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ADRENAL INSUFFICIENCY AND MORTALITY IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH SEPSIS AND SEPTIC SHOCK AT KENYATTA NATIONAL HOSPITAL
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ADRENAL INSUFFICIENCY AND MORTALITY IN CHILDREN AGED 3 MONTHS TO 12 YEARS WITH SEPSIS AND SEPTIC SHOCK AT KENYATTA NATIONAL HOSPITAL

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ABSTRACT

Background and objective: **Children with sepsis and septic shock may have adrenal insufficiency or an exaggerated cortisol level rise and this factors increase the rate of mortality. We aimed to find out what the mortality rate is in children with adrenal insufficiency and in those with exaggerated cortisol rise. This information would provide a basis of adaptation of the Surviving Sepsis Guidelines to reduce progression of sepsis to septic shock, improve shock reversal and reduce stay in ICU thus improving survival and outcomes.**

Methods: **Hospital based cross sectional study done over three months among children aged 3 months and 12 years at the pediatric outpatient unit, acute rooms of pediatric wards, pediatric ICU and main ICU in Kenyatta National Hospital. Consecutive sampling was done and children who met the inclusion criteria were enrolled into the study. A standard questionnaire was used for data collection and a blood sample taken from each participant for cortisol assay.**

Results: **80 participants were enrolled into the study. 35 died. Two (5.7%) participants who died had low cortisol, 7 (20%) had no rise in cortisol, 3 (8.6) had a normal response in cortisol rise while 23 (65.7%) had an exaggerated rise in cortisol. A significant association between the levels of cortisol and mortality (p= 0.027, Fishers exact test). Mortality was found to be higher in those found to have exaggerated levels of cortisol (p-value 0.007).**

Conclusion: **Mortality associated with exaggerated cortisol levels. Adrenal insufficiency had no impact on mortality rate.**

INTRODUCTION

Sepsis and septic shock is a leading cause of pediatric mortality globally and more likely in low and middle income countries. (6,7) In KNH, about 15% of admitted patients had sepsis and septic shock. (8)

The hemodynamic response in patients with sepsis and septic shock is linked with the functioning of the Hypothalamic- Pituitary-Axis (HPA). Cortisol levels are expected to rise when one has sepsis or is in septic shock. In critical illness this rise may not happen due to a dysfunctioning Hypothalamic-pituitary axis.

Adrenal Insufficiency is an endocrine disorder that occurs when the adrenal glands don't produce enough hormones, primarily cortisol. With sepsis and septic shock about 30-60% of these critically ill patients, have low baseline cortisol levels. (10,11) They are unable to maintain or mount an appropriate response to sepsis with an inadequate production of cortisol in relation to increased demand during stress periods.

Low base line cortisol levels of 275nmol/l or a cortisol rise of <248nmol/l in response to 250ug ACTH (ACTH Stimulation test) defines adrenal insufficiency. (1) Lack of rise in cortisol levels in critically ill patients is referred to as relative adrenal insufficiency.(1) It has also been shown that absolute or relative adrenal insufficiency in children, may contribute to development of catecholamine resistant shock (10) , increasing the risk of death in these patients. Levi-Shraga et al reviewed the prevalence, diagnosis and therapeutic approach to adrenal insufficiency in critically ill children. (1)

The mortality rate varies patients who have sepsis or septic shock based on the observed response to stress as measured by cortisol levels. The prognosis in patients with relative adrenal insufficiency is lower. It has also been shown that even though high concentrations of cortisol are normal during stress periods, concentrations >938nmol/l are predictors of mortality.(1,2).

The Survival Sepsis Guidelines (SSG) state that in children with fluid – refractory shock, catecholamine resistant shock and suspected or proven absolute/ relative adrenal insufficiency, hydrocortisone is indicated thus reducing death from absolute adrenal insufficiency, progression of sepsis to septic shock and enhance or improve reversal of septic shock which occurs within 8 hours of presentation. (5) The rationale behind this suggestion is that approximately 25% of children with septic shock have absolute/ relative adrenal insufficiency shown by cortisol levels. (2–4)

There is a gap locally in regard to how many critically ill children present with adrenal insufficiency, how to investigate for it and the impact on outcome. This study aims to fill this gap and looks to improve the outcomes of children with sepsis and septic shock.

