

PEDIATRIC ORIGINAL



Dynamics and prognostic value of the hypothalamus–pituitary–adrenal axis responses to pediatric critical illness and association with corticosteroid treatment: a prospective observational study

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Abstract

Purpose: Increased systemic cortisol availability during adult critical illness is determined by reduced binding-proteins and suppressed breakdown rather than elevated ACTH. Dynamics, drivers and prognostic value of hypercortisolism during pediatric critical illness remain scarcely investigated.

Methods: This preplanned secondary analysis of the PEPaNIC-RCT ($N = 1440$), after excluding 420 children treated with corticosteroids before PICU-admission, documented (a) plasma ACTH, (free)cortisol and cortisol-metabolism at PICU-admission, day-3 and last PICU-day, their prognostic value, and impact of withholding early parenteral nutrition (PN), (b) the association between corticosteroid-treatment and these hormones, and (c) the association between corticosteroid-treatment and outcome.

Results: ACTH was normal upon PICU-admission and low thereafter ($p \leq 0.0004$). Total and free cortisol were only elevated upon PICU-admission ($p \leq 0.0003$) and thereafter became normal despite low binding-proteins ($p < 0.0001$) and persistently suppressed cortisol-metabolism ($p \leq 0.03$). Withholding early-PN did not affect this phenotype. On PICU-day-3, *high* free cortisol and *low* ACTH independently predicted worse outcome ($p \leq 0.003$). Also, corticosteroid-treatment initiated in PICU, which further suppressed ACTH ($p < 0.0001$), was independently associated with poor outcomes (earlier live PICU-discharge: $p < 0.0001$, 90-day mortality: $p = 0.02$).

Conclusion: In critically ill children, systemic cortisol availability is elevated only transiently, much lower than in adults, and not driven by elevated ACTH. Further ACTH lowering by corticosteroid-treatment indicates active feedback inhibition at pituitary level. Beyond PICU-admission-day, low ACTH and high cortisol, and corticosteroid-treatment, predicted poor outcome. This suggests that exogenously increasing cortisol availability during acute critical

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illness in children may be inappropriate. Future studies on corticosteroid-treatment in critically ill children should plan safety analyses, as harm may be possible.

Keywords: Hypothalamus, Pituitary, Corticosteroids, Pediatrics, Critical illness

Introduction

Increased systemic cortisol availability is essential to cope with the severe physical stress imposed by surgery, trauma or severe illnesses. It has long been assumed that increased systemic cortisol availability in response to critical illnesses requiring admission to an intensive care unit (ICU) is predominantly driven by a sustained activation of the hypothalamus-pituitary-adrenocortical (HPA) axis, with a 6–10-fold increase in adrenocortical cortisol synthesis and secretion in response to increased ACTH release from the anterior pituitary. Also fasting, often a consequence of severe illness, is considered a metabolic stressor that can affect the HPA axis [1]. In critically ill adults, high as well as low plasma cortisol concentrations have been associated with adverse outcome [2]. More recently, it has become clear that in most adult patients, throughout the first 4 weeks in the ICU, hypercortisolism is present in the face of low or normal rather than high plasma ACTH concentrations, irrespective of whether or not nutritional goals are targeted early [3–5]. Instead of being determined by increased ACTH-driven cortisol production, the increased systemic cortisol availability during critical illness in adults was shown to be determined by reduced circulating levels of cortisol binding-proteins with suppressed binding affinity and by a suppressed cortisol breakdown in liver and kidney, which, together, via feedback inhibition, at least partially explain the low plasma ACTH [2–4, 6–9].

Although HPA axis alterations have been described in children suffering from meningococcal sepsis [10–12], the dynamics, drivers and prognostic value of systemic cortisol availability in the broader population of critically ill children have only scarcely been investigated [13, 14]. Nevertheless, studies have suggested that a substantial proportion of critically ill children may not be able to increase systemic cortisol availability enough to face the stress of the critical illness, which could cause hemodynamic instability and systemic hyperinflammation with need for vasopressor support [15, 16]. As a consequence, pediatric intensivists often prescribe systemic corticosteroids, often in quite high doses, although adequately powered RCTs investigating its clinical efficacy and safety in children are lacking [15, 16]. It currently remains debated whether or not such treatment improves morbidity and mortality of critically ill children and some studies have suggested possible harm [17–20].

