# The possible association of steroids with fluid accumulation in critically ill patients – a case of a potential bias

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**Research**

**Keywords:** Glucocorticoids, Steroids, Fluid, Balance, Sepsis, Septic Shock

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# The possible association of steroids with fluid accumulation in critically ill patients – a case of a potential bias

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**Abstract**

**Background:** Glucocorticoids (GCS) are commonly administered to critically ill patients. Due to their mineralocorticoid effect, GCS might have a substantial influence on a positive fluid balance. We assessed the association between glucocorticoids (GCS) therapy and fluid balance in critically ill patients with sepsis.

**Methods:** This is a retrospective study of patients with sepsis hospitalized during 2006-2018 in a general intensive care unit (ICU) at a 1100-bed tertiary medical center.

**Results** – We considered two definitions of exposure: daily exposure to GCS and GCS treatment at any time in the ICU. Of 945 patients with a diagnosis of sepsis, 375 were treated with GCS at any time and 570 were not. We applied four regression models to assess the association between GCS treatment and fluid balance; in our first model, fluid balance did not differ during days with GCS treatment, between patients who were and were not treated with GCS in the ICU (coefficient estimate 79.5 (-55.4 to 214.4), p=0.25). In our second model, daily fluid balance was increased by 139.8 ml (10.8 to 268.9; p=0.03) in patients who were ever treated with GCS during their ICU stay compared to untreated patients. In the third model, which included only patients treated with GCS during their ICU stay, GCS treatment days were not associated with daily fluid balance (coefficient estimate -190.6 (-485.1 to 103.9), p-value=0.21). In the last model, on "steroid free days", patients who received GCS treatment during their ICU stay had a positive fluid balance compared to those who were never treated with steroids (coefficient estimate 157.7 (-24.6 to 340.1), p-value=0.09).

**Conclusions** – Despite their known mineralocorticoid activity, GCS themselves appear not to contribute substantially to fluid retention. The findings highlight the importance of a clear definition of exposure.

**Keywords:** Glucocorticoids; Steroids; Fluid; Balance; Sepsis; Septic Shock

53 **Introduction**

54 A growing body of evidence suggests that a positive fluid balance in patients
55 hospitalized in intensive care is directly related to worse outcomes [1,2], and is an
56 independent negative prognostic factor in patients with sepsis [1,3]. Glucocorticoids
57 (GCS) are commonly administered to critically ill patients for a wide range of
58 indications, especially septic shock [4]. GCS might have a substantial influence on a
59 positive fluid balance, mostly due to their mineralocorticoid effect. Increased
60 mineralocorticoid activity and high aldosterone levels cause an increase in sodium
61 reabsorption in the renal tubule [5]. Additionally, some evidence suggests that GCS
62 may overcome the effect of decreased expression of the mineralocorticoid receptor,
63 due to increased levels of tumor necrosis factor-α in critical care patients [6], thus
64 contributing to fluid retention [7].

65 According to the "Surviving Sepsis Campaign" Guidelines for Management of
66 Sepsis and Septic Shock [8], GCS are recommended for septic shock that is refractory
67 to adequate fluid resuscitation and vasopressor administration. Consequently, patients
68 with sepsis who are treated with GCS are presumably with a more severe disease than
69 patients not treated with GCS. Thus, a possible association between GCS use and
70 fluid balance could be due to the indication for GCS treatment rather than the GCS
71 treatment itself. This raises a core question in the interpretation of observational
72 studies: is the association observed due to a true effect of the exposure or rather the
73 result of a bias?

74 We conducted a retrospective study to assess the association between GCS
75 therapy and fluid balance in critically ill patients with sepsis. To examine whether a
76 possible association might be due to an indication bias, we analyzed the data
77 according to two definitions of exposure: per GCS treatment at any time during

78 intensive care unit (ICU) stay and GCS treatment per day of stay. In the analysis that
79 used the latter definition, the control group included patients without any GCS
80 treatment and also "steroid-free days" of patients treated with GCS during their ICU
81 stay. We hypothesized that analyses using the two definitions of GCS treatment would
82 yield different results.

