

# Pediatric Adrenal Insufficiency (Addison Disease in Children): Pathogenesis and Management Strategies: Systematic Review

<sup>1</sup>ALSHAMRANI, MOHAMMED DAIL A, <sup>2</sup>ALSULAIMI, ABDULLAH MATAR M

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**Abstract:** Septic shock is a major cause of death in adult and pediatric intensive care units <sup>(1)</sup>. In this regard, the function of corticosteroid treatment in the management of septic shock has been extensively disputed for many years. Recently, private investigators have actually reported hemodynamic and survival advantages associated with the use of more physiologic steroid replacement treatment in adult patients with relative adrenal insufficiency and vasopressor-dependent septic shock .

Adequate adrenocortical function is important to endure vital health problem, and a lot of critically ill patients display an elevated plasma cortisol level, showing activation of the pituitary-adrenal-axis, which is thought about to be a homeostatic adjustment. Over the past years, private investigators have actually found that numerous adults with vasopressor-dependent septic shock have elevated cortisol levels however a depressed reaction to stimulation with 250 g of corticotropin (cortisol increment 9 g/ dL) . This state of "relative" adrenal deficiency is identified by an inadequate production of cortisol in relation to an increased need during periods of extreme tension. However, the occurrence, significance, and restorative method to adrenal insufficiency in critically ill children are less understood than in adults .

A short corticotropin test (250 g) was performed, and cortisol levels were measured at standard and 30 and 60 minutes posttest. Adrenal deficiency was specified by an action <9 g/dL. Outright adrenal insufficiency was further specified by a standard cortisol <20 g/dL and relative adrenal insufficiency by a baseline cortisol ><20 g/dL and relative adrenal deficiency by a baseline cortisol > 20 g/dL. Absolute adrenal deficiency was observed in 18%of children, all of whom had catecholamine-resistant shock. Relative adrenal insufficiency was observed in 26% of children, of whom 80%had catecholamine-resistant and 20 %had dopamine/dobutamine responsive shock. All children with fluid-responsive shock had a cortisol action > 9 g/dL. Children with adrenal insufficiency had an increased danger of catecholamine-resistant shock (relative risk, 1.88; 95% self-confidence interval, 1.26-2.79). Nevertheless, mortality was separately predicted by persistent disease or multiple organ failure (p <.05), not adrenal deficiency.

Relative and outright adrenal deficiency is common in children with septic shock and might contribute to the development of catecholamine-resistant shock; to puts it simply, it is related to an increased vasopressor requirement. However, doubts still continue regarding the efficacy of replacement treatment with low- dose steroids in children with catecholamine-resistant septic shock, and further studies are had to identify whether treatment of such patients changes morbidity and/or mortality .

**Keywords:** pediatric intensive care units, Septic shock, Addison Disease in Children.

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## 1. INTRODUCTION

Septic shock is a major cause of death in adult and pediatric intensive care units <sup>(1)</sup>. In this regard, the function of corticosteroid treatment in the management of septic shock has been extensively disputed for many years. Recently, private investigators have actually reported hemodynamic and survival advantages associated with the use of more physiologic steroid replacement treatment in adult patients with relative adrenal insufficiency and vasopressor-dependent septic shock <sup>(2, 3)</sup>.

Adequate adrenocortical function is important to endure vital health problem, and a lot of critically ill patients display an elevated plasma cortisol level, showing activation of the pituitary-adrenal-axis, which is thought about to be a homeostatic adjustment. Over the past years, private investigators have actually found that numerous adults with vasopressor-dependent septic shock have elevated cortisol levels however a depressed reaction to stimulation with 250 g of corticotropin (cortisol increment 9 g/ dL) <sup>(2)</sup>. This state of "relative" adrenal deficiency is identified by an inadequate production of cortisol in relation to an increased need during periods of extreme tension. However, the occurrence, significance, and restorative method to adrenal insufficiency in critically ill children are less understood than in adults <sup>(4,5)</sup>.

Hatherill et al. <sup>(6)</sup> and Menon and Clarson <sup>(7)</sup> studied the occurrence of adrenal insufficiency in seriously ill children. Hatherill et al. reported that 33 children with septic shock had a 52% incidence of adrenal deficiency with an increased inotrope and vasopressor requirements however no increase in mortality compared with those without adrenal insufficiency <sup>(6)</sup>. Menon and Clarson reported a 31% incidence of adrenal insufficiency in 13 seriously ill children <sup>(7)</sup>. In the present research study, we administered a brief corticotropin stimulation test to children with septic shock to determine the incidence of relative and outright advertisement renal deficiency and to examine the relationship of adrenal function to the advancement of catecholamine-resistant shock and outcome.

The main objective of this meta-analysis is to state that Corticosteroid replacement improves result in adults with relative adrenal deficiency and catecholamine-resistant septic shock. We assessed the relationship of outright and relative adrenal deficiency to catecholamine-resistant septic shock in children.