Take-home message

Despite low plasma cortisol binding proteins and reduced cortisol metabolism, systemic cortisol availability in critically ill children is elevated only transiently and to a much lower extent than in adults, and is not driven by elevated ACTH. Beyond the day of PICU-admission, low ACTH and high cortisol, as well as corticosteroid-treatment, independently predicted poor outcome, suggesting that exogenously increasing systemic cortisol availability during acute illness in children may be inappropriate.

In this study, we aimed at (a) documenting changes over time during the course of pediatric critical illness in plasma ACTH, (free)cortisol and cortisol metabolites, their prognostic value and the impact of withholding early supplemental parenteral nutrition (PN), (b) investigating the association between treatment with systemic corticosteroids and these parameters, and (c) assessing the independent association between treatment with systemic corticosteroids and patient-centered clinical outcomes.

Materials and methods

Patients and sample collection

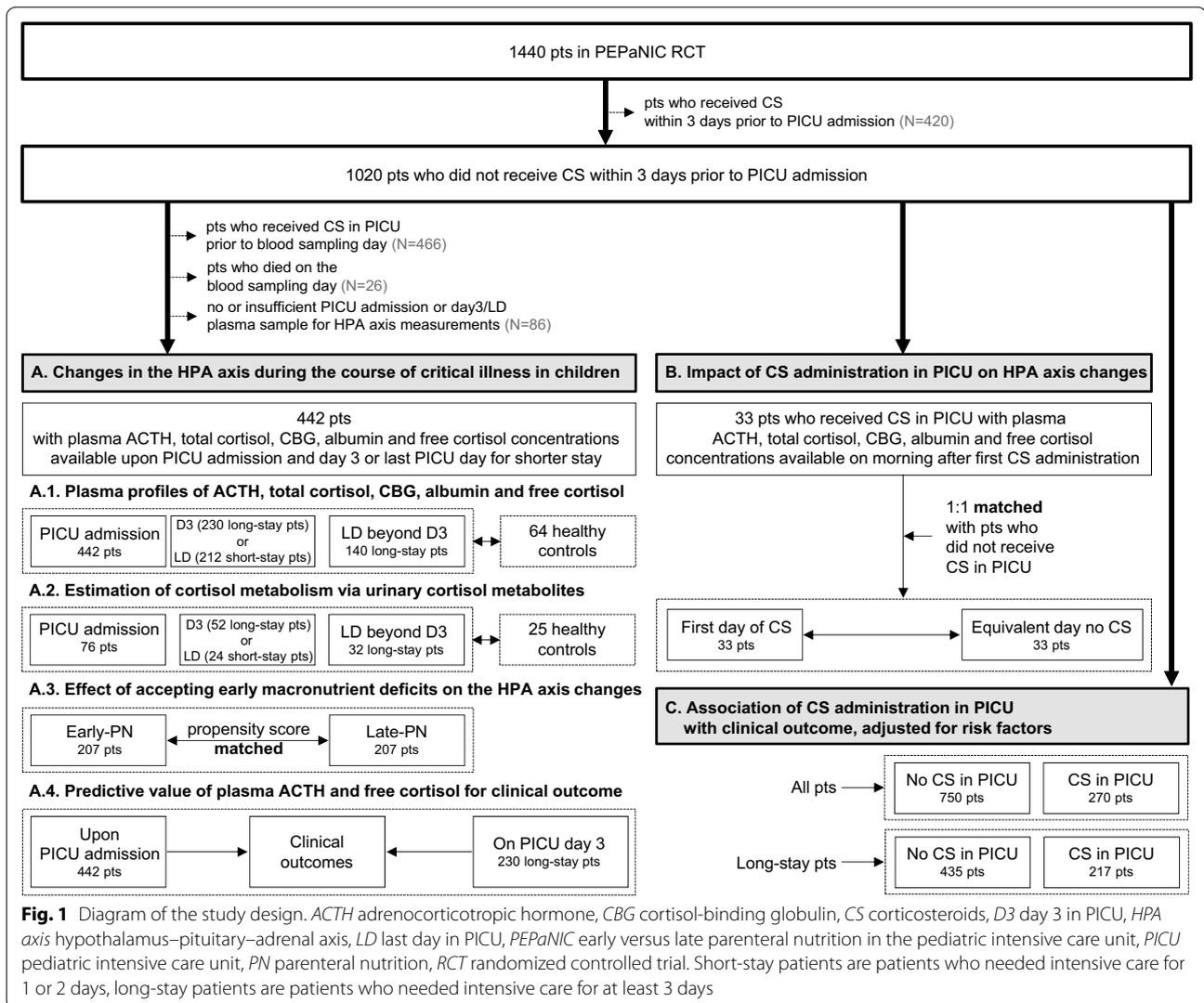
This study was a preplanned secondary analysis of the multicenter PEPaNIC randomized controlled trial (RCT) conducted in Belgium, the Netherlands and Canada (June 2012–July 2015) [21]. Written informed consent was obtained from parents or legal guardians. The institutional ethical review board at each participating center approved the protocol and consent forms of the study (ML8052, NL38772.000.12, Pro00038098), which was performed in accordance to the 1964 Declaration of Helsinki and later amendments. The detailed study protocol and primary results have been published [21, 22].

