Answering reviewers

Dear editor,

Please find, as requested, the revisions for the manuscript titled "Timing, Method, and Discontinuation of Hydrocortisone Administration for Septic Shock Patients".

The responses appear in bold below each comment.

We look forward to your response.

Title: "Timing, Method, and Discontinuation of Hydrocortisone Administration for Septic Shock Patients"

Authors: Ibarra-Estrada MA, Chávez-Peña Q, Reynoso-Estrella CI, Rios-Zermeño J, Aguilera-González PE, García-Soto MA, Aguirre-Avalos G.

Reviewers' comments:

1. **Reviewer 00502854:**

- I think it's a good paper, but it has a major weakness: because it is a non-randomized study carried out in two hospitals, it's essential that the data are analyzed according to the hospital where patients have been recruited. All the results could be explained by this variable. Hospital must be analyzed. May be you could add the data in Table 1 and add the variable in the multivariate analysis.

Response: patients with 'oncologic disease' were recruited from a center only (Instituto Jalisciense de Cancerología), there were no oncologic patients recruited at Hospital Civil Fray Antonio Alcalde. We added this clarification at 'Settings' on Methods section.

METHODS

"Setting
This was a prospective cohort study conducted in 2 medical/surgical intensive care units at tertiary academic hospitals from June 1st, 2015, through July 31st, 2016. All patients recruited in Instituto Jalisciense de Cancerología had oncologic disease; there were no oncologic patients recruited at Hospital Civil Fray Antonio Alcalde. Inclusion criteria for patients were…"

Therefore, multivariate analysis for this potential bias is already done in Table 4; however, we agree that hospitals must be analyzed; we added a new table

(Table S1) as a supplementary material, showing univariate analysis according to recruitment center.

"There were no significant differences in demographic and baseline clinical characteristics between patients in the continuous infusion and bolus groups (Table 1). We found no differences in these characteristics between recruitment centers (Table S1, supplementary material). Patients in the bolus group received…"

2. **Reviewer 02639698:**

- it is a well design study, though performed in a small group of patients. A paragraph on study limitations should be added to the discussion.

Response: the study limitations, including the lack of statistical power to detect differences between groups is already done.

"This study has some limitations; we did not address the effects of the use of some drugs known to affect adrenal function (eg, etomidate, antifungals, benzodiazepines, and opioids)[30]. Medical management for septic shock patients is always based on the current Surviving Sepsis Campaign Guidelines and are very similar at both hospitals; however, due to the observational and nonrandomized design of the study, we cannot ensure completely homogeneous treatment regarding other relevant variables associated with improving outcomes (eg, appropriateness and type of fluid resuscitation and correct and timely use of antibiotics). This study was powered to detect differences in short-term vasopressor requirements and to find the best cut-offs for initiation of hydrocortisone only; therefore, results concerning analysis between groups should be interpreted cautiously, and should be taken as hypothesis-generating data for the design of future clinical randomized controlled trials."

3. **Reviewer 03343282**

- A flow chart of the study should be added

Response: a flow chart was added as supplementary material

"Throughout the study period, 826 patients were admitted to both ICUs, of which 66 (7.9%) had a diagnosis of septic shock; 59 patients met the inclusion criteria because 7 subjects died within the first 48 hours (Figure S1, supplementary material). The median age was 57 years (IQR, 38–65), 26 patients…"

- There is an overpresentation of pneumonia. Was VAP or Health Care Associated Pneumonia?A comment about a possible bias should be added in discussion.

Response: we don't think there was an overrepresentation of pneumonia, the incidence at our study was 44.1%, and pneumonia has been reported as the most common infection source in many studies addressing septic shock: 50% in Briegel, et al. Crit Care Med 1999 (reference 6); 41-47% in Annane, et al. JAMA

2002 (reference 8); 70-80% in Keh, et al. Am J Respir Crit Care Med 2003 (reference 29); 35-50% in Oppert, et al. Crit Care Med 2005; 49% in De Backer, et al. NEJM 2010; 86-89% in Teng-Jen, et al. Adv Ther 2009; 45% in Luiz Buchele, et al. Crit Care Med 2009; 38-50% in Huh, et al. Respirology 2011 (reference 18). 39-57% in Gordon, et al. Crit Care Med 2014 (reference 28); 39-57% in Katsenos, et al. Crit Care Med 2014 (reference 25); 42% in Bentzer, et al. Intensive Care Med 2016 (reference 27); 54% in Hyvernat, et al. Shock 2016.

Most cases of pneumonia were ventilator associated; we added that subgroup analysis in table 1.

"Characteristics	Continuous Infusion n= 32	IV Bolus n= 27	*P* Value
Age, median (IQR)	50 (37 – 64)	61 (39 – 70)	0.19
Male gender, n (%)	12 (37.5)	14 (51.9)	0.27
Oncologic disease, n (%)	15 (46.9)	10 (37)	0.45
Surgical patients, n (%)	25 (78.1)	17 (63)	0.20
Infection source, n (%)			
Pneumonia	13 (40.6)	13 (48.1)	0.56
Ventilator associated	7 (21.8)	6 (22.2)	0.87
Health care associated	3 (9.3)	4 (12.5)	0.66
Community acquired	3 (9.3)	3 (11.1)	0. 52
Abdomen	14 (43.7)	10 (37)	0.60"

Subgroups according to this variable are clearly homogeneous; therefore we do not consider this variable as a potential bias.