## 2. METHODOLOGY

We performed a systematic review of literature on May 25, 2016 and updated the search on September 10, 2016. We searched keywords (A) septic shock; (B) sepsis; (C)adrenal insufficiency ; (D)corticosteroids ; (F) corticosteroids ;(G)cortisol ;(E)shock in PubMed (National Library of Medicine), Google-Scholar, Scopus, and Web of Knowledge databases. An article was considered to be eligible for inclusion if it met the following criteria: (A) clinical PDT application; (b) English language. Review articles were excluded. A total of 20 papers were included in this review.

## 3. RESULTS AND DISCUSSION

We registered 57 children with septic shock into the research study. Their typical age was 27.0 months (variety, 1-213 months), and their gender distribution was 60% female and 40% male. Persistent disease was present in 74% of patients, and the most regular diagnosis was oncologic (16%) followed by hepatic (14%) and neurologic (11%) diseases. Overall death was 39%, with death being 0% (n 0 of 8) in fluid-responsive shock patients, 17% (n 2 of 12) in dopamine/dobutamine-responsive shock patients, and 54% (n 20 of 37) in children with catecholamine-resistant shock (p. 05). The specific fluid, inotrope, and vasopressor requirements in these patients are summed up in Table 1.

**Table 1. Fluid resuscitation (mL/kg) and inotrope and vasopressor dosage ( g/kg/min) given to patients with sepsis or septic shock**

Variable	No. of Patients	Median	Range
<b>Fluid requirement, mL/kg</b>			
<b>Fluid-responsive shock</b>	8	50	10-120
<b>Fluid-refractory shock</b>	49	60	20-120
<b>Inotrope and vasopressor requirement, g/kg/min</b>			
<b>Dopamine</b>	42	12.5	5.0-20.0
<b>Dobutamine</b>	28	10.0	5.0-22.0
<b>Epinephrine</b>	8	1.5	0.8-5.0
<b>Norepinephrine</b>	21	0.9	0.1-0.4

The incidence of adrenal deficiency in our research study population was 44% (95% confidence period, 31.1%-56.9%) as defined by an action 9 g/dL posttest. Table 2 reveals the occurrence of adrenal insufficiency in our population when using six different sets of requirements published in 6 previous studies. Using these requirements, the incidence of adrenal insufficiency in our population varied from 9% to 44%.

The occurrence of absolute adrenal insufficiency was 18%, and the incidence of relative adrenal insufficiency was 26% (Table 3). The standard and peak post corticotropin stimulation cortisol levels are summed up in Table 3. The clinical qualities of the patients in the four adrenal function groups are shown in Table 3. There were no substantial differences in serum potassium, sodium, and glucose levels. There was no distinction in duration of positive-pressure ventilation, shock, or length of remain in the PICU; however, there were considerable distinctions in the age and multiple organ system failure rating during the PICU stay amongst the 4 groups. With regard to infection, the following microorganisms were separated in cultures (including blood, urine, pleural, and ascitic fluid): Gram-positive, 21% (n 12); Gram unfavorable (besides Neisseria meningitidis), 14% (n 8); fungi, 9% (n 5); and mixed representatives, 16% (n 9).

All children with fluid responsive shock had a corticotropin action 9 g/dL. Chi-square test for pattern revealed a substantial association in between inotrope/vasopressor requirement group and adrenal function group . Integrating groups 2 and 3-4, the relative threat of catecholamine-resistant shock was 1.88 (95% self-confidence interval, 1.26-2.79) for groups 1-2 compared to groups 3-4 (p 0.01). Stepwise regression analysis revealed that adrenal dysfunction (corticotropin reaction <9 ug/dL) and numerous organ failure separately predicted catecholamine resistant shock (p. 05). Chi-square test for trend was not substantial in between adrenal function group and mortality . Combining groups 1-2 and 3-4, the relative threat of death was not significant (1.72, 95% confidence period, 0.97-3.06) for groups 1-2 when compared with groups 3-4 (p. 12). Univariate analysis revealed that chronic disease, multiple organ system failure, and catecholamine-resistant shock forecasted death (p. 05). Step-by-step regression analysis showed that persistent health problem and numerous organ failure at ad- objective, not adrenal dysfunction (relative and absolute adrenal insufficiency), predicted outcome (p. 05).

Absolute and relative adrenal insufficiencies were both typical in children with catecholamine-resistant shock. Three indirect lines of proof assistance, however do not prove, the possibility that advertisement- kidney dysfunction contributed in part to the development of catecholamine- resistant shock in our patients. First, all the children with fluid-responsive shock had a typical adrenal response to corticotropin. Second, there was an independent association between the failure to install a 9 g/dL cortisol response to the brief corticotropin stimulation test and the advancement of catecholamine-resistant shock. Third, all patients with outright adrenal insufficiency had catecholamine resistant shock<sup>(12-15)</sup>.