The PEPaNIC trial investigated the clinical outcomes of withholding supplemental parenteral nutrition (PN) up to day 8 in the pediatric ICU (PICU), referred to as “late-PN”, as compared with early supplemental PN whenever enteral nutrition alone was insufficient to reach the caloric target, referred to as “early-PN”. Children aged 0–17 years were eligible for inclusion, if a PICU-stay of 24 h or more was expected, if they had a moderate or severe risk of malnutrition (score ≥ 2 on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids)), and if none of the predefined exclusion criteria were met.

Enteral nutrition was started as soon as possible in both groups. In the early-PN group, supplemental PN was initiated within 24 h after PICU-admission to reach the caloric target (Online Resource Table_1-2), whereas PN was withheld up to the morning of PICU day 8 for patients in the late-PN group. Although labeled “late-PN” group, the majority of these patients needed intensive care for less than 8 days and thus did not receive PN. In the late-PN group, a mixture of intravenous dextrose (5%) and saline was administered to match the intravenous fluid load given to the early-PN patients. Patients in both groups equally received intravenous trace elements, minerals and vitamins, and blood glucose control with insulin according to local targets. Blood was sampled upon admission and then daily at 6 a.m. until PICU-discharge or death, within limitations for amount of blood sampling

allowed by the institutional ethical review boards per center. For the quantification of hormonal parameters of the HPA axis, blood samples were collected in pre-chilled EDTA tubes and immediately placed on ice, centrifuged at 4 °C, with plasma stored at –80 °C until assay. Daily urine samples from a 24-h urine collection were stored in Vacuette urine tubes at –80 °C until quantification of the cortisol metabolites.

To investigate the time course of the changes in plasma concentrations of ACTH, total cortisol, free cortisol, CBG and albumin during critical illness in children (Fig. 1, Panel_A.1), patients who received corticosteroids within 3 days before inclusion (including in the emergency room) or prior to the blood sampling day were excluded, as well as those patients who died in PICU on the day of blood sampling to avoid bias evoked by the agonal stress



response. Of the remaining patients, we included those 442 patients for whom plasma samples were available upon admission and on day 3 (for 230 long-stay patients treated in PICU for at least 3 days, which is the median duration of PICU stay, Table 1) or last PICU day (for 212 short-stay patients treated in PICU for < 3 days). For comparison, 64 healthy children, who had never been critically ill and from whom blood was drawn immediately after intravenous catheterization prior to minor elective surgery, age- and gender-matched with the patients, were included (Fig. 1, Panel_A.1). The prognostic value for the clinical outcomes (new infection acquired in the PICU, time to live discharge from PICU and 90-day mortality) of the admission plasma concentrations of ACTH and free cortisol was assessed among these 442 patients (Fig. 1, Panel_A.4). The prognostic value of plasma ACTH and free cortisol on day 3 was also assessed for the 230 long-stay patients (Fig. 1, Panel_A.4). For the estimation of the activity of cortisol-metabolizing enzymes via urinary cortisol metabolites, a representative subset of 76 patients and 25 age- and gender-matched healthy control children was selected (Fig. 1, Panel_A.2).

To investigate whether late-PN, as compared with early-PN, altered the changes in endogenous, illness-induced HPA axis parameters, between PICU admission and day 3 or last PICU day for patients discharged earlier (Fig. 1, Panel_A.3), a propensity score-matched patient subset was selected, given the required exclusion of a substantial number of patients. Propensity scores were estimated with logistic regression based on baseline risk factors as covariates, including treatment center, risk of malnutrition (STRONGkids score), age group, diagnosis upon admission, severity of illness (PeLOD score reflecting degree of organ failure and PIM2 score estimating risk of death) and sepsis upon admission [23–26]. One-to-one nearest neighbor-matching without replacement and a caliper of 0.3 retained 414 patients.