- In norepinephrine dosage patient's weight was real or ideal?

Response: due to norepinephrine's short half-live, fast onset, and low volume of distribution, the use of ideal body-weight is suggested. We added a statement addressing how this was calculated at 'Data collection'.

Data collection

After patients with septic shock were deemed candidates for initiation of hydrocortisone, informed consent was obtained from patient or their next of kin, and data were prospectively collected. Recorded information included demographic data, comorbidities, maximal dose (calculated to ideal body weight) and length of vasopressor requirement…

4. **Reviewer 00502903**

The authors present an interesting observational study on use of hydrocortisone in septic shock patients at 2 academic hospitals in Mexico. Overall, the study should best be regarded as hypothesis generating, rather than helping to establish firm conclusions. Despite the many limitations of this paper, however, it does contribute provocative ideas to the literature. Specific comments below:

- The Aim "characterize the prescribing patterns for hydrocortisone for patients with septic shock and determine the best method of administration of hydrocortisone in these patients." suggests an untestable hypothesis, or at least one that cannot be addressed by the current study design.

Response: that's correct, sorry. An observational study is not a good way to determine the best method of treatment. We changed that statement.

"**AIM:** To characterize the prescribing patterns for hydrocortisone for patients with septic shock and perform an exploratory analysis in order to identify the variables associated with better outcomes.
METHODS: This prospective cohort…"

- It is not entirely clear how a prospective study design improves the data or conclusions as compared to a retrospective design using the same data. Elimination of protopathic bias is one potential benefit of a prospective design, but that is not clearly demonstrated.

Response: Agree, depending on quality and planning, a prospective design is not necessarily superior to a retrospective study. But we did not present just the "same" data, as studies addressing direct comparison between both methods of administration are lacking, and we identified interesting variables previously not (or barely) reported. We think that deleting the term "prospective" will eliminate that confusion.

"The main strength of this study is that it was ~~prospective and~~ specifically designed to compare the efficacy between both methods of administration of hydrocortisone, according to vasopressor requirement, indirectly assessing their affects on immunomodulation and vasomotor tone improvement."

- While comparisons are made between bolus vs infusion administration, the dosing (eg., mg/kg or mg/m^2) of hydrocortisone is not presented. Without this information, the effects of the administration strategy cannot be evaluated definitively.

Response: although hydrocortisone at "stress dose" is commonly used (as recommended) as a fixed dose at 200 mg/day, you have a good point. We added that univariate analysis in Tables 1 and S1.

Table 1:

Vasopressin use, n (%)	12 (37.5)	4 (14.8)	0.50
Maximum NE dose (mcg/kg/min)	0.25 (0.17-0.36)	0.33 (0.20-0.39)	0.55
Hydrocortisone dose (mg/kg/day)	2.63 ± 0.27	2.75 ± 0.31	0.13
NE to hydrocortisone (h)	8 (4-19.5)	14 (8-31.5)	0.01

Table S1:

Vasopressin use, n (%)	11 (32.4)	5 (20)	0.29
Maximum NE dose (mcg/kg/min)	0.31 (0.20-0.40)	0.27 (0.18-0.33)	0.07
Hydrocortisone dose (mg/kg/day)	2.71 ± 0.28	2.65 ± 0.31	0.44
NE to hydrocortisone (h)	14 (8-29)	8 (5-19)	0.09

- Data need to be presented on the number of categories of patients from each study site.

Response: It's already done, as suggested by reviewer 00502854. We added Table S1, with analysis according to recruitment center.

- Were any systemic steroids other than hydrocortisone administered?

Response: no, we added this statement

"was administered as a continuous infusion in 54.2% of patients; the median dose of norepinephrine at initiation of hydrocortisone was 0.3 mcg/kg/min (IQR, 0.18–0.39), there were no systemic steroids administered other than hydrocortisone, time from norepinephrine to initiation of hydrocortisone was 12 h (IQR, 6–27), and…"

- How was shock defined, as in relapse or reversal?

Response: definitions were added

"Inclusion criteria for patients were a diagnosis of septic shock, defined as sepsis induced hypotension persisting despite adequate fluid resuscitation[2], for which the attending intensivist determined the need for adjunct hydrocortisone therapy at a stress dose (no more than 200 mg/d), regardless of the timing and method of administration. Shock reversal was considered when the arterial pressure remained stable (SAP >90 mmHg or MAP >70 mmHg without requirement of new vasopressor infusion) for more than 24 hours. Relapse was defined as recurrence of septic shock, requiring norepinephrine resumption within first 7-days after reversal. Patients with…"

- The axes in Figure 2 would seem to be reversed. If Time to shock reversal is considered a dependent variable on Time to initiation of hydrocortisone, then Time to shock reversal would be more appropriately the Y-axis.

