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COMPARISON BETWEEN CONTINUOUS AND INTERMITTENT ADMINISTRATION OF HYDROCORTISONE DURING SEPTIC SHOCK: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Nejla Tilouche,[*†] Oussama Jaoued,[*†] Habiba Ben Sik Ali,[*†] Rim Gharbi,[*†] Mohamed Fekih Hassen,[*†] and Souheil Elatrous[*†]

[*]Intensive Care Unit, University Hospital Taher Sfar, Mahdia, Tunisia; and [†]Research Laboratory, University of Monastir, Mahdia, Tunisia

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ABSTRACT—**Objectives:** The best modality of administration of hydrocortisone during septic shock has been poorly evaluated and the guidelines remain unclear in this respect. This study aimed to compare bolus of hydrocortisone to a continuous infusion during septic shock. **Design:** Randomized controlled, open-label trial. **Setting:** Medical ICU of a university hospital. **Patients:** Adult patients with septic shock requiring more than 2 mg/h (approximately 33.3 μg/mn) of norepinephrine after adequate fluid administration were eligible. Patients already receiving corticosteroids or who have a contraindication to corticosteroids, patients who died within 24 h and those with a decision of not to resuscitate were excluded. **Interventions:** Patients were randomized either to receive hydrocortisone 200 mg/d by continuous infusion or by boluses of 50 mg every 6 h throughout the prescription of vasopressors with a maximum of 7 days. **Results:** Twenty-nine patients were included in each group. Shock reversal was significantly higher in the HC bolus group (66% vs. 35%, $P = 0.008$). The median time to shock reversal was 5 days (95% CI, 4.31–5.69) in the HC bolus group compared to 6 days (95% CI, 4.80–7.19) in the HC continuous infusion group (log Rank = 0.048). The number of hours spent with blood glucose ≥ 180 mg/dL was higher in the HC continuous infusion group with a median of 64 h [IQR (2–100)] versus 48 h [IQR (14–107)] in the HC bolus group, ($P = 0.60$), and daily insulin requirements were similar between the two groups ($P = 0.63$). The occurrence of other side effects, mortality, and ICU LOS were similar between the study groups. **Conclusion:** Hydro-Hydrocortisone administered by intermittent bolus was associated with higher shock reversal at day 7 compared with a continuous infusion.

KEYWORDS—Corticosteroids, morbidity, sepsis, shock reversal

INTRODUCTION

Sepsis is a life-threatening condition secondary to a dysregulation of the host response to infection (1). The diagnosis of septic shock is retained if vasoactive drugs are required to maintain a mean arterial pressure (MAP) higher than 65 mm Hg and if lactate level is greater than 2 mmol/L despite adequate fluid resuscitation (2). Relative adrenal insufficiency is seen in 60% of patients with septic shock and has a deleterious effect by precipitating the progression of sepsis to septic shock and death (3–5).

During septic shock, corticosteroids have been shown to be beneficial on shock resolution compared with placebo (6). This effect is due partly to a restoration of the sensitivity of myocardial and peripheral receptors to catecholamines (7). The ''Surviving Sepsis Campaign'' suggests the prescription of substitutive corticosteroid therapy only in persistent shock (8) and remains silent about the modality of its administration (continuous or bolus). Indeed, few studies evaluating the effect of the modality of corticosteroid administration on shock reversal found inconsistent results (9, 10). This question is raised because of the heterogeneity of the hemodynamic response to corticosteroids between patients, some may respond more quickly and with better tolerance, the mode of administration of corticosteroids may explain this variation. In addition, in normal individuals cortisol is released in the form of pulsations, according to a dynamic rhythm that underlies the classical circadian rhythm. The ''optimal'' glucocorticoid supplementation method may be the bolus since it reproduces better these oscillations compared to a continuous infusion. On the other hand intermittent bolus of corticosteroids exposes patients to hyperglycemia, higher doses of insulin, and an increased workload (11, 12) and may cause worse outcome.

We conducted this study to determine the impact of the modality of corticosteroid administration on the morbidity and mortality of septic shock.

PATIENTS AND METHODS

This is a randomized controlled study performed in the medical intensive care unit (ICU) of the EPS Taher Sfar of Mahdia between April 2013 and June 2016.