To investigate the association between treatment with corticosteroids in the PICU and plasma concentrations of ACTH, total cortisol, free cortisol, CBG and albumin (Fig. 1, Panel_2), the 33 patients who had a measurement the morning after the first day of corticosteroid-treatment were matched case-by-case to patients who had not been treated with corticosteroids and for whom a measurement was available for the same PICU-stay day (Fig. 1, Panel_2, Online Resource Methods_1). Distinction was made between hydrocortisone and synthetic corticosteroids given that the latter are not detected by the assay used for quantifying cortisol.

To investigate the independent association between treatment with corticosteroids initiated in the PICU and patient-centered clinical outcomes (new infection acquired in the PICU, time to live discharge from PICU

and 90-day mortality) (Fig. 1, Panel_4), all 1020 patients who had not been treated with corticosteroids before PICU admission were included.

Plasma and urinary analyses

Plasma ACTH concentrations were quantified by double-monoclonal immunoradiometric assay (Brahms Diagnostics) and plasma cortisol (Immunotech) and cortisol-binding-globulin (CBG) (Riazen) by competitive radioimmunoassay. Plasma albumin was quantified by the bromocresol-green colorimetric method (Sigma-Aldrich). Plasma free cortisol was calculated with the Coolens formula adapted for individual albumin and CBG concentrations, which has previously been validated as representative for measured plasma free cortisol concentrations in the ICU context [6, 27]. After deglucuronidation, the absolute urinary concentrations of cortisol (F), 5 α -tetrahydrocortisol (allo-THF), 5 β -tetrahydrocortisol (THF), cortisone (E), 5 α -tetrahydrocortisone (allo-THE) and tetrahydrocortisone (THE) were determined with liquid chromatography-tandem mass spectrometry (LC-MS/MS) as reported previously [4].

Statistical analyses

For research question A and C (Fig. 1), sample size was determined by availability. For research question B (Fig. 1), given lack of data for children in the PICU, sample size was determined based on published data regarding the impact of exogenous corticosteroids on plasma ACTH outside the context of critical illness [28, 29]. To detect a lowering in plasma ACTH in this order of magnitude, with 80% power and 95% certainty, 33 patients per group were required.

Continuous data and proportions were compared with Wilcoxon Rank Sum and Chi square tests, respectively. Data are presented as medians and interquartile ranges or numbers and percentages.

Independent associations of plasma concentrations of ACTH and free cortisol, or of corticosteroid-treatment, with patient-centered clinical outcomes were analyzed with multivariable logistic regression and proportional hazard analyses, adjusted for baseline risk factors [treatment center, risk of malnutrition (STRONGkids score), age group, diagnosis upon admission, severity of illness (PeLOD and PIM2), sepsis upon admission] [23–26]. Effect sizes are reported as odds ratios (OR) and hazard ratios (HR), respectively, with 95% confidence intervals (CI).

Propensity score matching was performed with SPSS R-menu R3.1 (Foundation for Statistical Computing) in IBM SPSS Statistics 25.0.0.0 (SPSS, Chicago, IL). All analyses were performed with JMP[®]Pro14.0.0 (SAS Institute