83 **Materials and Methods**

84 *Study design and study population*

85 We conducted a population-based retrospective cohort study at Soroka
86 University Medical Center, a tertiary care medical center that serves as the only
87 regional hospital in southern Israel (Beer-Sheva vicinity, estimated population of
88 1,000,000). We included all adult patients hospitalized with a diagnosis of sepsis in
89 the general ICU for 24 hours or more, between December 2006 and January 2018. We
90 identified patients with sepsis according to either the International Classification of
91 Diseases, 9th revision (ICD-9) codes or a diagnosis in the internal ICU medical
92 record. Comorbidities were also defined by ICD-9 codes. We used the Sequential
93 Organ Failure Assessment (SOFA) score to evaluate organ dysfunction at ICU
94 admission [9]. Exclusion criteria were hemofiltration or dialysis treatment during the
95 ICU stay.

96 *Clinical definitions and data sources*

97 GCS treatment was defined as the administration of one of the following
98 drugs, at least once, during the ICU stay: hydrocortisone, methylprednisolone, or
99 prednisone. Indications for steroid treatment were septic shock or acute respiratory
100 distress syndrome.

101 Using the first definition of GCS exposure, we compared patients who did and
102 did not receive GCS therapy during their ICU stay. Using the second definition of

GCS exposure, we aggregated patients' data to 24-hour periods. For each of these periods, we analyzed the use of steroids, the daily fluid balance, and serum creatinine for each patient. The daily fluid balance was calculated as the total daily input (nutrition, crystalloids, blood products, intravenous drugs) minus the total daily output (urine, fluids from body drains), and presented in milliliter units. We evaluated the creatinine level for every admission day. We used the average daily value when a particular test was performed more than once in a single day. Days in which patients were treated with diuretics were excluded from the analysis. For patients who had more than one admission in the ICU during the study period, we used only the first admission. We limited the analysis to the first 21 ICU hospitalization days. For both definitions of exposure, the outcome was the daily fluid balance during the ICU admission.

*Statistical analysis*

The results are presented by means ± SDs for continuous variables, medians and interquartile ranges for ordinal variables, and percentages for categorical data. The Chi-square test was used for categorical variables, the t-test for continuous variables, and the Mann-Whitney test for ordinal variables.

Linear generalized estimating equation (GEE) models with unstructured correlation matrices were used to estimate associations between steroid treatment on each day of admission and the daily fluid balance. GEE models were used to account for repeated measurements of fluid balance in the same patient. In all the models, the dependent variable was the total daily fluid balance in milliliters. The independent variables were defined a priori as fixed effects; firstly, steroid treatment per day or at any time during the ICU stay, depending on the approach used. In addition, the

following variables were considered: age, sex, SOFA score at admission, average serum creatinine level, and admission day number in the ICU.

We applied four models to determine the contribution of steroid treatment to the fluid balance (Figures 1-4). In the first model, we compared the fluid balance between all the days with GCS treatment and all the days without GCS. The latter was derived from two sub-groups: the first, "steroid-free days" in patients receiving GCS treatment during their ICU stay; and the second, all ICU days of patients who were not treated with GCS. In the second model, we compared all the days of patients who were not treated with GCS during their ICU stay to all the days of patients who received GCS treatment during their ICU stay. In the third model, we included only the patients who were treated with GCS during their ICU stay. We compared days with GCS treatment to days without GCS treatment. In the last model, we compared all the days of patients who were never treated with GCS during their ICU stay to "steroid-free days" of those who received GCS treatment at some time during their ICU stay. SPSS IBM software, version 25.0, was used for statistical analysis.

*Data availability*

The data used in the analysis of this study are not publicly available due to the national regulations but are available from the corresponding author upon request.

## Results

*Study Population*

The study included 945 patients: 375 (39.7%) who were treated with GCS during their ICU stay and 570 who were not. Table 1 summarizes the characteristics of the study population: the mean age was lower among those treated than not treated with GCS (57.5 ± 21.3 vs. 61.2 ± 18.9, p=0.006). The majority of the patients in both

152 groups were males (61.6% and 59.5%, respectively). The admission SOFA Score
153 (median, interquartile range (IQR)) was higher among those treated than not treated
154 with GCS (11 (9-13)) vs. (10 (7-12)), p<0.001. Patients with a history of chronic
155 obstructive pulmonary disease constituted 6.1% of those treated with GCS and 1.9%
156 of those not treated (p<0.001). The duration of hospitalization (median, IQR) and the
157 mortality rate in the ICU were higher among those treated than not treated with GCS
158 (10 (3-26) days) vs. (4 (1-14) days) and 25.6% vs. 14.6%, respectively.