METHODOLOGY

Study setting and design: Hospital Based Cross-Sectional study. Patients aged 3 months to 12 years with sepsis or septic shock from Kenyatta National Hospital at the pediatric emergency clinic, acute rooms of pediatric wards, the pediatric intensive care unit and the main ICU.

Sample size determination and sampling: The Sample size was determined using the Fisher's Formula. [n = z2p (1-p)/d2]. n = estimated minimum sample size, z = standard normal deviate for 95% confidence interval (= 1.96), p = Percentage with adrenal insufficiency (30%) (10–11) and d= degree of precision was taken at 10%.

n= (1.96*1.96)0.3(1-0.3) = 80.6
0.1*0.1

Study sample of 85 was taken.

Sampling: Consecutive screening, enrollment and sampling was done till desired sample size reached. Participants identified and enrolled into the study, assigned a study number and blood samples taken between 7.00am and 10.00am within 48 hours of admission by the primary investigator and a research assistant.

A potential confounder is that majority of these children are from low socioeconomic status with some already having pre-existing chronic malnutrition or suffered infections such as Tuberculosis which can result in adrenal insufficiency. Since majority of children were from the same category, we did not think it had an impact on study outcomes. We also did not include children with malnutrition or active tuberculosis into the study. Consecutive sampling can introduce a self-selection bias in this study. Parents/guardians who were better educated may have been easier to select due to ease of communication. To avoid this bias, questionnaires were administered in Kiswahili.

Data Collection Tool: A standardized questionnaire was used for collecting data from the enrolled participants and the time of admission. The questionnaire included independent variables such as patient's demographic data; clinical signs and symptoms of sepsis and septic shock. The outcome variables were levels of cortisol and death/survival at 72 hours and 5 days. Blood samples were collected for estimation of cortisol levels. The measured and assessed clinical signs for initial recognition of sepsis and septic shock were done by the investigator.

Case definition of septic shock:

1. Suspected sepsis (suspected infection with SIRS) manifested by:

a) Abnormal core temperature: >38.5 °C or <36 °C.

With one or both of the following SIRS signs (b or c)

b) Tachycardia (age dependent)

c) tachypnoea (age dependent)

AND

2. Signs of altered perfusion (all signs have to be present)

a) Reduced or altered consciousness (GCS)

b) Capillary refill time - >2second or <1 second

c) Pulse- weak, thready, absent or bounding.

d) Extremities-cold, mottled or flushed.

Study Personnel: Principal investigator: Supervisor whose role was to ensure proper procedures; data collection and recording was done in the questionnaire for all enrolled participants. Ensured all materials needed were available and all data collected computed every 72 hours. One research assistant, a clinical officer, assisted in data collection following training, under supervision.

Study variables:

Blood Sample collection for Cortisol levels

Equipment required for sample collection was put together for easy reach and maintenance of sterility. Person collecting the sample put on gloves, cleaned area of sample collection using sterile cotton and spirit, sample was then collected at one ml and put in a red vacutainer. A pressure bandage was then placed on the area to ensure that there was no bleeding. The sample bottle was labeled appropriately and attached to appropriately filled lab request form. Samples were transported by foot at room temperature to the KNH lab for analysis. Time of sample collection was recorded in the

questionnaire. Level of cortisol analyzed was recorded.

In-hospital Outcome

Within 72 hours and 5 days of admission was recorded in the questionnaire.

i) The enrolled patient was identified as survived or died.

ii) The time of death in hours from the time of admission was recorded.

Statistical Analysis: Quantitative data was carried out using STATA 14 software. Means with standard deviations calculated for normal distribution and skewed data expressed in terms of medians with interquartile ranges (IQR). Frequency and percentages were calculated for categorical variables. P-value of <.005 was considered statistically significant.

Ethics, Consent, And Permissions: A comprehensive explanation of the study was given to each parent/guardian. Written consent in English/Kiswahili was then signed by the parent/guardian or an assent by the child aged 8-12 years to participate in the study. Participant information was and is being handled with strict confidentiality. Electronic databases are password protected with the principal investigator. Before carrying out the study, the principal investigator ensured approval from the KNH Ethics Research Committee to carry out the study at KNH (P398/06/2018).