Table 1 Characteristics of PICU patients and healthy control children

	HPA axis changes			Association of CS administration with HPA axis			Association of CS administration with outcome
	Patients	Controls	P	No CS	CS	P	
Baseline characteristics	N = 442	N = 64		N = 33	N = 33		N = 1020 ^e
Age (years), median (IQR)	2.6 (0.4–7.6)	2.0 (0.7–6.7)	0.68	6.4 (1.1–11.5)	3.1 (0.8–10.8)	0.37	1.4 (0.3–6.7)
Age < 1 year, N (%)	167 (37.8)	25 (39.1)	0.84	8 (24.2)	10 (30.3)	0.58	463 (45.4)
Male gender, N (%)	250 (56.5)	37 (57.8)	0.85	21 (63.6)	21 (63.6)	> 0.99	593 (58.1)
Weight (SD score), median (IQR)	− 0.5 (− 1.4 to 0.5)			0.1 (− 0.6 to 0.8)	− 0.4 (− 1.4 to 0.6)	0.12	− 0.5 (− 1.4 to 0.5)
Height (SD score), median (IQR)	− 0.4 (− 1.5 to 0.6)			− 0.2 (− 1.2 to 1.2)	− 0.2 (− 1.3 to 0.9)	0.63	− 0.4 (− 1.5 to 0.7)
Treatment center, N (%)						0.55	
Leuven	387 (87.6)			23 (69.7)	19 (57.6)		544 (53.3)
Rotterdam	46 (10.4)			8 (24.2)	12 (36.4)		401 (39.3)
Edmonton	9 (2)			2 (6.1)	2 (6.1)		75 (7.4)
STRONGkids risk level, N (%) ^a						0.55	
Medium	415 (93.9)			32 (97)	31 (93.9)		907 (88.9)
High	27 (6.1)			1 (3.0)	2 (6.1)		113 (11.1)
PeLOD score, first 24 h in PICU, median (IQR) ^b	23 (21–32)			21 (12–32)	23 (10–32)	0.60	21 (11–31)
PIM2 score, median (IQR) ^c	− 2.9 (− 3.8 to − 1.8)			− 2.9 (− 4.1 to − 1.3)	− 3.0 (− 3.8 to − 1.7)	0.89	− 2.8 (− 3.7 to − 1.6)
PIM2 probability of death, %, median (IQR)	5.2 (2.3–14.5)			4.6 (2.2–13.9)	5.4 (2.3–15.3)	0.97	5.8 (2.3–17)
Emergency admission, N (%) ^d	168 (38)			17 (51.5)	16 (48.5)	0.80	615 (60.3)
Diagnostic group, N (%)						0.92	
Surgical							
Abdominal	16 (3.6)			0 (0)	0 (0)		112 (11)
Burns	3 (0.7)			0 (0)	0 (0)		10 (1)
Cardiac	222 (50.2)			10 (30.3)	10 (30.3)		294 (28.8)
Neurosurgery-traumatic brain injury	35 (7.9)			8 (24.2)	8 (24.2)		80 (7.8)
Thoracic	21 (4.8)			1 (3)	2 (6.1)		57 (5.6)
Transplantation	0 (0)			0 (0)	1 (3)		8 (0.8)
Orthopedic surgery-trauma	41 (9.3)			3 (9.1)	2 (6.1)		53 (5.2)
Other	11 (2.5)			2 (6.1)	1 (3)		39 (3.8)
Medical							
Cardiac	18 (4.1)			2 (6.1)	2 (6.1)		59 (5.8)
Gastrointestinal-Hepatic	2 (0.5)			0 (0)	0 (0)		4 (0.4)
Oncologic-Hematologic	0 (0)			0 (0)	1 (3)		9 (0.9)
Neurologic	22 (5)			1 (3)	1 (3)		84 (8.2)
Renal	0 (0)			0 (0)	0 (0)		1 (0.1)
Respiratory	28 (6.3)			0 (0)	0 (0)		141 (13.8)
Other	23 (5.2)			6 (18.2)	5 (15.2)		69 (6.8)
Condition on admission, N (%)							
Mechanical ventilation required	391 (88.5)			28 (84.9)	28 (84.9)	> 0.99	875 (85.8)
ECMO or other assist device required	7 (1.6)			0 (0)	1 (3)	0.23	29 (2.8)
Infection	123 (27.8)			12 (36.4)	11 (33.3)	0.79	429 (42.1)
Sepsis	93 (21)			11 (33.3)	9 (27.3)	0.59	308 (30.2)
Randomization group, N (%)							
Early PN	227 (51.4)			15 (45.5)	10 (30.3)	0.20	504 (49.4)

Table 1 (continued)

	HPA axis changes			Association of CS administration with HPA axis			Association of CS administration with outcome
	Patients	Controls	P	No CS	CS	P	
Late PN	215 (48.6)			18 (54.6)	23 (69.7)		516 (50.6)
Duration of PICU stay, days, median (IQR)	3 (1–6)			2 (1–3)	2 (1–3)	>0.99	4 (2–8)
Acquisition of a new infection in PICU, N (%)	47 (10.6)			1 (3)	2 (6.1)	0.55	140 (13.7)
90-day mortality, N (%)	12 (2.7)			2 (6.1)	4 (12.1)	0.39	61 (6)