159 *Steroid treatment and fluid balance*

160 The first model compared fluid balance between all the days with GCS
161 treatment and all the days without GCS. Female sex, older age, higher SOFA score on
162 admission, and high creatinine were all shown to be associated with significantly
163 increased daily fluid balance (Figure 1). This model demonstrated no significant
164 association of GCS treatment with daily fluid balance (coefficient estimate 79.5 (-55.4
165 to 214.4), p-value=0.25).

166 The second model compared all the days hospitalized in the ICU, between
167 patients not treated with GCS and patients who received GCS treatment. All the
168 variables mentioned above were associated with significantly increased daily fluid
169 balance (Figure 2). However, the daily fluid balance was increased in patients treated
170 than not treated with GCS, by 139.8 ml (10.8 to 268.9; p=0.03).

171 The third model included only patients treated with GCS during their ICU stay
172 and compared "steroid-free days" to days with GCS treatment. We found no
173 significant association of GCS treatment with daily fluid balance (coefficient estimate
174 -190.6 (-485.1 to 103.9), p-value=0.21) (Figure 3).

175 In the last model, patients who received GCS treatment during their ICU stay
176 had a positive fluid balance on their "steroid-free days" compared to those who were

never treated with steroids (coefficient estimate 157.7 (-24.6 to 340.1), p-value=0.09) (Figure 4).

## Discussion

Our analysis of data according to two definitions of GCS exposure yielded different results, thus confirming our hypothesis. Specifically, in our cohort of patients with sepsis, we found an association of GCS therapy with positive fluid balance when the exposure was defined as any treatment with GCS during the ICU stay. However, when the exposure was defined as daily exposure to GCS, this association did not hold. Thus, this observational study suggests that evidence of an association between GCS therapy and fluid balance is due to an indication bias, and not to a true effect of GCS treatment. The bias stems from the greater disease severity of the patients treated with GCS. In further support of this interpretation, a positive fluid balance was observed on "steroid-free days" in patients treated with GCS compared to patients not treated with GCS during their ICU stay.

Steroids are widely used in patients with septic shock, while survival benefit has been shown only among those who remained hypotensive after fluid and vasopressor resuscitation [10]. The rationale for glucocorticoid administration in this population is based on data suggesting that critical illness induces a relative adrenal insufficiency that may contribute to shock. Previous studies identified positive fluid balance as a predictor of clinical outcome [2,11]. Moreover, some authors support restrictive intravenous fluid therapy in patients with sepsis to avoid edema within vital organs and organ dysfunction, with impairment of oxygen delivery [11].

In this study, we applied four models to determine the contribution of steroids treatment to fluid balance in patients hospitalized in the ICU with sepsis. Our first

202 model examined GCS per treatment days. Days with GCS treatment were compared
203 to days without GCS treatment, between patients who were treated with GCS at any
204 time during their ICU stay and those who were not treated with GCS during their ICU
205 stay. This model showed no association of GCS treatment with daily fluid balance.
206 However, in the second model, we compared between patients who received GCS
207 treatment at least once to those who did not receive GCS treatment during their ICU
208 stay. GCS treatment was shown to be associated with a positive daily fluid balance.
209 The conclusion from these two models is that the steroids themselves do not influence
210 the daily fluid balance. Rather, the propensity to treat the more severe patients with
211 GCS may explain the positive balance in those patients. This hypothesis is supported
212 by the third model, which assessed only patients who received GCS treatment. Here,
213 no difference was observed in daily fluid balance between the days with and without
214 GCS treatment. The last model compared only days without GCS treatment, between
215 patients who were and were not treated with GCS. Patients who received GCS
216 treatment at any time during their ICU admission demonstrated positive fluid balance.
217 This again shows that the clinical characteristics leading to steroid treatment rather
218 than steroids themselves are responsible for the fluid retention.
219 The severity of disease in the patients treated with GCS is evidenced by their
220 older age, higher SOFA scores, longer admission times, higher ventilation rates, and
221 higher mortality rates. This is consistent with the indications for GCS according to the
222 guidelines for patients with septic shock [8,10]. The differences in characteristics
223 between the study groups support our supposition that the association between GCS
224 treatment and a positive fluid balance stems from an indication bias, whereby patients
225 with more severe illness and a positive fluid balance are treated with steroids.

