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New insight of adrenal responses in premature neonates versus full term neonates in critical care setting.

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Abstract

Objectives: This prospective observational study recruited 60 neonates divided into 3 groups (A) 30 critical ill neonates with septic shock on inotropic support, group(B)15 patients with sepsis with no inotropic support and control group (C) (n=15).
Methods: Clinical and laboratory assessment of the neonates for adrenal insufficiency and measuring diurnal ACTH and serum diurnal and nocturnal cortisol level.
Results: Serum cortisol was significantly higher in group A (58.3 ± 24.1) and B (44.6 ± 18.7), while it was lower in group C (15.3 ± 5.1). Group A had lower blood pressure despite higher cortisol level as compared to groups B and C, that was improved after vasopressor drug administration and the full term neonates showed better response to inotropic support as compared to preterm neonates.
Conclusion: Relative adrenal insufficiency occurs in neonate in sepsis and septic shock and it is especially evident among premature babies.

Keywords: NICU, Adrenal, Relative insufficiency, Critically ill, Neonate.

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Introduction

Neonatal sepsis and shock are two of the most serious neonatal morbidities and the leading cause of death in Neonatal Intensive Care Units (NICUs). The attack rate for neonatal sepsis varies from 1 percent to >35% of newborns depending on gestational age and time of onset of sepsis; early onset <72 hours after birth or late onset >72 hours after birth). Septic shock is a fairly common condition. The prevalence of septic shock is approximately 1.3%, with concomitant mortality being as high as 71% for extremely low birth weight neonates [1].

Sepsis is a Systemic Inflammatory Response Syndrome (SIRS) caused by an infection. During sepsis, the body's defence response to noxious stressors such as infection, trauma, surgery, acute inflammation, and ischemia is exaggerated in order to eliminate the source of the insult, which is known as SIRS. SIRS symptoms include a temperature of more than 38°C or less than 36°C, a heart rate of 90 beats per minute, and a respiratory rate of more than 20 per minute, as well as a total leucocyte count of >12 × 10^9/L or >10% immature cells. Sepsis with one or more end organ failures is referred to as severe sepsis. Septic shock is defined as hemodynamic instability in the presence of intravascular volume replacement [2].

While the cytokine storm that occurs in response to bacterial toxins serves a defensive role in SIRS, it can also trigger a massive inflammatory cascade, resulting in reversible or permanent end-organ failure and even death if the infection progresses unabated, especially if patients present late. Proinflammatory mediators reduce the number and sensitivity of catecholamine receptors, and long-term use of exogenous catecholamines causes catecholamine receptor down regulation, catecholamine malfunction, and refractory hypotension [2]. Corticosteroids help reverse this process, which is mediated by an increase in adrenergic receptor transcription [3].

Although absolute adrenal insufficiency is extremely uncommon in critically ill neonates, Relative Adrenal Insufficiency (RAI) is quite common. This is due to deficiency in the Hypothalamic Pituitary Adrenal Axis (HPA) or to glucocorticoid resistance [2]. This validated the poor response to vasopressor medications and the immature hemodynamic compensatory mechanisms [4]. Because of prolonged stress and HPA failure anywhere from the hypothalamus to the adrenals, neonates with sepsis and septic shock have relative RAI. Because of the down regulation of cardiovascular adrenergic receptors caused by chronic stimulation, neonates in sepsis have impaired consciousness, hypoglycemia, hyponatremia, and hypotension that are resistant to fluids and vasopressor therapy.

Because of the down regulation of cardiovascular adrenergic receptors caused by chronic stimulation, these symptoms are very common, lack specificity, and respond to steroids, making AI suspicion critical. Corticosteroids increase catecholamine release from sympathetic cells, restoring the sympathetic effect

of catecholamines on the heart and vessels while also sensitizing tissues to exogenous catecholamine. The magnitude of the secretory pulses differs throughout the day, peaking between 6 am and 8 am quickly declining until noon, and then gradually decreasing until midnight [5].