^a Evaluates risk of malnutrition with scores ranging from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4–5 indicating high risk. ^bScores range from 0 to 71, with higher scores indicating more severe illness. ^cHigher scores indicate a higher risk of mortality. ^dElective admissions comprise those requiring post-operative intensive care after scheduled surgery (often complex cardiac surgery or surgery on other vital organ systems). Unplanned transfers to the PICU from the general pediatric ward, from the emergency department or from elsewhere are considered emergency admissions. ^eOf whom 270 received CS. CS corticosteroids, ECMO extracorporeal membrane oxygenation, HPA axis hypothalamic–pituitary–adrenal axis. PeLOD pediatric logistic organ dysfunction score first 24 h in PICU. PICU pediatric intensive care unit. PIM2 pediatric index of mortality 2 score. PN parenteral nutrition, STRONGkids screening tool for risk on nutritional status and growth

Inc, Cary, NC). Two-sided *p* values <0.05 were considered to indicate statistical significance.

Results

For the three main research questions, depicted in Fig. 1, comparisons of the patient characteristics are provided in Table 1 and Online Resource Table_3–4.

Time course of the changes in plasma concentrations of ACTH, total cortisol, free cortisol, CBG, and albumin and estimations of cortisol metabolism during critical illness, prognostic value and impact of late-PN versus early-PN

Upon PICU-admission, plasma ACTH concentrations were not significantly different from those in the matched healthy children and became low thereafter throughout PICU stay (Fig. 2a). Plasma total cortisol concentrations were only above normal at PICU-admission and became normal thereafter (Fig. 2b). Also, plasma free cortisol concentrations were only higher than in healthy children upon PICU-admission. Thereafter, plasma free cortisol levels were no longer elevated (Fig. 2c), despite plasma CBG and albumin concentrations that were mostly low (Fig. 2d, e) and despite the observation that the estimated activities of cortisol-metabolizing enzymes, 11 β -hydroxysteroid-dehydrogenase-2 and the A-ring reductases 5 α -reductase and 5 β -reductase, remained low throughout PICU stay (Fig. 2f–i).

The use of late-PN, as compared with early-PN, did not affect the changes over time in plasma concentrations of ACTH, (free)cortisol, CBG, or albumin (Online Resource Fig. 1).

Adjusted for baseline risk factors, including type and severity of illness among others, upon PICU-admission plasma concentrations of ACTH and free cortisol were not independently associated with the clinical outcomes

(Online Resource Table_5). However, among long-stay patients, higher plasma ACTH concentrations on day 3 in the PICU were independently indicative of a *higher* likelihood of earlier live discharge from PICU, whereas higher plasma free cortisol concentrations on that day were independently indicative of a *lower* likelihood of earlier live discharge from PICU (Table 2). There were no independent associations between plasma ACTH or free cortisol on day 3 and the risk of new infections or the risk of 90-day mortality.

Association between treatment with corticosteroids initiated in the PICU and plasma concentrations of ACTH, total cortisol, free cortisol, CBG and albumin

Among the 33 selected patients who received corticosteroids on median day 2 (IQR 1–3), 28 received synthetic corticosteroids and 5 received hydrocortisone. Corticosteroid-treatment further suppressed plasma concentrations of ACTH as compared with the 33 matched patients who did not receive corticosteroids and were also assessed on median day 2 (IQR 1–3) (Fig. 3). Expectedly, the use of synthetic corticosteroids lowered plasma total and free cortisol concentrations (Fig. 3), whereas hydrocortisone increased plasma total and free cortisol. There was no association with the plasma concentrations of CBG or albumin.

Independent association between treatment with corticosteroids initiated in the PICU and patient-centered clinical outcomes

Of the 1020 patients who had not been treated with corticosteroids prior to PICU admission, 270 (26.5%) received corticosteroids initiated on median day 2 (IQR 1–5) after admission to the PICU. Among the 652 long-stay patients in PICU for at least 3 days, 217 (33.3%) received corticosteroids initiated on median day 3 (IQR 1–6) after PICU