RESULTS

A total of 85 patients were enrolled into the study. 85 questionnaires were filled, and 85 samples collected. Of these, a total of 80 valid questionnaires were used in data analysis while 5 were not used due to missing data.

Sociodemographic characteristic of study population

Males were 51 (63.8%) while females were 29 (36.3%). More infants were enrolled into the study at 44 (55%) while older children more than 5 years of age were least at 5 (6.3%). The median age was 11.5 months with an inter-quartile range of 7-24 months. Children admitted directly from home were 44 (55%) while those referred to KNH from other health facilities were 36 (45%).

Table 1

Socio-demographic data for participants

CHARACTERISTIC	TOTAL FREQUENCY (N=80)	SEPSIS n = 43 (53.75%)	SEPTIC SHOCK n = 37 (46.25%)
Age (months)			
3 – 12	44 (55%)	20(46.51%	24(64.86%
>12- 59	31 (38.75%)	18(41.86%	13(35.14%
>59	5 (6.25%)	5 (11.63%)	0 (0%)
MALE	51 (63.75%)	32(74.42)	19(51.35)
FEMALE	29 (36.25%)	11(25.58%	18(48.65%
Self-referral	44 (55%)	27(62.79%	17(45.95%
Referred	36 (45%)	16(37.21	20(54.05%)
Underlying illness			
Severe pneumonia	31 (38.75%)	21(48.84)	10(27.02)
Meningioencephalitis	9 (11.25%)	2(4.65)	7(18.92)
meningitis	13 (16.25%)	9(20.93)	4(10.81)
malaria	3 (3.75%)	2(4.65)	1(2.7)
Acute kidney injury	4 (5%)	3(6.98)	1(2.7)

Urinary tract infection	5 (6.25%)	3(6.98)	2(5.41)
Gastroenteritis(G/E)	4 (5%)	0(0)	4(10.81)
S.Pneu/G/E	6 (7.50%)	2(4.65)	4(10.81)
Meningitis/G/E	2 (2.50%)	0(0)	2(5.41)
others	3(3.75%)	0(0)	3(8.12)

Most participants 31 (38.8%) had a diagnosis of severe pneumonia leading to sepsis or septic shock. The next most common conditions were meningitis 13 (16.3%), meningio-encephalitis 9 (11.3%) and those with co-morbid conditions like severe pneumonia with gastroenteritis as shown on the table above had a more severe disease pattern.

Initial clinical signs of children diagnosed with sepsis and septic shock

The participants were stratified to either have sepsis or septic shock. Of the 80 participants, 37 (46.3%) were diagnosed to have septic shock and 43 (53.75%) had a diagnosis of sepsis. Figure one below shows that of these, 27 (77.1%) with septic shock died while 8 (22.9%) who had sepsis died at day 5.