While absolute adrenal insufficiency can be diagnosed by basal cortisol levels below 4 mg/dL or ACTH triggered levels below 18 mg/dL, relative adrenal insufficiency is difficult to detect due to the lack of a definitive diagnosis, and it is commonly defined as insufficient cortisol response for the patient's level of stress, despite a cortisol level that appears normal. Preterm patients, in particular, have a different adrenal response and exhibit vasopressor resistant hypotension. The study's goal was to demonstrate different cortisol and ACTH levels and their correlation with clinical data from neonates with sepsis and septic shock [6].

Materials and Methods

This was a prospective descriptive case control study that included 60 neonates (gestational age 32-36 weeks) who were admitted to the NICU at Ain shams university hospital from January to June of 2020. The Ethical committee approved the study protocol. Parents or legal guardians of included neonates were asked to provide informed consent.

The sixty neonates were divided into three groups based on clinical and laboratory criteria, with each group further subdivided based on gestational age into preterm and full term. Group A consisted of 30 critically ill patients (15 preterm and 15 full terms) who were clinically and laboratory proven to be in septic shock and required inotropic drugs. Patients in Group A were given either dopamine or dobutamine at a dose of 5-20 mcg/kg/min or noradrenaline at a dose of 0.1 to 0.5 mcg/kg/min.

Group B consisted of (n=15; 9 preterm, 6 full term) patients who had sepsis but did not require inotropic support.

Group C consists of 15 healthy control neonates (8 preterm, 7 full term)

Both cases (Group A, B) and controls (Group C) were sex and age matched.

Inclusion criteria

Sepsis, septic shock, Systemic Inflammatory Response Syndrome (SIRS), hemodynamically unstable neonates, hypotension, and patients needed inotropic support.

Exclusion criteria

Suspected adrenal insufficiency, proven adrenal haemorrhage, ambiguous genitalia, birth asphyxia, congenital heart disease, congenital malformations (such as brain, clinical syndromes, and renal malformations), encephalitis and meningeoencephalitis, cephalic trauma, surgical procedures, postnatal exogenous steroid treatment, antibiotic and steroid administration prior to inclusion, inborn error of metabolism and evidence of maternal adrenal disease. Hypotension is defined as the mean arterial pressure <2 SD for the gestation age [7]. All patients underwent a full history, with an emphasis on maternal illnesses, gestational age, NICU diagnosis, clinical examination, and laboratory investigations.

Laboratory investigations

Routine: complete blood count, CRP, bacterial blood culture and other cultures, random blood sugar, electrolytes.

Specific: Serum cortisol levels the serum cortisol level was determined twice: once in the morning (8-9 am) and once in the evening (8-9.30 pm). Cortisol levels in the blood are measured. On the immulite, an enzyme chemiluminescent technique was used.

Specimen collection: 2 mL of venous blood was drawn and allowed to clot.

The procedure: The Roche cobas e 4111 was used for testing. The materials were provided by ABIA. Germany. Company sera were separated and stored at -20°C. The procedure is based on a solid phase competitive chemiluminescent enzyme immunoassay. The Reagents:

They were supplied by the

- Cortisol test units (100): Each barcode-labeled unit has one head. 1 Kco equals 100 units.
- Cortisol reagent wedge (LCO,) 6.5 mL alkaline phosphatase (bovine calf intestine) conjugated to cortisol in buffer Keep refrigerated and capped.
- Cortisol adjusting hormones (LCOL, LCOH): Cortisol in processed human serum, two 3 mL vials (low and high).

Serum ACTH measurement: done once in the morning (8-9 am).

Cortisol testing units (100): Each unit is labelled with a barcode. Obtaining Samples Instructions: A morning specimen of 5 cc venous blood was collected by vein puncture in a pre-chilled lavender top (EDTA) tube and transported in an ice tube, which was immediately centrifuged and frozen in plastic tubes at -20°C. LAC1 ACTH test units (100 units). Each unit with a barcode contains one bead.