Patients

We included patients with the following criteria: Age ≥ 18 years in whom we retained the diagnosis of septic shock, defined as a persistent hypotension induced by sepsis (systolic blood pressure < 90 mm Hg or mean blood pressure < 65 mm Hg despite fluid resuscitation and the administration of more than or equal to 2 mg/h (approximately 33.3 μg/mn) of Norepinephrine for more than 1 h). Initial fluid administration is fixed at 30 mL per kilogram of body weight over the first 3 h.

Patients not included in our study were: Patients under long-term corticosteroid therapy; patients who developed septic shock while under corticosteroids; the presence of a contraindication to corticosteroids (active digestive hemorrhage, peritonitis, fungal infections, and progressive ulcer). Patients who died within 24 h and those with a decision of not to resuscitate were excluded.

Address reprint requests to Nejla Tilouche, MD, EPS Taher Sfar, 5100 Mahdia, Tunisia. E-mail: tilouche.nejla@gmail.com

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Study protocol

Informed consent was obtained from patients or their relatives if they met the inclusion criteria. Patients then were randomized either to receive steroids 200 mg/d by continuous infusion or by boluses of 50 mg every 6 h. Corticosteroids were administered throughout the prescription of vasoactive drugs with a maximum of 7 days (regardless of shock reversal). Randomization was type 1: 1, carried out by sealed envelopes, numbered in the order of the inclusions. The synacthene test was not performed since it is not routinely recommended.

All patients were managed according to the Surviving Sepsis Campaign guidelines 2012 (13). Initially, they had a rapid infusion of 30 mL/kg of crystalloids within the first 3 h, then we added norepinephrine to have a mean arterial pressure $\geq$ 65mm Hg, a level of lactate $<$ 2 mmol/L and a urine output $\geq$ 0.5 mL/kg/h. Dobutamine or epinephrine are added in case of persistent signs of tissue hypo perfusion despite fluid resuscitation Norepinephrine and source control associated with ScVO2 $<$ 70%. Dopamine and vasopressin are not used. Antibiotic therapy was administered immediately after recognition of sepsis or septic shock.

Intravenous insulin therapy was started at two consecutive values of blood glucose (BG) higher than 180 mg/dL, infusion rate was adjusted every hour according to the following scale: 2 IU/h insulin if BG was between 180 and 200 mg/dL, 4 IU/h insulin if BG was between 201 and 250 mg/dL, 6 IU/h insulin, if BG was between 251 and 300 mg/dL and 8 IU/h insulin if BG was higher than 300 mg/dL.

Recorded data were: Demographic characteristics, comorbidities, SAPS II score at day 1, SOFA score for the first 5 days following randomization, hemodynamic parameters, type of vasoactive drugs other than norepinephrine, vasopressors free-days and time on vasopressors, modality and time to hydrocortisone administration, the duration of mechanical ventilation, ICU and hospital length of stay, the total dose of insulin required, complications related to corticosteroids including hyperglycemia: defined by two consecutive blood glucose values $>$ 180 mg/dL, Hypokalemia, Hypernatremia, digestive hemorrhage, neuromyopathy, delirium, and another episode of sepsis or septic shock (another episode of sepsis or septic shock after reversal of the first episode).

Outcomes

The primary endpoint was shock reversal on day 7 defined as no need to vasopressors for consecutive 24 h. Shock reversal was defined as no need to vasopressors to ensure correct tissue perfusion for 24 consecutive hours, and it was considered absent in patients dead before day 7 of shock.

Secondary endpoints were: 28 day mortality, number of days under vasopressors and vasopressors free-days, ICU and hospital length of stay, duration of mechanical ventilation, occurrence of superinfection or new episode of septic shock, episodes of hyperglycemia, dose of insulin administered and the occurrence of side effects to corticosteroids (mentioned above).

Statistical analyses

The sample size was calculated to detect a difference in shock reversal of 25% at day 7 between the study groups. Providing a proportion of shock reversal with hydrocortisone of 68% (14) and according to the two-sided formulation, 29 patients were needed in each group (α=0.05 and power at 80%).

The collected data were analyzed by SPSS statistical software version 23.0. The statistical analysis was conducted consistent with the intention-to-treat (ITT) principle.