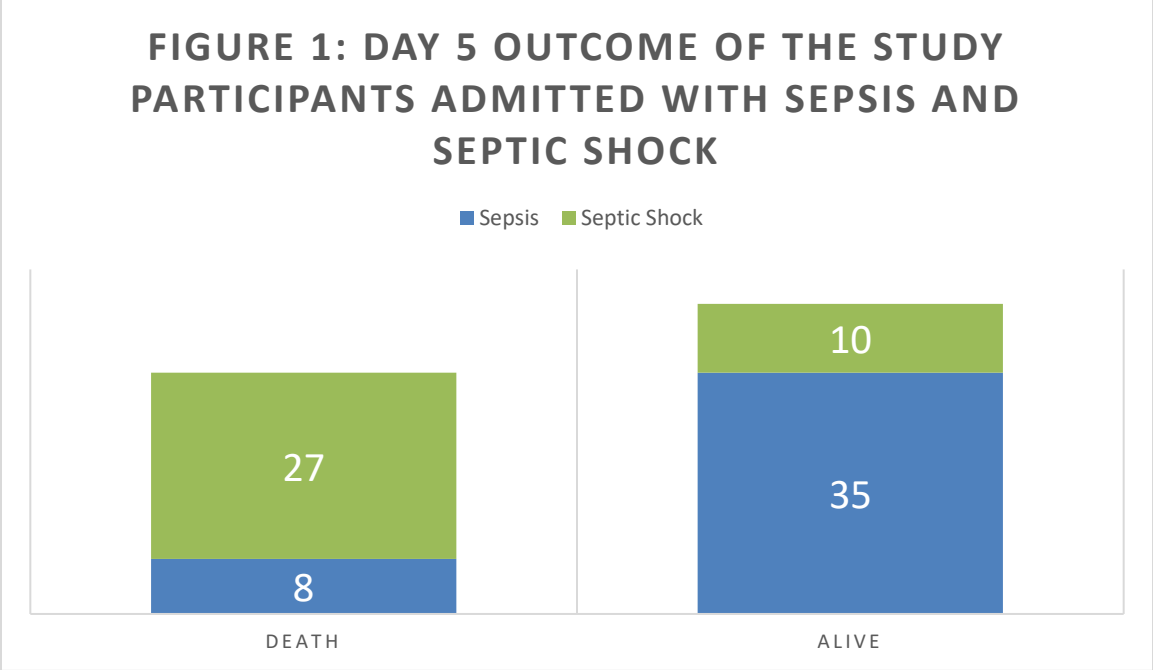

Table 2

Clinical characteristics of participants

CHARACTERISTICS	**Overall FREQUENCY among those who died**	**PATIENTS WHO DIED N=35**		**P -chi-square/ Fischer's**	**Overall FREQUENCY among those who survived**	**Patients who survive N=45**		**P -chi-square/ Fischer's**
		SEPSIS N=8	SEPTIC SHOCK N=27			SEPSIS N=35	SEPTIC SHOCK N=10	
Outcome at day 5								
Died	35 (43.75%)	8 (22.9%)	27 (77.1%)		45 (56.2%	35 (77.7%)	10 (28.6%)	
Hours since admission								
<24 >24 – 48 >48 – 72 >72 – 96 >96 – 120	8 (10%) 11 (13.75%) 10 (12.50%) 3 (3.75%) 4 (5%)	1(30%) 3(27.3%) 1(10%) 2(66.7%) 1(25%)	7(70.0%) 8(72.7%) 9(90.0%) 1(33.3%) 3(75.0%%)	0.303		35 (79.6%)	10 (20.4%)	0.222
Cortisol Levels								
Low (A.I) (<275nmol/L) Normal (RAI) (275-772nmol/L) Normal Response (772-938nmol/L) High levels (>938nmol/L)	2 (5.71) 7 (20%) 3 (8.57%) 23 (65.71%)	0(0%) 3(42.9%) 2(66.7%) 3(13.0%)	2(100%) 4(57.1%) 1(33.3%) 20(87%)	0.075		3(75%) 12(85.7 %) 9 (75%) 11(73.3 %)	1(25%) 2 (14.3%) 3 (25%) 4 (26.7%)	0.876
Self-referral Referred	14 (40%) 21 (60%)	2(14.2%) 6(28.6%%)	12(85.7%) 15(71.4%)	0.324		25(71.4 % 10(28.6 %	5(50%) 5(50%)	0.205
Male Female	20(57.14%) 15(42.86%)	5(6.25% 3(3.75%)	15(75% 12(80%)	0.527		27(77.1 % 8 (22.9%)	4(20%) 6 (60%)	0.035
Age (months)								
3 – 12 >12 – 59 >59	25(71.43%) 10(28.57%) 0(0%)	6(24.0%) 2(20.0%) 0(0%)	19(76.0%) 8(80.0%) 0(0%)	0.589		14(73.7 % 16(76.2 % 5 (100%)	5 (26.3%) 5 (23.8%) 0	0.685
Initial Diagnosis								
S. PNEUMONIA M.E MENINGITIS MALARIA	12(34.28%) 6(17.14%) 5(14.29%) 1(2.86%)	4(25%) 1(1.25%) 3(60%) 0(0%)	8(75%) 5(83.3%%) 2(40%) 1(100%)	0.756		17(89.5 % 1 (33.3%)	2 (10.5) 2 (66.7%) 2 (25%) 0	0.027

AKI	1(2.86%)	0(0%)	1(100%)			6 (75%)	0	
UTI	1(2.86%)	0(0%)	1(100%)			2 (100%)	1 (25%)	
G/E	2(5.71%)	0(0%)	2(100%)			3 (100%)	2 (100%)	
S.PNEU/GE	4(11.43%)	0(0%)	4(100%)			3 (75%)	0	
MENING/GE	1(2.86%)	0(0%)	1(100%)			0	1 (100%)	
OTHERS	2(5.71%)	0(0%)	2(100%)			3 (100%)	0	
						0		
						0		

Table 2 above shows that most of the participants who died before 24 hours of admission had a more severe disease than those with sepsis. Higher cortisol levels were associated with more deaths at 23 of the 35 participants who died (65.7%) and of these 87% had more severe disease. More died from the younger age group of 3-12 months 25(71.4%).