The strengths of our study include a lengthened period of data collection with a relatively large cohort. Yet, our study has a number of limitations. First, it is a retrospective study that included patients with sepsis from a single center. Second, we analyzed associations of overall GCS therapy with fluid balance, while the different steroids that were used to treat our patients (hydrocortisone, methylprednisolone) have unequal mineralocorticoid activity [3].

## Conclusions

We suggest that GCS themselves, though known to have mineralocorticoid activity, do not contribute substantially to fluid retention in critically ill patients. This finding may help elucidate the "fluid balance" concept in critically ill patients with sepsis who receive GCS and reduce the concern that GCS causes a positive fluid balance in this population.

## List of abbreviations

GCS, glucocorticoids; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; GEE, generalized estimating equation; IQR, interquartile range

## Declarations

### Ethics approval and consent to participate

The study was approved by the Soroka University Medical Center Ethics Committee. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The Ethics Committee approval exempted the study from informed consent due to the retrospective data collection that maintained subject confidentiality. Patient records were anonymized and de-identified prior to analysis.

## Consent for publication

Not applicable

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

## Funding

No external funding was used for this work.

## Authors' contributions

AF Review & Editing

RA Review & Editing

YB Methodology and Formal Analysis

AB Methodology and Formal Analysis

VN Conceptualization

EB Validation

AZ Writing – Original Draft Preparation

MK Supervision

All the authors read and approved the final manuscript.

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311
312

313 **Table 1 – Characteristics of patients at admission to the intensive care unit.**

| Variable | Treated with steroids during their ICU stay (N=375) | Not treated with steroids during their ICU stay (N=570) | P-value |
|---|---|---|---|
| **Age (Mean ± SD)** | 61.2 ± 18.9 | 57.5 ± 21.3 | **0.006** |
| **Male (n, %)** | 223 (59.5%) | 351 (61.6%) | 0.52 |
| **Comorbidities (n, %)** | | | |
| **CAD** | 74 (19.7%) | 134 (23.5%) | 0.17 |
| **COPD** | 23 (6.1%) | 11 (1.9%) | **0.001** |
| **HF** | 39 (10.4%) | 63 (11.1%) | 0.75 |
| **HTN** | 189 (50.4%) | 263 (46.1%) | 0.20 |
| **Cancer** | 89 (23.7%) | 103 (18.1%) | **0.03** |
| **DM** | 115 (30.7%) | 194 (34.0%) | 0.28 |
| **PVD** | 20 (5.3%) | 42 (7.4%) | 0.22 |
| **SOFA Score (Median, IQR)** | 11 (9-13) | 10 (7-12) | **<0.001** |
| **Cardiovascular sub-score** | 4 (4-4) | 3 (2-4) | **<0.001** |
| **Renal sub-score** | 0 (0-1) | 0 (0-1) | **<0.001** |
| **Coagulation sub-score** | 0 (0-1) | 0 (0-1) | 0.89 |
| **Respiration sub-score** | 3 (2-4) | 3 (2-4) | **0.003** |
| **Liver sub-score** | 0 (0-1) | 0 (0-1) | 0.37 |
| **CNS sub-score** | 4 (2-4) | 4 (0-4) | **0.003** |
| **GCS treatment days (Median, IQR)** | 3 (2-10) | – | – |
| **In-ICU death (n, %)** | 96 (25.6%) | 83 (14.6%) | **<0.001** |
| **ICU admission days** | 10 (3-26) | 4 (1-14) | **<0.001** |
| **Mechanically ventilated (n, %)** | 354 (94.4%) | 440 (77.2%) | **<0.001** |

314

315 ICU – Intensive Care Unit; CAD – Coronary Artery Disease; COPD – Chronic Obstructive
316 Pulmonary Disease; HF – Heart Failure; HTN – Hypertension; DM – Diabetes Mellitus; PVD
317 – Peripheral Vascular Disease; SOFA – Sequential Organ Failure Assessment; GCS –
318 glucocorticoids; CNS – central nervous system.