Quantitative variables are expressed as means $\pm$ standard deviation or median and interquartile as appropriate. Qualitative variables are expressed by their numbers and percentages.

In univariate analysis, the Mann–Whitney test and the χ^2 test were used to compare quantitative and qualitative variables between the hydrocortisone continuous infusion group and the hydrocortisone bolus group, the statistical significance level "*P*" was set at 0.05. Time to septic shock resolution was estimated using the non-parametric analysis of Kaplan–Meier and the Log Rank test was used to compare the two groups.

RESULTS

During the study period, 70 patients met the inclusion criteria and were randomized. Eight patients in the hydrocortisone bolus group and four patients in the hydrocortisone continuous infusion group died within 24 h (Fig. 1).

The mean SOFA score was 11 ± 2 and the overall ICU mortality was 48% (28/58).

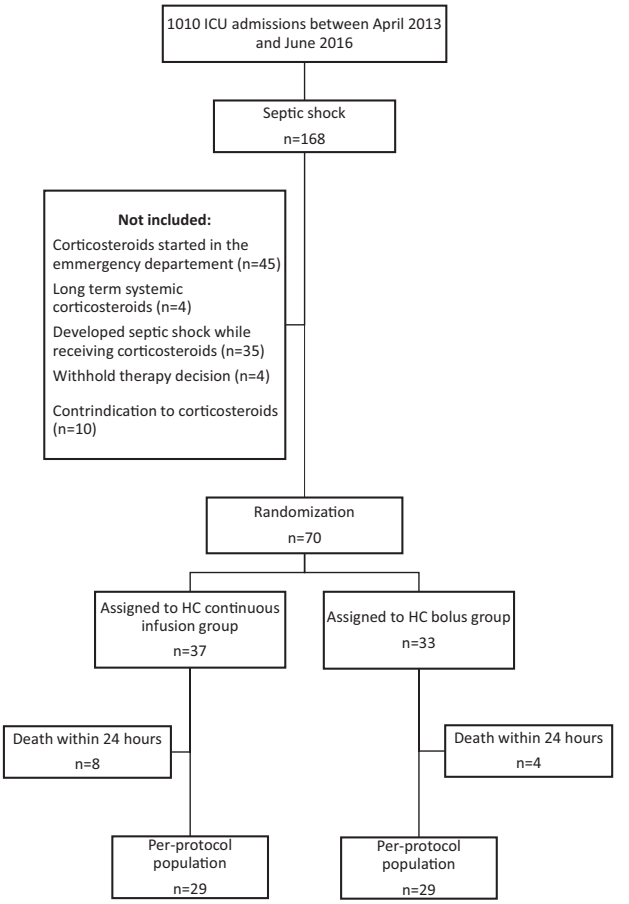

Fig. 1. **Patient's chart flow.**

Adrenaline was associated with Norepinephrine in six patients and Dobutamine in seven other patients, either for insufficient hemodynamic response or for low ScVO2.

Demographic characteristics, clinical characteristics, and the type and site of infection were well balanced between the study groups at inclusion (Table 1).

Sixty-six percent (22/33) of patients in the hydrocortisone bolus group were weaned from vasopressors at day 7, compared to 35% (13/37) in the continuous group ($P = 0.008$), the difference remains significant after excluding patients who died within 24 h after randomization ($P = 0.01$). The median time between shock and hydrocortisone initiation was similar between the two groups [median 3 h (2–5) vs. 3 h (1–12), $P = 0.88$] (Table 2).

The median time to shock reversal was 5 days (95% CI, 4.31–5.69) in the hydrocortisone bolus group compared with 6 days (95% CI, 4.80–7.19) in the hydrocortisone continuous infusion group (log Rank = 0.048) (Fig. 2).

Forty-one subjects developed acute renal failure (70.7%): 18 in the bolus group and 23 in the continuous infusion group, $P = 0.14$.

Mortality at day 28 was higher in the continuous infusion group [24/37 (64%) vs. 16/33 (48%), $P = 0.25$].