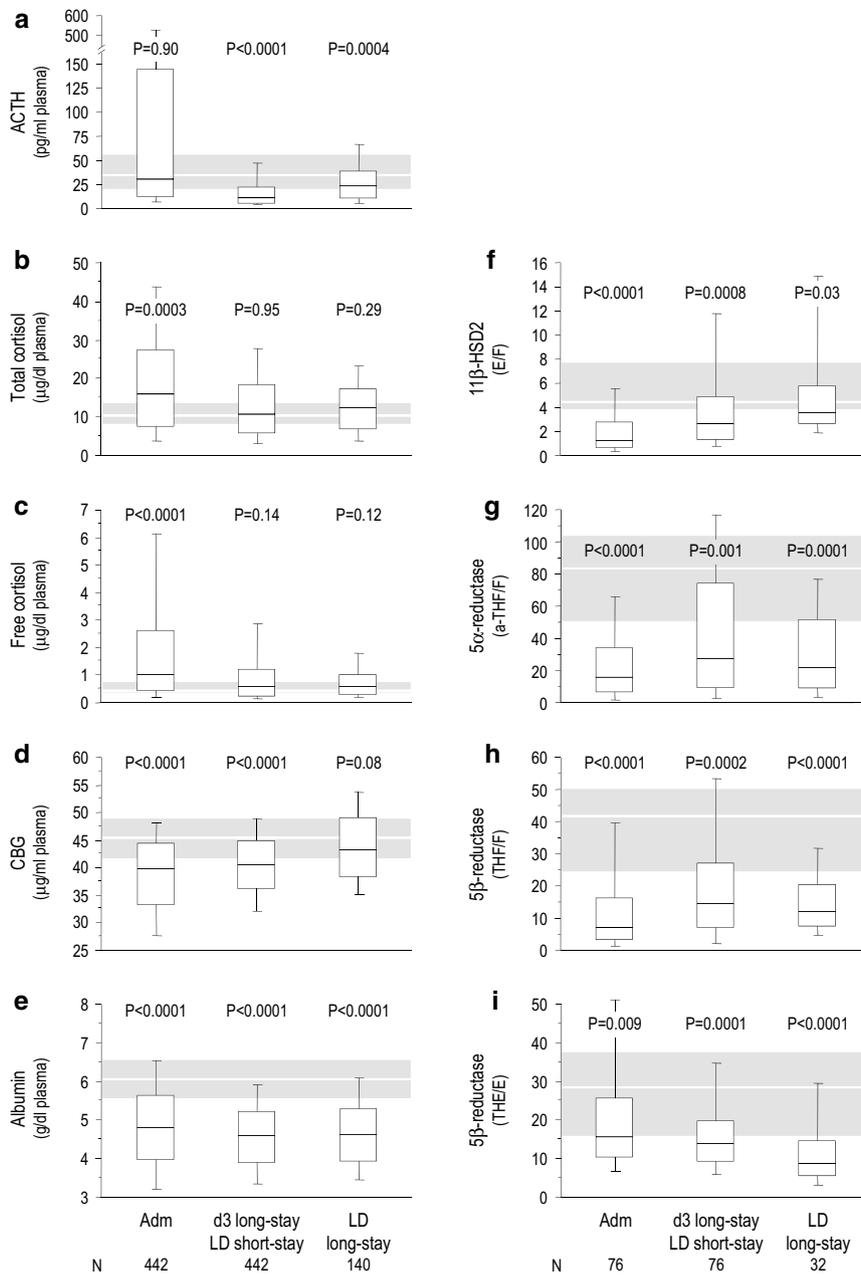


Fig. 2 Time course of the changes in plasma concentrations of ACTH, total cortisol, free cortisol, CBG and albumin, and estimations of cortisol metabolism during critical illness. Plasma concentrations of ACTH (**a**), total cortisol (**b**), free cortisol (**c**), CBG (**d**) and albumin (**e**) were quantified, and activities of the cortisol metabolizing enzymes 11β-HSD2 (**f**), 5α-reductase (**g**) and 5β-reductase (**h**, **i**) were estimated upon PICU admission, on PICU day 3 or last PICU day for patients with a shorter PICU stay, and on the last PICU day beyond day 3 if still in PICU beyond day 3. Results overall apply irrespective of the presence of sepsis, and irrespective of whether patients were admitted after cardiac surgery or for other reasons. Box plots show medians, interquartile ranges, and 10th and 90th percentiles. The grey bars represent the interquartile ranges obtained for the healthy control children, with the white lines indicating the medians. ACTH: adrenocorticotropic hormone, aTHF: allo-THF (5α-tetrahydrocortisol), 11β-HSD2: 11β-hydroxysteroid-dehydrogenase type 2, CBG: cortisol-binding globulin, D3: day 3 in PICU, E: cortisone, F: cortisol, LD short-stay: last day in PICU for patients who needed intensive care for 1 or 2 days, LD long-stay: last day in PICU beyond day 3 for long-stay patients who needed intensive care for at least 3 days, PICU: pediatric intensive care unit, THE: tetrahydrocortisone, THF: 5β-tetrahydrocortisol