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322

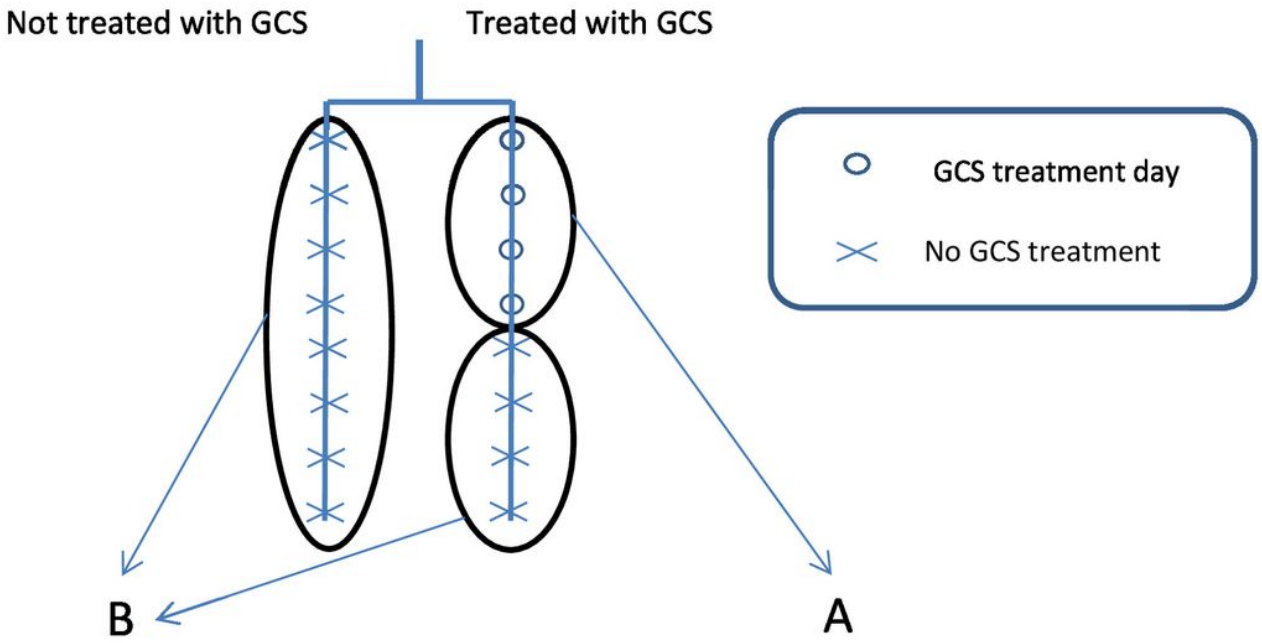
323 **Figure Legends**
324
325 **Figure 1** – Model 1 of the estimated effect of glucocorticoids (GCS) treatment per
326 day on daily fluid balance (ml) in patients with sepsis in the intensive care unit (ICU).
327 In this model, all the days with GCS were compared to all the days without GCS.
328
329 **Figure 2** – Model 2 of the estimated effect of glucocorticoids (GCS) treatment per
330 day on daily fluid balance (ml) in patients with sepsis in the intensive care unit (ICU).
331 In this model, all the hospitalized days of patients who were treated with GCS were
332 compared to all the hospitalized days of patients who were not treated with GCS.
333
334 **Figure 3** – Model 3 of the estimated effect of glucocorticoids (GCS) treatment per
335 day on daily fluid balance (ml) in patients with sepsis who were treated with GCS
336 during their stay in the intensive care unit (ICU). This model included only patients
337 treated with GCS during their ICU stay and compared between GCS days and GCS-
338 free days.
339
340 **Figure 4** – Model 4 of the estimated effect of ever being treated with glucocorticoids
341 (GCS) on daily fluid balance (ml) in patients with sepsis in the intensive care unit.
342 This model included only days without GCS treatment.
343

344

# Figures

| Variable | Coefficient estimate (ml) (95% CI) | p-value |
|---|---|---|
| **Male vs. Female** | -291.5 (-423.9 to -159.2) | **<0.001** |
| **GCS treatment days** | 79.5 (-55.4 to 214.4) | 0.25 |
| **Age (for every added year)** | 12.1 (9.1 to 15.2) | **<0.001** |
| **SOFA score (for every added point)** | 51.9 (30.6 to 73.1) | **<0.001** |
| **Creatinine (for every rise in 1 mg/dL)** | 126.7 (41.7 to 211.7) | **0.003** |

SOFA – Sequential Organ Failure Assessment.