The number of hours spent with blood glucose $\geq$ 180 mg/dL during the first 7 days of shock was higher in the continuous group with a median of 64 h [IQR (2–100)] vs. 48 h [IQR

TABLE 1. **Baseline characteristics of the study population**

	HC continuous infusion group n = 37	HC bolus group n = 33	*P*
Age, years, median (IQR)	69 (57–77)	70 (62–78)	0.28
Sex (male), n (%)	21 (57)	22 (67)	0.39
Comorbidities, n (%)			
Hypertension	16 (43)	13 (39)	0.74
COPD	11 (30)	10 (33)	0.95
Diabetes	13 (35)	9 (27)	0.47
Chronic renal failure	2 (5)	5 (15)	0.17
SAPS II, median (IQR)*	48 (33–61)	44 (36–54)	0.71
SOFA, median (IQR)*	12 (10–13)	10 (8–12)	0.08
MAP, (mm Hg), median (IQR)*	54 (50–65)	60 (54–71)	0.87
HR, (bpm), median (IQR)*	120 (100–127)	110 (90–123)	0.21
Lactate, mmol/L, median (IQR)*	3 (2.3–5)	3 (2.3–4)	0.33
T0 Cortisol, median (IQR),	265 (188–409)	313 (232–415)	0.28
Community acquired infection, n (%)	21 (57)	19 (57)	0.78
Site of infection, n (%)			0.34
Lung	26 (70)	19 (57)	
Urinary tract	4 (11)	9 (26)	
Vascular	3 (8)	2 (6)	
Abdomen	2 (5)	1 (3)	

*Severity scores were calculated the day of shock and vital signs were measured at the first hour following hypotension.
HC indicates hydrocortisone; HR, heart rate; MAP, mean arterial pressure; SAPS II, The Simplified Acute Physiology Score II; SOFA, Scores on the Sequential Organ Failure Assessment.

(14–107)] in the bolus group, ($P = 0.60$), and daily insulin requirements were similar between the two groups, ($P = 0.63$) (Figs. 3 and 4).

Hypokalemia was observed in 38% of cases in the continuous group versus 58% in the bolus group. This difference was not statistically significant.

There were no other adverse events related to steroids between the two groups (Table 3).

DISCUSSION

In our study, hydrocortisone administered by intermittent bolus during septic shock resulted in higher shock reversal at day 7 compared with a continuous infusion of hydrocortisone. Time to shock reversal was shorter with the bolus administration. Moreover, the modality of administration of hydrocortisone in patients with septic shock did not impact mortality, duration of mechanical ventilation, and length of stay and did not affect the incidence of side effects related to corticosteroids.

The strength of our study lies in its methodology and originality: this is the second randomized controlled trial that compared the hemodynamic effect of two modalities of substitutive corticosteroid administration during septic shock. The main limitations are the limited sample size and the absence of monitoring of nutrition and caloric intake so the effect of the modality of corticosteroids administration on blood glucose and insulin requirements in our patients cannot be accurately assessed.

While the relevance of substitutive corticotherapy during septic shock is well defended by several studies, the modality of administration remains controversial and poorly evaluated. The conference of surviving sepsis campaign (SSC) in 2012 recommended the use of the continuous modality for corticosteroids to avoid glycemic imbalance that would be more common with the discontinuous route (13). This recommendation on the modality of steroid administration is no longer included in the last conference of the SSC in 2016 (8).

Dysregulation of the adrenal response to sepsis-induced stress affects both cortisol production and its use by cells

TABLE 2. **Outcomes**

	HC continuous infusion group	HC bolus group	*P*
Shock reversal at day 7, n (%)			
Intent-to-treat group	13/37 (35)	22/33 (66)	0.008
Per protocol	13/29 (44)	22/29 (75)	0.01
Time from shock to HC initiation, h, median (IQR),	3 (1–12)	3 (2–5)	0.88
Time from ICU admission to randomization, d, median (IQR)	1 (0–5.5)	0 (0–1)	0.20
Mean ± SD	6.3 ± 14.6	5.3 ± 14.4	0.78
Vasopressors-free days, median (IQR)	7 (1.5–12.5)	10 (1.5–18)	0.59
ICU LOS, d, median (IQR)	11 (7.5–30)	16 (10–26)	0.78
Hospital LOS, d, median (IQR)	13 (8–30)	17 (10–32)	0.35
Duration of MV, d, median (IQR)	10 (5.5–25.5)	12 (9–22.5)	0.58
28-d mortality, n (%)			
Intent-to-treat group	24/37 (64)	16/33 (48)	0.25
Per protocol	16/29 (55)	12/29 (41)	0.43