Mortality compared to the older groups. Those referred from other facilities also had a higher mortality rate at 60% compared to 40% of those who were not referrals. These participants also presented with more severe disease (septic shock) with 15 participants (71.4%) of the 21 referred participants who died.

Table 3

Factors associated with death

FACTORS	**DEATH**	**SURVIVED**		
Hours since admission				
<24	8	72		
>24-48	10	62		
>48 -72	10	52		
>72-96	3	49		
>96 - 120	4	45		
	Death (n=35)	Survived (n=45)	OR (95%CI)	p-value
Age (months)				
3 – 12	25	19	1.0	
12-59	10	21	0.36(0.1,0.9)	0.04
>59	0	5	Not calculatable	
Cortisol level (nMol/L)				
< 275	3	7	1.0	
275-772	8	15	0.80 (0.15-4.09)	0.792
772-938	1	7	3.00 (0.21-41.38)	0.388
>938	23	16	0.29 (0.06-1.41)	0.105
Cortisol level as a binary value				
>938nmol/l	23(65.71%)	16(35.56%)	3.47(1.4,8,8)	0.007
<938nmol/l	12(34.29%)	29(64.44%)	1	
Sepsis	8	35	1	
Septic shock	27	10	11.8 (4.1,34.0)	<0.0001

REFERRED	21(60%)	15(33.33%)	3 (1.2,7.5)	0.017
NOT REFERRED	14(40%)	30(66.67%)	1	
Clinical Condition				
Severe pneumonia	12	19	1.26 (0.43-3.65)	0.661
Meningoencephalitis	6	3	0.40 (0.07-2.04)	0.255
Meningitis	5	8	1.28 (0.32-5.03)	0.720
All other conditions	12	15	1.0	

In table above, of the 80 participants, 45 (56.3%) survived at the end of 5 days from admission and that 35 (43.8%) died by the end of 5 days from admission. Eight (18.6%) had a diagnosis of sepsis while 27 (72.98%) had a diagnosis of septic shock. A fishers test to determine the likelihood of a child dying diagnosed with septic shock verses sepsis alone yielded a p-value <0.001, with an OR of 11.8. Two (5.7%) of the participants who died had low cortisol levels, 7 (20%) had no rise in cortisol levels, 3 (8.6) had a normal response in cortisol level while 23 (65.7%) had an exaggerated rise in cortisol levels. There was a significant association between the levels of cortisol and mortality (p= 0.027, Fishers exact test).

The prevalence of mortality in those with cortisol levels above 938nmol/l was at 65.7% (95% confidence interval 48.3-79.7) and those with levels below 938nmol/l had a prevalence of 34.3% (95% confidence interval 20.26-51.71). An association between cortisol levels >938nmol/l and mortality gave a p- value of 0.007 and an OR of 3.47(1.4,8.8).

Eight (10%) died within 24 hours, 11 (13.8%) within >24hr - 48 hours, 10 (12.5%) within > 48hr – 72 hours, 3 (3.6%) died within >72hr – 96 hours and 4 (5%) died within >96hrs- 120 hours of admission. Of those who died, 14 (40%) were admitted to KNH directly from home while 21(60%) were referrals from other health facilities to KNH. Chi test run here to determine if referrals had an impact on outcome particularly mortality, a value of 5.65 with a p value of 0.017 was found. Children diagnosed with severe pneumonia as their main illness had the highest mortality at 34.3% OR 1.26(C. I 0.43-3.65).

A multi – variate analysis to show significant variables against outcomes was done. A diagnosis of septic shock showed an Odds ratio of 11.8 (C.I 4.1-34.0) with a P-value of <0.0001. Referral from other facilities was associated with mortality (Odds ratio of 3, C.I 1.2-7.5) and a P- Value of 0.017. Age of <12 to <59 months was similarly associated with mortality (Odds ratio of 5.6 (C.I 1.15 -27.0) with a P-Value of 0.032.