The procedure: The Roche cobas e4111 was used for testing. The materials were provided by EDI. USA. The Roche Adrenocorticotropic Hormone (ACTH) assay is a sandwich electrochemiluminescence immunoassay that uses a biotinylated monoclonal ACTH-specific antibody as well as a monoclonal ACTH-specific antibody labelled with a ruthenium complex. Normal detective value of ACTH test=10-60 pg/ml, cortisol level=5-25 ug/dl

Statistical analysis

Data were gathered, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 20 to be processed as follows: Numbers and percentages were used to represent qualitative data, while mean, standard deviations, and ranges were used to represent quantitative data. Independent t-test was used to compare two independent

groups with quantitative data and parametric distribution. The paired t-test was used to compare two paired groups with quantitative data and parametric distribution. One way Analysis of Variance (ANOVA) was used to compare more than two groups with quantitative data and parametric distribution, followed by LSD post hoc analysis.

The spearman correlation coefficients were used to determine the significance of a relationship between two parameters with quantitative data from the same group. The confidence interval was set at 95%, and the acceptable margin of error was set at 5%. As a result, the p-value was deemed significant as follows:

- P>0.05: Non significant
- P<0.05: Significant
- P<0.01: Highly significant

Results

The Three groups were selected to participate in the current study:

Group A included 30 critically ill patients (15 preterm and 15 full term) who had been clinically and laboratory proven to be in septic shock and needed inotropic drugs.

Group B included (n=15; 9 preterm, 6 full term) sepsis patients who did not require inotropic support.

In three groups, age and gender were matched. In terms of mode of delivery, sex, or age, there was no statistically significant difference between the three groups studied. Table 1 displays additional demographic data.

		Group A septic neonate, hemodynamically unstable (n=30)		Group B septic neonate, hemodynamically stable (n=15)		Group C normal neonate (n=15)		Chi square test
		N	%	N	%	N	%	P value
Mode of delivery	VD	16	53.3%	4	26.67%	7	46.7%	0.23
	CS	14	46.7%	11	73.33%	8	53.3%	
Maturity	PT	15	50%	9	60%	8	53.3%	0.81
	FT	15	50%	6	40%	7	46.7%	
Sex	Males	15	50%	4	26.67%	8	53.3%	0.25
	Females	15	50%	11	73.33%	7	46.7%	

Table 1. Demographic data representation among the included groups.

In terms of sepsis, both groups A and B had significantly higher total leukocytic count, neutrophil count, and CRP than the control group. Both groups A and B had 63.3% and 53.3% positive blood cultures, respectively, with Gram positive *S. aureus* and *E. coli* having the highest proportion of culture yield (25% each). *Klebsiella* proved cultures were found in (3.6%) of patients, after Streptococci and Pneumococci (7.1% each).

Laboratory evaluation of the three studied groups showed that TLC and neutrophils were significantly higher in the cases than in the control group. Also the morning cortisol and ACTH were significantly higher in the cases than in the control group, Table 2.

	Group A septic neonate, hemodynamically unstable (n=30)		Group B septic neonate, hemodynamically stable (n=15)		Group C normal neonate (n=15)		One way ANOVA
	Mean N*	SD%*	Mean N*	SD%*	Mean N*	SD%*	P-value
TLC (10^9/L)	16.3	5.6	12.5	52.5	9	2.5	0.04
Neutrophils (10^9/L)	9.9	4.6	9.8	5.3	4.6	1.8	0.0001
CRP(mg/L)	60.6	28.6	36.8	26.7	-	-	0.1
Blood culture*	19	63.3	8	53.3	-	-	-
Na(mEq/L)	134.4	6.9	136.9	3.8	138	1.8	0.05
K(mEq/L)	4.8	1.03	4.32	0.8	4.1	0.5	0.02
Glucose mg/dl	91.5	19.3	108.3	19.4	104.8	18.1	0.05

Cortisol am (ug/dl)	58.3	24.1	44.61	18.7	15.3	5.1	0
Cortisol pm (ug/dl)	45.3	26.51	29.31	18.6	5.8	3.7	0.2
ACTH am pg/ml	25.8	8.1	15.4	5.1	12.64	2.91	0.001

Table 2. Lab data representation among the included groups. *: Significance of P-value.

Because group A had significantly lower blood pressure than the other two groups (p=0.001), 22 patients (73.3%) were given a double inotropic drug combination of dopamine and dobutamine, while 8 patients received both drugs plus nor-adrenaline. Group A neonates' blood pressure improved but remained significantly lower than the other two groups (p=0.008).