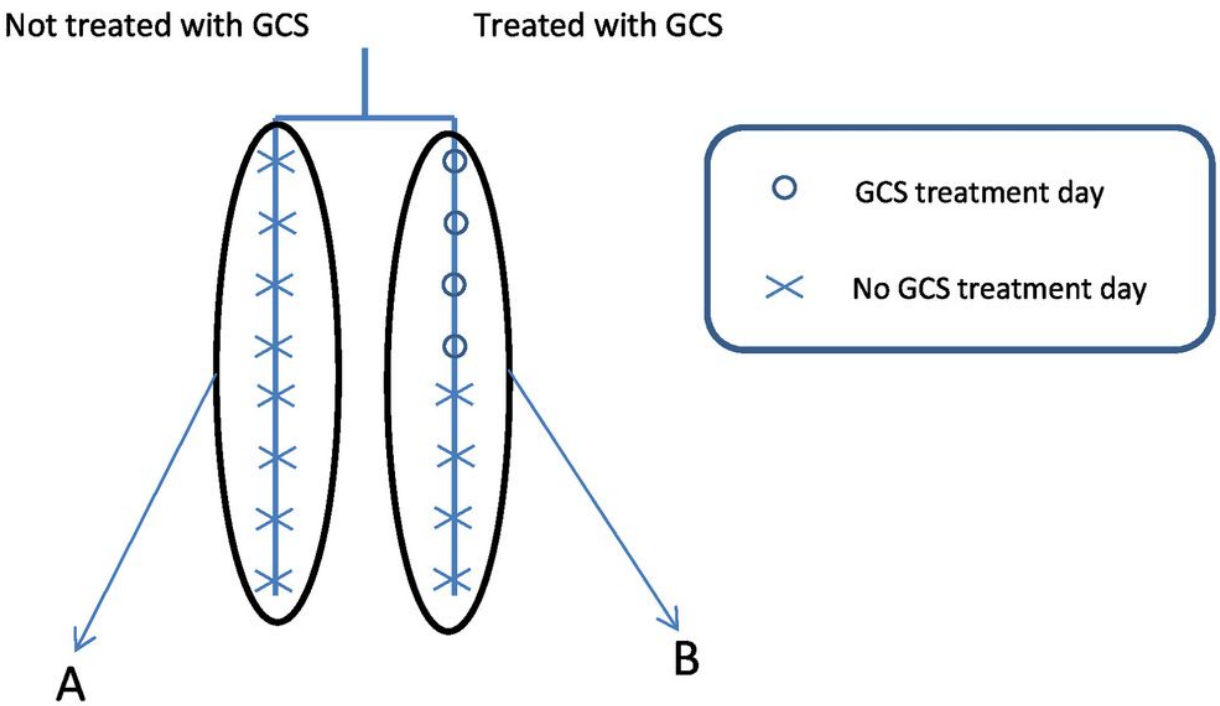

**A –** Days with GCS treatment
**B –** Days without GCS treatment in patients treated with GCS, and days in the ICU of patients not treated with GCS

**Figure 1**

Model 1 of the estimated effect of glucocorticoids (GCS) treatment per day on daily fluid balance (ml) in patients with sepsis in the intensive care unit (ICU). In this model, all the days with GCS were compared to all the days without GCS.

| Variable | Coefficient estimate (ml) (95% CI) | p-value |
|---|---|---|
| **Male vs. Female** | -289.7 (-422.2 to -157.2) | **<0.001** |
| **GCS treatment ever** | 139.8 (10.8 to 268.9) | **0.03** |
| **Age (for every added year)** | 12 (8.9 to 15.1) | **<0.001** |
| **SOFA score (for every added point)** | 49.4 (28.2 to 70.5) | **<0.001** |
| **Creatinine (for every rise in 1 mg/dL)** | 129.6 (44.8 to 214.4) | **0.003** |

ICU – Intensive Care Unit; SOFA – Sequential Organ Failure Assessment.



