant in the *FER* gene and a reduced risk of death in patients admitted to intensive care units with pneumonia. As Schöneweck et al. [1] state in their letter, we observed the association only in patients with sepsis due to pneumonia, not in the overall sepsis cohort; consequently, failure to replicate in their mixed population of patients is perhaps unsurprising. When limited to patients with severe sepsis due to pneumonia, their sample size is extremely small ($N = 298$ with 65

deaths, compared to 2091 patients with 465 deaths in our total pneumonia cohort). This translates into only 49 % statistical power to detect an association at a significance level of 0.05 with our observed odds ratio of 0.56. The lack of statistical power is further reflected in their very wide 95 % confidence interval (0.65–1.9), which overlaps with ours (0.45–0.69). We caution against over-interpretation of the findings of underpowered studies, particularly when presented to refute the results of significantly larger and adequately powered cohorts.

Although our study was based on a meta-analysis of four independent cohorts, we agree with the authors that further replication in adequately powered, homogeneous, comparable patient groups and larger meta-analyses are required to confirm our findings. We also agree that demonstrating clinical utility of GWAS findings is challenging and that perhaps such associations are more useful in understanding biological mechanisms and identifying potential novel targets for therapy or prevention than for risk stratification of individual patients [3]. Nevertheless, if our findings are confirmed by others, we would contend that targeting the high risk homozygous group (mortality of about 25 %; 10 % higher than in heterozygotes and 15 % higher than in those homozygous for the minor allele) with therapies designed to modify the function of *FER* or the associated

molecular pathways might prove to be an effective strategy.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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