In terms of clinical evaluation, systolic and diastolic blood pressure in groups B and C were nearly equal (p>0.05), but significantly lower in group A. Despite the fact that blood pressure improved after the addition of inotropes (group A), diastolic and systolic pressures were lower than in the other two groups, as shown in Table 3.

Blood pressure		**Group A septic neonate, hemodynamically unstable (n=30)**		**Group B septic neonate, hemodynami cally stable (n=15)**		**Group C normal neonate (n=15)**		**F/Z***	**One way ANOVA**
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**3.4**	**P value**
Before inotropic treatment	Systolic	45.86	6.68	70.1	6.55	72.8	9.7	9.2	0.001
	Diastolic	23.3	4.6	41.7	7.67	41.3	5.8	2.5*	0.001
After inotropic treatment	Systolic	60.6	8.6	70.1	6.55	72.8	9.7	2.21*	0.001
	Diastolic	35.6	5.8	41.7	7.67	41.3	5.8	2.3*	0.002

Table 3. Blood pressure representation among the included groups.

Group A preterm neonates had significantly lower blood pressure before inotropes than groups B and C, and their blood pressure improved significantly afterward.

To compare the responses of premature and full-term babies to vasopressor drugs (group A), 11 preterm neonates were given double inotropic support, while the remaining four were given triple inotropic support. The difference in response to vasopressor drugs between full term and preterm neonates can be seen by improved systolic blood pressure in full term post inotropic support compared to preterm (p<0.05). As a result, full-term babies had a statistically significant increase in systolic blood pressure when compared to preterm patients, Table 4.

Blood pressure			**Group A septic neonate, hemodynamically unstable (n=15)**		**Group B septic neonate, hemodynami cally unstable**		**Group C normal neonate**		**One way ANOVA**
			Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
Preterm neonates	Before inotropic treatment	Systolic	44.6	6.8	68.7	6.9	65.4	8.5	<0.001
		Diastolic	22.9	4.36	39.2	6.9	40.6	4.7	<0.001
	After inotropic treatment	Systolic	57.5	7.6	68.7	6.9	65.4	8.5	0.005
		Diastolic	33.6	4.8	39.2	6.9	40.6	4.7	0.047
Fullterm	Before inotropic treatment	Systolic	48.6	6.4	68.7	6.9	79.4	4.5	<0.001
		Diastolic	24.1	3.4	39.2	6.9	44.6	5.7	0.001
	After inotropic treatment	Systolic	65.3	8.3	73.1	5.9	79.4	4.5	0.02
		Diastolic	37.3	6.5	45.3	7.4	44.6	5.7	0.6

Table 4. Blood pressure representation among the included preterm and full term neonates of the three studied groups.

As a result, full-term babies had a statistically significant increase in systolic blood pressure when compared to preterm patients, Table 4. Cortisol levels were then measured in each of the three groups, and there was a significant difference between cases and controls, indicating that relative adrenal insufficiency can be either quantitative, as shown in the neonates with relative low cortisol levels (mean serum cortisol 19 ug/dl), indicating adrenal exhaustion, or functional, as shown in the neonates with very high cortisol levels.

According to the concept of "tissue resistance," mean serum cortisol levels in preterms (55.2 ug/dl) and full terms (59.3 ug/dl) in group A (septic neonates with inotropic support) showed a significant and highly significant reversed correlation to both systolic and diastolic blood pressure, as shown in Tables 5-7.

Pituitary adrenal axis among the three groups		**Group A septic neonate, hemodynamically unstable**		**Group B septic neonate, hemodynamically stable**		**Group C normal neonate**		**One way ANOVA**
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
Preterm	Cortisol am (ug/dl)	55.2	25.5	50.1	19.5	13.5	5.2	0
	Cortisol pm (ug/dl)	43.4	22.5	33.1	14.7	4.4	1.1	0.02
	ACTH am pg/ml	33.2	22.7	13.4	3.2	15.6	2.9	0.02
Fullterm	Cortisol am (ug/dl)	59.3	23.7	44.7	18.4	15.1	5.1	0
	Cortisol pm (ug/dl)	44.1	26.3	29.3	18.3	5.8	3.6	0.1
	ACTH am pg/ml	25.4	7.8	4.9	5.1	12.5	2.8	0.001

Table 5. Pituitary and adrenal hormonal illustration among the included main groups.

