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LETTER

The effect of vasopressin and hydrocortisone on cytokine trajectories

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Dear Editor,

Life-threatening septic shock is caused by dysregulated host response to infection [1]. A failure of regulatory pathways leads to systemic and overwhelming pro-inflammatory cytokine release [2]. Higher admission cytokine levels in sepsis are associated with higher mortality rates [3]. Dampening the inflammatory cytokine response with pharmacological agents may help prevent organ damage and promote recovery. Little is known about the impact of routinely used drugs on cytokines in intensive care.

In the VANISH Trial [4] patients with septic shock were randomised to receive either noradrenaline or vasopressin and either hydrocortisone or placebo.

Plasma samples were collected at up to four timepoints from randomisation. In this post-hoc analysis, trajectories of 13 cytokines were compared over the first 72 h of treatment between treatment groups. Trajectories were compared using quadratic mixed models of natural log transformed cytokine concentrations [5] with a random intercept term based on patient identifier. To identify which drugs or outcomes were associated with different cytokine trajectories a mixed model with an interaction term between the drug/outcome and time was compared with a mixed model without an interaction term using analysis of variance (ANOVA) for each cytokine. Detailed methodology is in the online supplement.

Patients who died by day-28 had features of more severe disease and higher baseline monocyte chemoattractant protein-1 (MCP1) and interleukin- 8 (IL-8) than survivors but there were no differences in baseline cytokines or clinical features between drug allocations (supplementary tables 1–4). Analysis of 501 samples from 196 patients found no difference in cytokine trajectories between survivors and non-survivors or between patients randomised to vasopressin ($n=100$) compared to noradrenaline ($n=95$) (supplementary Fig. 2 and 3).

Hydrocortisone ($n=69$) was associated with a faster decline in MCP1, interleukin-6 (IL-6) and interferon gamma-induced protein 10 (IP-10) compared to placebo ($n=66$), with no differences in the other cytokines (Fig. 1, supplementary Fig. 4). Patients who received hydrocortisone whose rate of decline of the natural log of the IL-6 or MCP-1 concentration was in the slowest 50% over the first 24 h had a higher mortality at day 28 compared to those in the fastest 50% (IL-6, odds ratio (OR) 7.65, 95% confidence interval (CI) 1.37–42.71, $n=38$, MCP1 OR 7.65, 95% CI 1.37–42.71, $n=38$). This was not the case for IP-10. For each unit increase in the slope of the natural log of the IL6 concentration (ln(IL-6)) over the first 24 h there was a 1.79 (95% CI 1.01–3.17) increased risk of death, such a relationship was not seen for MCP1 or IP-10. No association was seen between rate of decline of cytokine concentrations and outcome in the placebo group (supplementary results).

Exploratory analysis of the effect the four combinations of drugs (noradrenaline and vasopressin, each with and without hydrocortisone) on cytokine trajectories confirmed a differential effect for MCP-1, IL-6, and

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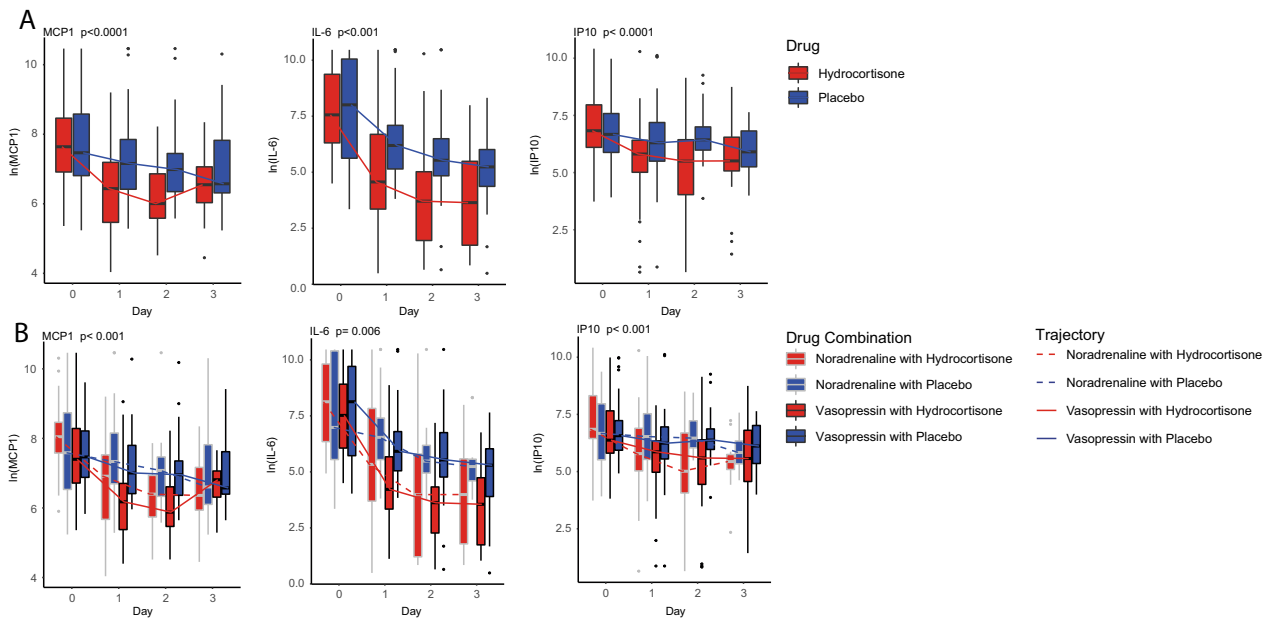

Fig. 1 Comparison of cytokine trajectories for patients receiving **A** hydrocortisone (red) or placebo (blue) and **B** combinations of noradrenaline (grey outline, dashed line) or vasopressin (black outline, solid line) with either hydrocortisone (red) or placebo (blue) for monocyte chemoattractant protein-1 (MCP-1), Interleukin-6 (IL-6) and interferon gamma-induced protein-10 (IP10). Data are displayed as box plots of the natural log of the cytokine concentrations (pg/ml) for each day after enrolment into the study with median values connected by a coloured line to illustrate trajectory. *P* values are those from comparing models with and without an interaction term between day and drug/drug combination after correction for multiple comparisons using the Benjamini–Hochberg procedure. These results were unchanged in the sensitivity analyses performed

IP-10 (Fig. 1, supplementary Fig. 5). Pairwise comparisons showed that for MCP-1 and IP-10 the addition of hydrocortisone to either vasopressin or noradrenaline drove this difference. Hydrocortisone only led to significantly greater reduction in IL-6 compared to placebo when added to vasopressin (supplementary table 6), however, this is possibly a result of the limited statistical power of this analysis.

In summary, this work confirmed the anti-cytokine effect of hydrocortisone in septic shock, in particular on IL-6, MCP1 and IP-10, and indicates that the response of IL-6 and MCP1 could be used to identify treatment responders.

Supplementary Information

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Author contributions

DBA had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the final decision to submit for publication. Study concept and design: DBA, ACG, TM, CC. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: CC, TM, DBA. Critical revision of the manuscript for important intellectual content: all authors. Statistical Analysis: CC, DBA. Obtained funding: ACG. Administrative, technical or material support: DBA, JKW, TM, CB, FA-B, ACG.

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Declarations

Conflicts of interest
ACG reports that he has consulted for GSK and 30 Respiratory, with funds paid to his institution. Other authors declare that they have no competing interests.

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