DISCUSSION

We found that about 46.25% were diagnosed to have septic shock. This is higher than what was found in a recent study done in KNH showing a prevalence of septic shock at 15%. This can be attributed to the fact that during this study all cases of septic shock were recognized early by the primary clinician and the primary investigator which was not the case in the previous study on prevalence of septic shock at KNH.(9) In the previous study on prevalence of septic shock, about 44% of cases with septic shock were missed by admitting clinician.

Most of the children admitted with critical illness were infants and a diagnosis of septic shock decreased with increase in age. This can be attributed to low immunity in infants, which predisposes them to infections as compared to the older age groups.

The most prevalent underlying condition or co-morbidity was found to be severe

pneumonia. Severe pneumonia is one of the five major causes of infant mortality in developing communities. We found that nearly 33% of our study population had adrenal insufficiency. This is similar to other studies done globally. Dubey A, Boujoukos et al (11) and Menon K et al (10) showed that adrenal insufficiency is seen in about 30-60% of critically ill patients.

About a third of the patients with adrenal insufficiency had a diagnosis of septic shock. We suspect that this is because the patients are unable to mount an appropriate response to illness and thus would progress faster to septic shock. These patients would be candidates for an infusion of hydrocortisone, in an attempt to replicate the physiological circadian rhythm thus enabling patients to mount an appropriate response to illness and reduce progression of sepsis to septic shock, reverse septic shock faster and prevent catecholamine resistant shock secondary to adrenal insufficiency (12,13)

A normal expected cortisol rise was found in less than a third of the study population. More of these patients had a diagnosis of sepsis and statistically, normal levels of cortisol did not have an association with diagnosis or mortality. Exaggerated cortisol level rise was seen in slightly less than half of the study population. Most of these patients had a diagnosis of septic shock. We found that higher cortisol levels were associated with a more severe diagnosis septic shock.

Slightly less than half of the study population died. This is a high mortality rate, though it was less than what has been found in previous local studies. (9). This could be attributed to early recognition of sepsis and septic shock by primary clinician thus permitting for early intervention which would potentially reduce loss of patients. However, mortality in those who had septic shock was slightly higher than what has been found locally. (8). Although there was early recognition of septic shock, there is inadequate care given to these patients thus increasing the risk of mortality. Kenyatta National Hospital's PICU, has a 5-bed capacity. This is inadequate and many children were therefore not able to get access to ICU care. Proper care of patients with septic shock would reduce mortality.

About a third of the patients with adrenal insufficiency died. Of these, two thirds had a diagnosis of septic shock. In our study, we found that statistically, a low level of cortisol did not have an impact on mortality. This is contrary to what was found in previous studies that found a high mortality rate being associated with adrenal insufficiency.

Exaggerated cortisol level rise, >938nmol/l has been associated with mortality. (1). We found that those patients that had an exaggerated cortisol rise, had a high mortality rate, where more than half died.

Children admitted directly from home were more than those admitted at the KNH as referrals from other health facilities. This was not expected given the fact that KNH is a tertiary hospital, and it would be expected that more children would have been admitted as referrals from other health facilities. We found that mortality was also independently predicted by severity of the condition and referral status of the child. A child was more likely to die if diagnosed to have septic shock and a child who was referred into KNH was more likely to die.

A multi - variate analysis of the several variables - cortisol level, age, diagnosis, referral status - against mortality showed that age of >12 - <59, a diagnosis of septic shock and having been referred were associated with a higher risk of mortality. Cortisol levels did not have a statistically significant impact on mortality. We attribute the reason for higher

mortality in the age group of >12 - <59 to be that care givers tend to wait till the child is sicker to seek care.

Limitations

Determining factors surrounding referral and time of referral was difficult due to missing information.

CONCLUSION

Adrenal insufficiency was found in 33% of the participants. Mortality higher in those who had an exaggerated response in cortisol level rise. Referral status and a diagnosis of septic shock increased chances of a participant dying.

RECOMMENDATION

1. A cortisol level taken between 7.00 am and 10.00am may be used to determine which patients have adrenal insufficiency during critical illness.
2. 33% of the population studied had adrenal insufficiency. With this information, this could pave way for further studies on the use of hydrocortiosone, with caution to find out if this would benefit children and reduce morbidity.

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