Patients	**Parameter evaluated**	**Mean cortisol level**	
		r	**P value**
Preterm neonate after inotropic support (N=15)	Systolic blood pressure	-0.4	0.03
	Diastolic blood pressure	-0.5	0.006
	ACTH (33.2 pg/dl)	-0.08	0.7
Full term neonate after inotropic support (N=15) Group A	Systolic blood pressure	-0.61	0
	Diastolic blood pressure	-0.07	0.001
	ACTH (33.2 pg/dl)	0.53	0.006

Table 6. Correlation of mean cortisol level with the systolic and diastolic blood pressure among the included preterm and full term neonates of group A.

	Category A				**Category B**		**Category C**		**One way ANOVA**
	Adrenal stimulation				**Reversed rhythm**		**Adrenal exhaustion**		
	Blunted circadian rhythm		**Preserved circadian rhythm**						
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
Cortisol am (ug/dl)	71.1	15.7	70.5	8.3	54.3	10.2	18.1	2.9	0
Cortisol pm (ug/dl)	57.1	17.6	18.1	1.6	64.1	6.1	14.8	3.3	0
ACTH am pg/ml	26.1	15.1	28.9	9.3	27.1	9.1	40.1	26.2	0.4

Table 7. Categorical representation of adrenal hormones secretion of neonates of group A.

ACTH and serum cortisol were poorly correlated with demographic and lab data, with the exception of the reverse correlation between neutrophil count and cortisol level. In group A, the addition of inotropes had no effect on ACTH or cortisol circadian rhythms. Furthermore, no statistically significant difference in serum cortisol and ACTH levels was found between normal preterm and normal full terms.

Discussion

Group A and B had culture for gram negative organisms mainly E coli and klebsiella species. This was supported by Macharashivii et al. and Couto et al. who reported 18%-78% of neonatal sepsis were due to gram negative organism [8,9].

While hypotension was evident in group A before and after inotropic support as compared to the other two groups and the difference was highly statistically significant.

This difference was more evident in premature neonates; indicating a more poor response to vasopressors and immature hemodynamic compensatory mechanisms in preterm neonates. This came in agreement of with Biniwale et al. who described a vasopressor resistance hypotension in preterm neonates [10].

Also Higgins et al. stated that some preterm are either vasopressor resistant and/or dependent due to the relative adrenal insufficiency [11]. This could be explained by the genomic actions of corticosteroids which cause up regulation of receptors and the down regulation thought to be due to RAI.

Other diagnostic clues of RAI include hyponatremia, hyperkalemia and hypoglycemia [12]. In the present study, on monitoring the laboratory clues for adrenal insufficiency, potassium level was statistically higher in group A as compared to the other two groups, this was in concordance with one study who reported a hyperkalemic state in ill preterm presenting with inadequate adrenal insufficiency [13].

The current study, normal neonates (group C) showed a circadian rhythm of an (am to pm) ratio (3:1) in both preterms and full terms, with a range of (3.5-35 ug/dl) in am values and range of (2.9-6.9 ug/dl) in pm values.

On the contrary, Vermes et al. mentioned that diurnal rhythms were still absent in first 2 months [14]. Second, total serum cortisol level shows a highly statistical significant rise in both group A and B together with loss of the recorded rhythm in group C (normal neonates), this was in acceptance of two studies confirmed the normal circadian rhythm of cortisol secretion, that was lost during critical illness [15,16].

Also study done by Asare stated that for critically ill patients, it was not necessary to obtain cortisol levels at a specific time of the day because most patients lose the diurnal variation in their cortisol levels [17].

In the current study it was also found that in group A, a quantitative folding of mean total serum cortisol level together with dysrythmic pattern were detected, categorizing this group into four response patterns.

The studied neonates of group A had different adrenal response, where 50% had high cortisol level with absent rhythm, 16.6% had high cortisol with am to pm ratio of more than 3:1 and this was supported by one study that stated that severe sepstic neonates had cortisol values three fold higher than normal, 10% had reversed rhythm with a pm values higher than am values and 23% had RAI; in this category preterm represents 71%, this came in concordance with Asare who defined RAI as a random cortisol level of less than 25 ug/dl [13,17]. Also one study stated that very preterm neonates had increased risk for cortisol insufficiency in the face of acute illness and stress [8].