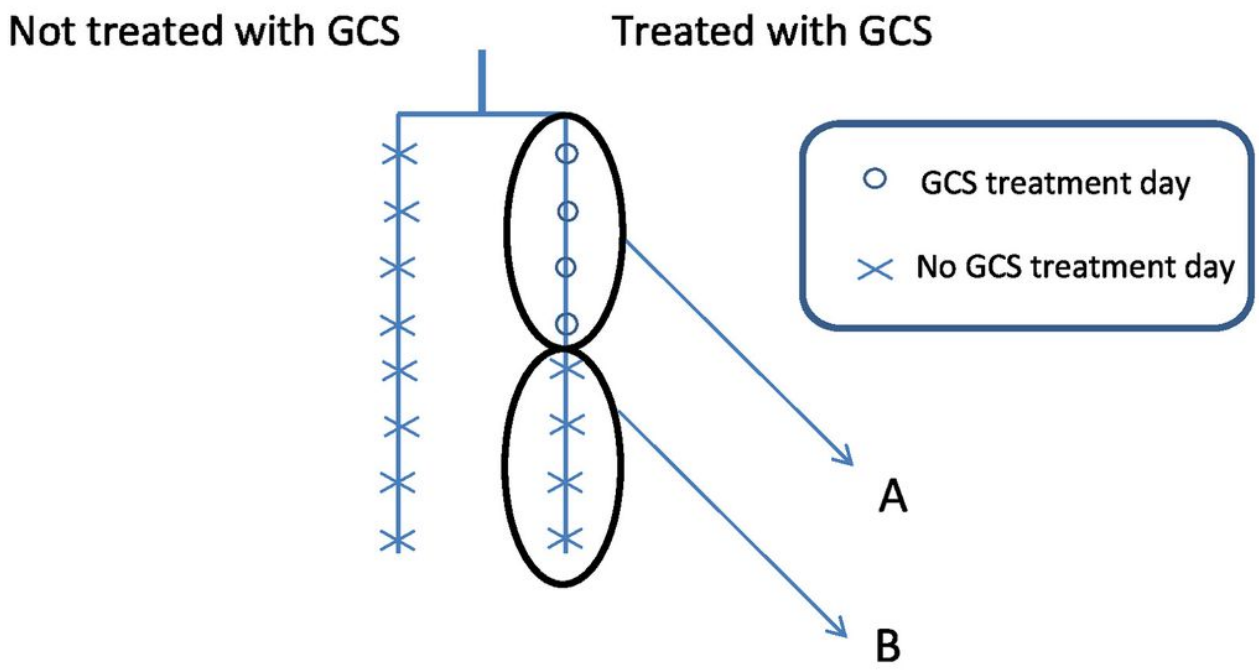

**A –** All the days of patients who were not treated with GCS
**B –** All the days of patients who were treated with GCS

Figure 2

Model 2 of the estimated effect of glucocorticoids (GCS) treatment per day on daily fluid balance (ml) in patients with sepsis in the intensive care unit (ICU). In this model, all the hospitalized days of patients who were treated with GCS were compared to all the hospitalized days of patients who were not treated with GCS.

| Variable | Coefficient estimate (ml) (95% CI) | p-value |
|---|---|---|
| **Male vs. Female** | -272.9 (-476.4 to -69.3) | **0.01** |
| **Days with GCS treatment** | -190.6 (-485.1 to 103.9) | 0.21 |
| **Age (for every added year)** | 12.4 (7.3 to 17.6) | **<0.001** |
| **SOFA score (for every added point)** | 39.2 (1.7 to 76.7) | **0.04** |
| **Creatinine (for every rise in 1 mg/dL)** | 180.4 (41.3 to 319.5) | **0.01** |

SOFA – Sequential Organ Failure Assessment.