Response: the axes were corrected (it's figure 3)

- Vasopressin is used in 37.5% of the continuous group, but 15% of the bolus group. While the p-value is above 0.05, it would be plausible that this observation could account for the difference in norepinephrine administration and "shock reversal."

Response: as you refer in your following comment, the small number of patients limits the ability to detect differences between groups; given that subgroup stratification reduces the "n" for analysis, it would be even more difficult that this variable plays a significant role on the outcome. After adjustment with Cox proportional hazards regression, the difference in shock reversal remained significant at P= 0.02, we added that result.

"…with a significant interaction between groups (*P* = 0.04; Figure 1). At Kaplan-Meier analysis, continuous infusion was also significantly associated with a higher proportion of shock reversal at 7 days after presentation of shock (83% vs 63%; *P* = 0.004; Figure 2); this difference remained significant after adjustment for vasopressin use with Cox proportional hazards regression (P= 0.02)."

We acknowledge it sounds intuitive that vasopressin could account for a greater proportion of shock reversal, therefore we performed the logistic regression again (Table 4), including "vasopressin use" in the model despite its P value was >0.20 at univariate analysis. There was no significant association between vasopressin use and shock reversal after adjustment.

Table 4. Univariate and multivariate logistic regression analysis for relevant factors associated with shock reversal.

Variable	Univariate		*P* Value	Multivariate	*P* Value
	Shock reversal n= 41	Non-reversal n= 18		Adjusted OR (95%CI)	
Age (y), SD	53 ± 16.3	50 ± 16.3	0.46		
Male gender, n (%)	15 (36.6)	11 (61.1)	0.08	1.4 (0.21-10.1)	0.68
Medical disease, n (%)	11 (26.8)	6 (33.3)	0.61		
Oncologic disease, n (%)	20 (48.8)	5 (27.8)	0.13	1.0 (0.18-6.3)	0.92
AKI, n (%)	17 (41.5)	14 (77.8)	0.01	0.3 (0.05-2.0)	0.23
ARDS, n (%)	12 (29.3)	9 (50)	0.12	2.7 (0.4-16.9)	0.27
Superinfection, n (%)	5 (12.2)	3 (16.7)	0.68		
APACHE II score	20 ± 5.4	23 ± 6.4	0.16	1.1 (0.9-1.3)	0.18
SOFA score	10 ± 3.0	10 ± 2.4	0.69		
Vasopressin use, n (%)	10 (24.4)	6 (33.3)	0.48	2.5 (0.4-15.4)	0.31
Early hydrocortisone (≤13 h from NE), n (%)	28 (68.3)	2 (11.1)	0.0001	13.8 (1.4-129)	0.02

NE dose at hydrocortisone initiation ≤0.28 mcg/kg/min, n (%)	28 (68.3)	2 (11.1)	0.0001	32.4 (2.7-382)	0.005

Goodness-of-fit (Hosmer-Lemeshow) $x^2 = 7.01$, $P = 0.53$; AUC, 0.91 (0.80 – 0.96), $P = < 0.0001$.

- The small numbers of patients in this study limit the ability to detect differences between groups.

Response: we addressed this in "discussion"

"This study has some limitations; we did not address the effects of the use of some drugs known to affect adrenal function (eg, etomidate, antifungals, benzodiazepines, and opioids)[30]. Medical management for septic shock patients is always based on the current Surviving Sepsis Campaign Guidelines and are very similar at both hospitals; however, due to the observational and nonrandomized design of the study, we cannot ensure completely homogeneous treatment regarding other relevant variables associated with improving outcomes (eg, appropriateness and type of fluid resuscitation and correct and timely use of antibiotics). This study was powered to detect differences in short-term vasopressor requirements and to find the best cut-offs for initiation of hydrocortisone only; therefore, results concerning analysis between groups should be interpreted cautiously, and should be taken as hypothesis-generating data for the design of future clinical randomized controlled trials."

- The overall tone of Discussion suggests that firm clinical conclusions can be drawn from the presented results. It would be more appropriate simply to note the observations and suggest further testing in randomized controlled trials.

Response: agree, we changed some terms in discussion to avoid drawing solid conclusions

"CONCLUSION: Continuous infusion of hydrocortisone could hasten the resolution of septic shock compared to bolus administration. Earlier initiation corresponds with…"

"The main finding in our study is that, compared to bolus strategy, the administration of hydrocortisone by continuous infusion may lead to a faster reversal of shock and is associated with a higher proportion of vasopressor-free patients at 7 days. Furthermore, we identified optimal cut-off criteria for initiation of hydrocortisone, either based on the time from initiation of vasopressor, or the current maximal dose of norepinephrine. This study also suggests there is no benefit of the tapering strategy because…"

"Another interesting finding of this study is the apparent lack of benefits to the tapering strategy for discontinuation of hydrocortisone. The Surviving Sepsis Campaign Guidelines suggest…"

"In conclusion, we found that continuous infusion of hydrocortisone could hasten resolution of septic shock compared with bolus administration and that earlier initiation based on time and/or norepinephrine dose is related with a higher probability of shock reversal. The tapering strategy appears unnecessary and may be only related to additional adverse effects."