The current study found neonates with sepsis had initial activation then exhaustion of the adrenal gland, similarly, many studies mentioned that HPAA is activated, initially leading to increased free cortisol then, the entire axis is exhausted and peripheral cortisol resistance leads to the development of adrenal insufficiency [18-20].

While others reported that an inadequate HPA axis response to stress can aggravated by peripheral resistance to glucocorticoids [21,22].

Many studies believed that a random cortisol level in severely stressed patients (*i.e.* with hypotension) should be above 25 mcg/dl and that higher levels may be appropriate in patients with septic shock due to “tissue cortisol resistance [23,24,9]. Studies recorded that random cortisol value of <15 mcg/dl is considered to be a clear evidence of adrenal insufficiency [13,24,25].

Also Soliman et al. proved that septic term newborns had basal cortisol values of <15 mcg per 100 ml [25]. Many studies reported that prevalence rates of Adrenal Insufficiency (AI) in critically ill patients vary according to the characteristics of the study population and approach as high as 60%-90% [18,26-29].

There was reversed significant correlation between serum cortisol level and both systolic and diastolic blood pressure in preterm and full term of group A.

This finding could demonstrate the intact HPA axis while reflects the resistance at the tissue levels. While we reported a significant correlation between ACTH and serum cortisol in full term ($p=0.007$); the same correlation was not found in preterm group ($p=0.68$).

In the current study, it was concluded that ACTH showed a highly statistically significant rise in group A as compared to the other two groups that indicated either a direct stimulation of the HPA provoked by the septic inflammatory mediators in case of severe sepsis and septic shock (a hypothalamic pituitary dependent mechanism), loss of the normal negative

feedback mechanism (negative feedback block) between the adrenal and pituitary glands, indicating a central resistance of the hypothalamic/pituitary to the adrenal glucocorticoids. A poor adrenal response to ACTH can be also a contributing factor. These factors collectively lead to the creation of a pseudo positive feedback loop between pituitary and adrenals.

The non-significant levels of ACTH in group B reaching (mean=14.17 pg/dl) nearly the normal values in group C (mean=14.1 pg/dl), despite the rise in serum cortisol level (mean=48 ug/dl), indicates that the initial rise m serum cortisol in response to sepsis may occur as "a pituitary independent mechanism" in cases not reaching the septic shock state, or may be in part due to reduction in negative feedback effect of cortisol on hypothalamic pituitary axis (negative feedback block). This was supported by Sharaga et al. who mentioned that although severe stress activates the HPA axis, dissociation may occur between plasma ACTH and cortisol concentrations, as demonstrated by suppressed ACTH and elevated cortisol concentrations [26]. Addingly, a study done by Boonen et al. suggested a pituitary independent mechanism for increased cortisol production during critical illness [30].

In group A, 26.6% neonates received antiepileptic drugs (phenytoin) and 16.6% antifungal (fluconazole) usage was reported. 5/30 (16.6%) received antifungal therapy (fluconazole), 25% of them were preterm and showed a relatively low serum cortisol level, this came in agreement of Kawai et al. that confirmed accelerated metabolism of cortisol and glucocorticoids by inducing hepatic enzymes, and association between high-dose fluconazole and adrenal insufficiency in critically ill patients [31,32].

Conclusion

Septic shock causes a state of relative adrenal insufficiency that contributes to the higher mortality rate. Early steroid measurement and replacement can improve vassopressor resistance and hypotension leading to a better clinical outcome.

Passing through the adrenal gland response in critical situations, an idea about the state of the Hypothalamic Pituitary Axis (HPA) activation behaviour in sepsis and septic shock, where a stage of initial rise occurs in serum cortisol level followed by exhaustion of the adrenal gland. Very high cortisol levels indicates a state peripheral tissue resistance to glucocorticoids, while the relatively low levels indicates a state of an adrenal exhaustion.

Limitations

The small number of prematures involved necessitates additional research involving a larger number of prematures. Further research involving the trial of stress doses of steroids could be very promising.

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