

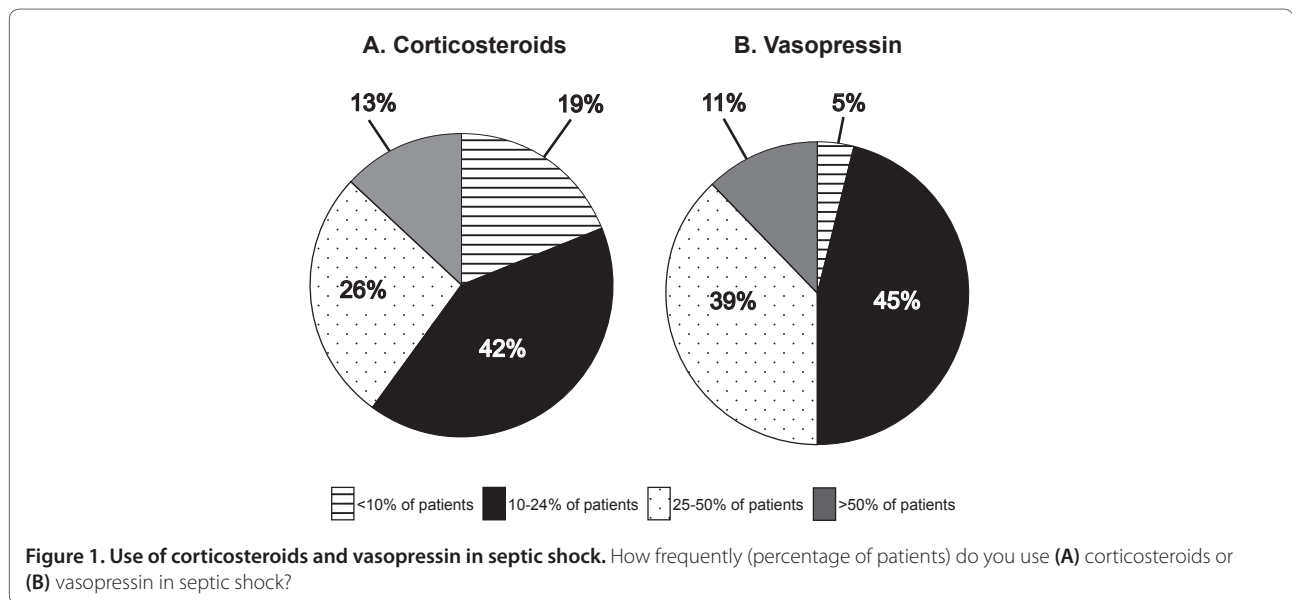
LETTER

# Potential for overuse of corticosteroids and vasopressin in septic shock

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Guidelines recommend corticosteroids and vasopressin to treat septic shock as per specific indications [1]. However, the results from trials evaluating both drugs conflict. For corticosteroids, the 2002 Annane and colleagues study showed a survival benefit for hydrocortisone/fludrocortisone treatment in patients with an inappropriate cortisol response to a high-dose adrenocorticotropic hormone (ACTH) test [2], while the Corticosteroid Therapy of Septic Shock (CORTICUS) trial found no difference in survival by patients' response to ACTH [3]. The Vasopressin and Septic Shock Trial (VASST) demonstrated a survival benefit in less severe septic shock, but guidelines espouse use 'in patients refractory to other vasopressors' [1,4]. Clinical variability, leading to overtreatment, may have negative effects on survival. To evaluate the impact of these evidence limitations, we surveyed physicians in the Critical Illness Outcomes Study (CIOS).

