Appendix 1 (as submitted by the authors)

Definitions and Exclusion Criteria:

The diagnosis of cirrhosis was based on liver biopsy findings or on clinical and laboratory evidence including the presence of portal hypertension, endoscopically-proven esophageal varices, ascites or abnormal liver function tests and coagulopathy (1). Sepsis was defined according to the 2001 International Sepsis Definitions Conference (2). Septic shock was defined as sepsis and persistent hypotension (systolic arterial pressure below 90 mmHg or mean arterial blood pressure below 65 mmHg for at least one hour despite adequate volume resuscitation requiring vasoactive support with more than 5 mcg/kg/min of dopamine or any dose of norepinephrine, vasopressin, phenylephrine or epinephrine). Exclusion criteria included: hemorrhagic shock, known adrenal insufficiency, any prior systemic steroids usage, contraindications for systemic steroids, post-cardiac arrest and Do-Not-Resuscitate status.

Data Collection

Baseline data collection included demographics, etiology of cirrhosis, and Acute Physiology and Chronic Health Evaluation II (3), Sequential Organ Failure Assessment (4) and Child Pugh (5) scores. We documented the source of infection, the type (community-acquired vs. healthcare-associated), the isolated organisms, the presence of bacteremia, the duration of shock before inclusion and the use of etomidate (Etomidate- Lipuro®, B-Braun, Germany or Hypnomidate®, Janssen-Cilag, UK).The following parameters were recorded at inclusion, then every 6 hours: vasopressor doses, mean arterial pressure, heart rate, central venous pressure, intra-abdominal pressure (using the bladder technique), central venous gas saturation, blood glucose, peak and mean airway pressure, and positive end expiratory pressure. The following parameters were

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collected daily: fluid intake and output, blood product transfusions and volume of administered albumin and synthetic colloids.

Statistical Analysis:

There are no prior randomized controlled trials studies examining the effect of hydrocortisone on the outcome of cirrhotic septic patients. Based on our previous study of critically ill cirrhosis patients, we estimated 28-day mortality to be 90% (1). We anticipated 20% absolute risk reduction and 22% relative risk reduction with hydrocortisone therapy. In the study by Annane and colleagues of critically ill patients in general with sepsis, 28-day mortality was reduced from 63% to 53% (10% absolute risk reduction and 16% relative risk reduction) (6). This assumption was further supported by a later study by Marik and colleagues on a heterogeneous group of liver disease patients, observing a mortality difference of 20% (46% v. 26%) with glucocorticoid treatment (7). As such, we needed 75 patients in each group, using a two-sided type-I error of 5% and power of 80%.

Baseline characteristics and outcome variables were compared using T-test, Chi-square, and proportional tests, as appropriate. Kaplan-Meier Curves for cumulative survival were constructed and compared using the log-rank test. Additionally, we carried out stratified analyses by the presence or absence of relative adrenal insufficiency, the use of etomidate, the duration of shock before inclusion, Child Pugh Score, Acute Physiology and Chronic Health Evaluation II I score, shock relapse and the development of gastrointestinal bleeding to detect any modification of the association between the intervention and 28-day mortality based on any of these risk factors or complications. For stratification, we categorized continuous variables into two groups based on median values. We also performed stratified analysis based on the

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duration of treatment with study drug of < or ≥ 5 days and based on whether the target mean arterial pressure was achieved within 6 hours of starting vasopressors or not. For sub-group analyses, we first tested for interaction between the intervention and the subgroups by assessing the association with chi-square test. Additionally, we examined the association between the treatment and 28-day mortality using a logistic regression model which included an interaction term between the intervention and each of the above mentioned variables. For all tested subgroups, we found no significant interaction between the intervention and the subgroups. Statistical significance was defined as p-value < 0.05.

References:

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