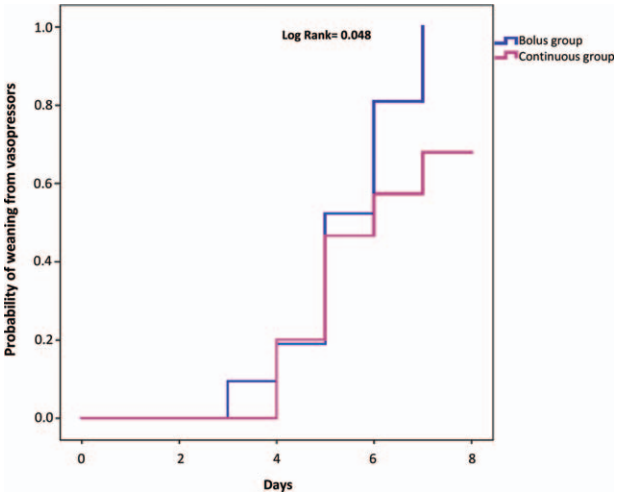

Fig. 2. **Time to weaning from vasopressors.**

(15). Corticosteroids during sepsis have a beneficial effect on resolution of hemodynamic instability compared to placebo (6), while their effect on mortality remains uncertain (16). Corticosteroids can restore blood volume through fluid retention and vascular resistance increase, which subsequently leads to an improvement in cardiac function. On the other hand, the anti-inflammatory and immunomodulating action of steroids helps to prevent the occurrence of organ failure (6).

In agreement with our results, Loisa et al. (11) observed more shock reversal at day 5 in the bolus group (83% vs. 63%, $P = 0.48$) and it was associated with an increase in systemic resistance (1.061 ± 200 vs. 832 ± 214).

Chen et al. (17) found also a significant increase in mean blood pressure after a rapid infusion of hydrocortisone of 200 mg/d compared with a continuous infusion of hydrocortisone.

In a recent study, the impact of the mode of administration of hydrocortisone during septic shock was retrospectively evaluated in 51 patients (9). The modality of administration of hydrocortisone had no impact on shock reversal time (2 days in the bolus group and 3 days in the continuous infusion group, $P = 0.41$) but shock reversal was obtained in a larger number of patients in the bolus group (45% vs. 28%). In these three studies, mortality and length of stay were similar between the two groups.

Unlike our findings, Ibarra-Estrada et al. (10) showed in a prospective observational study that continuous infusion of corticosteroids was significantly associated with shock reversal at 7 days compared to bolus administration (83% vs. 63%, $P = 0.004$) and shock reversal time was slower ($P = 0.001$) in patients in the bolus group. This was related to earlier administration of corticosteroid therapy in the continuous group (Spearman correlation coefficient of 0.80, $P \leq 0.001$).

In a "network meta-analysis" (18) comparing in the included studies, molecules used and steroid administration modalities, comparison of bolus administration with continuous infusion of hydrocortisone showed no difference in shock reversal or mortality. However, this indirect comparison of corticosteroid administration modalities cannot yield conclusions as robust as those given by a direct comparison such as that made by our study.

The high ICU mortality rate in our patients can be explained by the initial severity as shown by the severity score (SAPSII) and the SOFA score, by the high proportion of nosocomial infection, and also by the glycemic imbalance, as a poor glycemic control has been associated with high ICU mortality (19).

Despite the faster drug withdrawal, we did not observe a significant difference in mortality on day 28 between the two groups.

There is no clear data showing a direct relationship between faster drug withdrawal and decreased mortality.

Our results are similar to those of Loisa et al. (11), who evaluated the variation of blood glucose level according to the modality of corticosteroid administration. The goal of blood glucose was lower between 0.72 and 1.26 g/dL and caloric intake was monitored. They found no significant difference in mean glucose and insulin requirements between the two groups. The glycemic target was reached in both groups, unlike our patients who, following the recommendations that opted for the blood glucose threshold at 180 mg/L, remained for almost half the time above this threshold (median at 10 h per day), but Loisa et al. (11) excluded diabetic patients which explains an easier control of glycaemia.