**Table 2. Incidence of adrenal insufficiency in our study population and the according to the various published definitions**

Adrenal Insufficiency Definitions		Adrenal Insufficiency Incidence	
Author (Yr)	Cortisol Level ( g/dL)	According to Literature, %	In Our Study Population, %
Rothwell <i>et al.</i> (1991)	Increment 9 after ACTH stimulation test	40	44
Hatherill <i>et al.</i> (1999)	Increment 7,5 after ACTH stimulation test	52	37
Soni <i>et al.</i> (1995)	Cortisol 18 after ACTH Stimulation test	24	9
Marik & Zaloga (2001)	Baseline cortisol 25 and peak cortisol 25	61	28
Loisa <i>et al.</i> (2002)	Baseline cortisol 25 and increment 9	15	21
Menon & Clarson (2002)	Baseline cortisol 7 or cortisol 18 after ACTH stimulation test	31	9

There are no recognized and accepted requirements to define adrenal deficiency in seriously ill patients. The specified incidence of adrenal insufficiency in our population differs according to exactly what set of released requirements are used. It could be as low as 9% and as high 44% according to these research studies<sup>(6, 7, 16-19)</sup> (Table 2). The criteria we have utilized, taking into consideration a cortisol reaction 9 g/dL, appear to be the most inclusive<sup>(2, 16)</sup>. We embraced a cortisol cutoff prior to and after corticotropin stimulation test of 20 g/dL (550 nmol/L)<sup>(20-22)</sup>.

The rapid corticotropin stimulation test is extensively utilized as a simple technique to identify adrenocortical hypo-responsiveness, but there is an ongoing debate about the dosage to be used and the timing for measurement of plasma cortisol. The 250-g corticotropin dosage is basic, but a low dosage of 1 g for the corticotropin stimulation test has actually just recently been proposed with the idea that it may be more delicate. We decided to utilize the traditional standard for the corticotropin stimulation test considering that further recognition was necessary, at the time our study began, for the low-dose test<sup>(18, 23-25)</sup>.

Adrenal insufficiency was related to aggravating of several organ failure in our pediatric population. Loisa et al. <sup>(19)</sup> likewise discovered a relationship between reduced adrenal action to corticotropin and development of more severe multiple organ failure in adults with septic shock. The explanation of this discovering remains a matter of investigation. Plasma from septic topics as well as growth necrosis factor-hinders adrenal synthesis of cortisol <sup>(4, 18, 26, 27)</sup>. It appears that extreme systemic inflammation is the pathophysiologic trademark of adrenal in addition to other organ dysfunction in patients with septic shock and severe sepsis.

Annane et al. <sup>(2)</sup> previously reported that standard cortisol level and cortico- tropin-stimulated cortisol level increment prognosticated outcome in adults with vasopressor-dependent septic shock. Particularly, patients with a baseline 34 g/dL and an increment 9 g/dL had a good prognosis (26% mortality); patients with a standard cortisol 34 g/dL and an increment 9 g/dL or a standard 34 g/dL and an increment 9 g/dL had an intermediate diagnosis (death 67%); and patients with a standard cortisol 34 g/dL and an increment 9 g/dL had a poor prognosis (82% mortality). In our population, an excellent prognosis (24% death) was observed in children with standard cortisol 20 g/dL and increment 9 g/dL; an intermediconsumed diagnosis (33% death) was observed with baseline 20 g/dL and increment 9 g/dL; and a poor prognosis was observed in children with a standard cortisol 20 g/dL and increment 9 g/dL (50% death) or standard cortisol 20 g/dL and increment 9 g/dL (53% mortality). Surprisingly, Annane and colleagues reported no absolute adrenal deficiency in their adult mate. The explanation for this may be an age-associated phenomenon since outright adrenal deficiency was more common in the children in our associate study.

On the other hand, we showed that in the pediatric population, the contribution of adrenal deficiency to mortality was not obvious, especially when controlling for chronic disease and several organ failure. These findings resemble the previous report by Hatherill et al. <sup>(6)</sup>.

**Table 3. Clinical characteristics in the four adrenal function groups**

Variables	Absolute Adrenal Insufficiency n 10	Relative Adrenal Insufficiency n 15	Cortisol 20 g/dL n 15	Adequate Response Cortisol 20 g/dL n 17	p Value
Age, months	75.5 (16–213)	47.0 (3–201)	5.0 (1–91)	23 (4–175)	.01
Risk of mortality, %	17.6 (0.56–98.6)	10.0 (1.63–81.9)	10.8 (2.36–88.8)	6.7 (0.36–94.1)	.76
Admission MOSF score	2.5 (0–6)	2.0 (1–3)	2.0 (0–4)	1.0 (0–3)	.11
MOSF score during PICU stay	3.5 (1–7)	2.0 (1–5)	2.0 (0–4)	1.0 (0–4)	.02
Level sodium, mg/dL	136.5 (119.5–154)	140.5 (118.5–159)	136.5 (122–140)	138 (127–192)	.22
Level potassium, mg/dL	4.2 (3.3–6.0)	3.7 (1.5–5.5)	3.9 (2.5–6.8)	4.2 (1.9–5.9)	.52

#### 4. CONCLUSION

Relative and outright adrenal deficiency is common in children with septic shock and might contribute to the development of catecholamine-resistant shock; to puts it simply, it is related to an increased vasopressor requirement. However, doubts still continue regarding the efficacy of replacement treatment with low-dose steroids in children with catecholamine-resistant septic shock, and further studies are had to identify whether treatment of such patients changes morbidity and/or mortality <sup>(28, 29)</sup>.

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