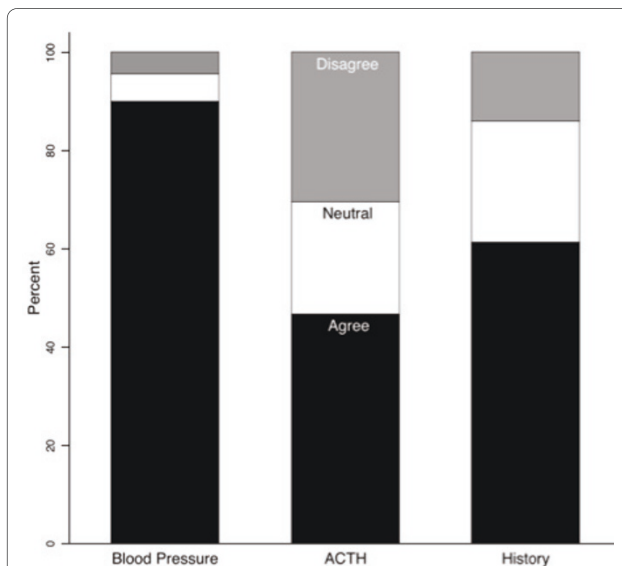
We developed a 15-item, self-administered survey to characterize physician practice patterns for use of corticosteroids and vasopressin in septic shock. The survey, conducted anonymously and with implied consent, was distributed to 92 members of the CIOS listserv. Recipients were encouraged to solicit survey completion by their colleagues. CIOS is a multicenter study among 68 ICUs designed to determine whether ICU-based organizational and structural factors are associated with patient-related outcomes. The survey fulfilled Stanford Institutional Review Board exemption guidelines. To address when clinicians would use corticosteroids, we asked participants to rate their agreement (five-point Likert scale) for the following situations: blood pressure poorly responsive to fluid resuscitation and vasopressor therapy; an inappropriate response to ACTH testing [2]; and a history of treatment with corticosteroids within the prior 6 months. Likert responses were evaluated by Pearson



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**Figure 2. Indications for corticosteroid use in septic shock.** Three scenarios were evaluated. Blood pressure: whether blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy. Adrenocorticotropic hormone (ACTH): whether there is an inappropriate response to a high-dose ACTH stimulation test (change in cortisol <9 µg/dl). History: whether the patient has been treated previously with corticosteroids (within the previous 6 months). Concordance with Surviving Sepsis Guidelines: 88% for blood pressure, 47% for ACTH and 62% for history.

correlation coefficients. For vasopressin, we asked whether physicians preferentially used vasopressin in more or less severe septic shock, as defined by the VASST [4].

Per 140 completed surveys (87% from academic institutions), corticosteroids and vasopressin were used commonly in septic shock (90% and 99%, respectively). Thirty-nine percent used corticosteroids in more than one-quarter of septic shock patients (Figure 1). Eighty-eight percent of respondents agreed with Surviving Sepsis guidelines for blood pressure-based corticosteroid therapy; however, fewer agreed with ACTH-based (47%) or history-based (62%) indications (Figure 2). Agreement with these indications among providers was poorly correlated: 0.38 between blood pressure and ACTH indications, and 0.13 between blood pressure and history. Eighty-seven percent used vasopressin in more severe septic shock.

Substantial variability exists in use of corticosteroids and vasopressin in septic shock. Although agreement exists regarding the use of corticosteroids for refractory hypotension, other indications demonstrated poor to modest guideline concordance. Nearly one-third of respondents considered failure to respond to an ACTH test as an appropriate indication for corticosteroid use, despite negative results from the CORTICUS trial and variability of current cortisol assays [3,5]. Overtreatment

with corticosteroids could increase incidence of secondary infections [3]. Vasopressin use contradicted the conclusions from the VASST [4]. As septic shock mortality remains high, work is needed to reduce variability through research and adherence to evidence from clinical trials [2-4].

#### Abbreviations

ACTH, adrenocorticotropic hormone; CIOS, Critical Illness Outcomes Study; CORTICUS, Corticosteroid Therapy of Septic Shock; TNF, tumor necrosis factor; VASST, Vasopressin and Septic Shock Trial.

#### Competing Interests

JAR reports holding stock in Sirius Genomics Inc., which has submitted patents owned by the University of British Columbia (UBC) and licensed to Sirius Genomics, that is related to the genetics of sepsis and its treatment. The UBC has also submitted a patent related to the use of vasopressin in septic shock. JAR reports being an inventor on these patents. JAR reports receiving consulting fees from Ferring Pharmaceuticals (which manufactures vasopressin and is developing a selective V1a agonist), from Astra Zeneca (which is developing an anti-TNF $\alpha$ ), from BioCritica (which used to sell activated protein C in the USA), from Melmmune, and from Sirius Genomics Inc. JAR reports having received grant support from Sirius Genomics, Ferring Pharmaceuticals, Astra Zeneca and Eli Lilly that is provided to and administered by the UBC. JAR has received speaking honoraria from Pfizer and Eli Lilly.

#### Authors' contributions

JLH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JLH, AJP and JAR were responsible for study concept and design. JLH, AJP, GSM and JAR were responsible for acquisition of data. JHL and VL were responsible for statistical analysis. JLH, VL, AJP, GSM and JAR were responsible for administrative, technical, and material support. JLH and JAR were responsible for study supervision. All authors were responsible for analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content.

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