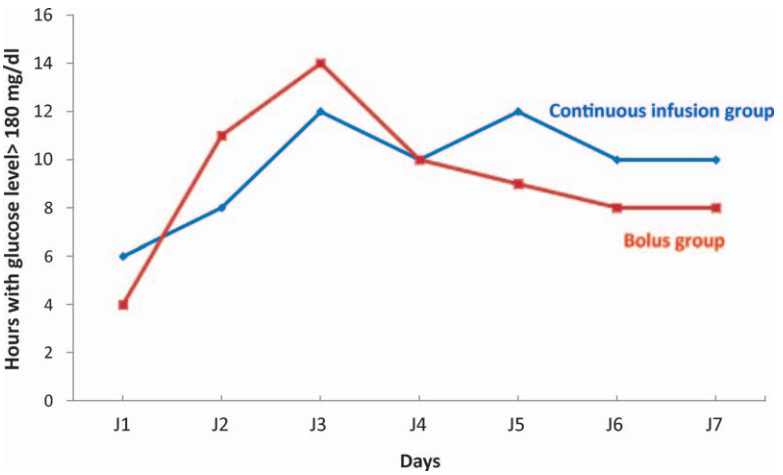

Fig. 3. **Time spent with a glucose level higher than 180 mg/dL (hours).**

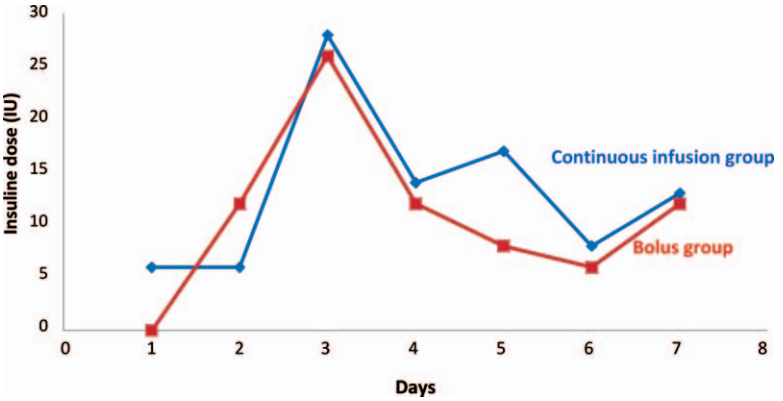

FIG. 4. **Daily insulin requirements (mean).**

TABLE 3. **Adverse events**

	HC continuous infusion group n = 29	HC bolus group n = 29	*P*
New sepsis, n (%)	7 (24)	10 (34)	0.38
New shock, n (%)	2 (7)	5 (18)	0.22
Time with glucose level ≥1.8 g/dL, (h), median (IQR)	64 (2–100)	48 (14–107)	0.60
New onset hypokaliemia, n (%)	11 (38)	17 (58)	0.10
New onset hypernatremia, n (%)	9 (31)	7 (24)	0.55
Hypertension, n (%)	3 (11)	5 (18)	0.44
Gastrointestinal bleeding, n (%)	1 (3)	4 (14)	0.16
ICU-AW, n (%)	7 (24)	4 (14)	1
Delirium, n (%)	2 (7)	2 (7)	1

Other studies found also more episodes of hyperglycemia with bolus of hydrocortisone compared with continuous infusion (9, 12, 17).

Hypokalemia was the most reported complication. None of these episodes of hypokalemia were associated with severe rhythm disturbances.

In the APROCCHSS study (20), the occurrence of adverse events at day 180 was lower with hydrocortisone bolus compared to the placebo group (53% vs. 58%, $P = 0.08$) arguing to the safety of such a treatment especially if it is administered in physiological doses during septic shock and for short periods. In another study (16), the occurrence of more episodes of superinfections in the bolus hydrocortisone group was likely secondary to the longer-term use of corticosteroid therapy (11 days) compared to our study and the APROCCHSS (20).

In conclusion, in our study administration of hydrocortisone by intermittent bolus during septic shock resulted in more shock reversal at Day 7 compared with continuous infusion. Vasopressors withdrawal was faster with bolus administration and mortality were comparable between the two groups.

There was no impact on side effects depending on the method of hydrocortisone administration used. The incidence of hyperglycemia seems unmodified.

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