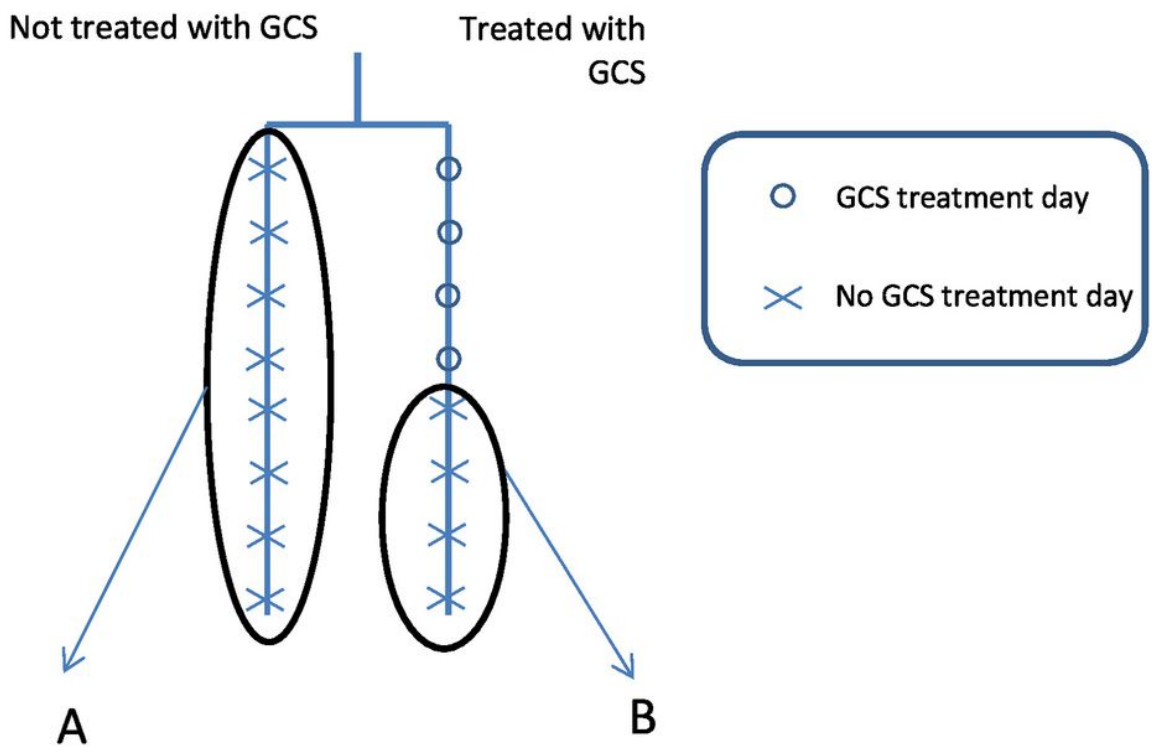

**A –** Days with GCS treatment
**B –** "GCS-free days", in patients who were ever treated with GCS during their hospital stay.

Figure 3

Model 3 of the estimated effect of glucocorticoids (GCS) treatment per day on daily fluid balance (ml) in patients with sepsis who were treated with GCS during their stay in the intensive care unit (ICU). This model included only patients treated with GCS during their ICU stay and compared between GCS days and GCS-free days.

| Variable | Coefficient estimate (ml) (95% CI) | p-value |
|---|---|---|
| **Male vs. Female** | -250.5 (-420.2 to -80.8) | **0.004** |
| **GCS treatment ever** | 157.7 (-24.6 to 340.1) | **0.09** |
| **Age (for every added year)** | 12.2 (8 to 16.5) | **<0.001** |
| **SOFA score (for every added point)** | 35.5 (5.4 to 65.6) | **0.02** |
| **Creatinine (for every rise in 1 mg/dL)** | 100.1 (-26.4 to 226.7) | **0.121** |

SOFA – Sequential Organ Failure Assessment.




**A –** All the days of patients who were never treated with GCS.
**B –** "GCS-free days" of patients who were ever treated with GCS.

**Figure 4**

Model 4 of the estimated effect of ever being treated with glucocorticoids (GCS) on daily fluid balance (ml) in patients with sepsis in the intensive care unit. This model included only days without GCS treatment.