Table 2 Prognostic value of the changes in the HPA axis for patient-centered clinical outcomes and independent association between treatment with corticosteroids in the PICU and those outcomes

	Prognostic value of HPA axis changes in long-stay patients ^a N = 230		Association of CS administration in PICU with outcome of long-stay patients ^a N = 652	
	OR/HR (95%CI)	P	OR/HR (95%CI)	P
Risk of new infection^b				
Infant versus child ^c	1.082 (0.427–2.743)	0.86	1.143 (0.680–1.922)	0.61
Center—Rotterdam versus Leuven	3.567 (1.014–12.547)	0.04	1.563 (0.796–3.072)	0.19
Center—Edmonton versus Leuven	0.000 (0.000–inf)	0.99	2.192 (0.944–5.089)	0.06
High versus medium risk of malnutrition ^d	2.241 (0.601–8.357)	0.22	1.934 (1.053–3.554)	0.03
PeLOD score (per unit added) ^e	1.046 (0.991–1.103)	0.09	1.033 (1.006–1.060)	0.01
PIM2 score (per unit added) ^f	1.518 (1.080–2.135)	0.01	1.306 (1.095–1.558)	0.003
Diagnostic group		0.004		0.94
Sepsis versus no sepsis upon admission	0.218 (0.068–0.700)	0.01	0.411 (0.236–0.714)	0.001
Randomization to late-PN versus early-PN	0.540 (0.242–1.202)	0.13	0.507 (0.320–0.802)	0.003
ACTH (per pg/ml added)	0.987 (0.967–1.007)	0.15		
Free cortisol (per µg/ml added)	1.082 (0.861–1.359)	0.52		
CS therapy versus no CS therapy in PICU			1.057 (0.648–1.724)	0.82
Likelihood of earlier live PICU discharge				
Infant versus child ^c	0.709 (0.513–0.983)	0.03	0.788 (0.652–0.953)	0.01
Center—Rotterdam versus Leuven	0.830 (0.516–1.311)	0.42	0.752 (0.594–0.954)	0.01
Center—Edmonton versus Leuven	1.191 (0.406–2.789)	0.72	0.928 (0.672–1.264)	0.63
High versus medium risk of malnutrition ^d	1.076 (0.561–1.894)	0.81	0.832 (0.641–1.066)	0.14
PeLOD score (per unit added) ^e	0.998 (0.980–1.017)	0.85	0.990 (0.981–1.000)	0.04
PIM2 score (per unit added) ^f	0.719 (0.633–0.813)	<0.0001	0.785 (0.732–0.842)	<0.0001
Diagnostic group		0.11		0.15
Sepsis versus no sepsis upon admission	1.038 (0.715–1.508)	0.84	0.925 (0.765–1.118)	0.42
Randomization to late-PN versus early-PN	1.006 (0.758–1.337)	0.96	1.336 (1.132–1.578)	0.0006
ACTH (per pg/ml added)	1.009 (1.003–1.013)	0.0003		
Free cortisol (per µg/ml added)	0.906 (0.840–0.964)	0.003		
CS therapy versus no CS therapy in PICU			0.677 (0.563–0.814)	<0.0001
Risk of 90-day mortality				
Infant versus child ^c	1.871 (0.290–12.058)	0.51	1.602 (0.727–3.529)	0.24
Center—Rotterdam versus Leuven	0.134 (0.007–2.478)	0.17	1.139 (0.442–2.939)	0.78
Center—Edmonton versus Leuven	0.000 (0.000–inf)	0.99	0.000 (0.000–inf)	0.99
High versus medium risk of malnutrition ^d	2.387 (0.223–25.502)	0.47	0.693 (0.220–2.185)	0.53
PeLOD score (per unit added) ^e	0.943 (0.845–1.052)	0.27	1.011 (0.973–1.051)	0.57
PIM2 score (per unit added) ^f	2.722 (1.435–5.165)	0.0004	1.860 (1.435–2.411)	<0.0001
Diagnostic group		0.61		0.79
Sepsis versus no sepsis upon admission	0.966 (0.141–6.613)	0.97	1.322 (0.571–3.058)	0.51
Randomization to late-PN versus early-PN	0.285 (0.051–1.586)	0.15	0.498 (0.235–1.057)	0.06
ACTH (per pg/ml added)	0.979 (0.937–1.023)	0.30		
Free cortisol (per µg/ml added)	1.190 (0.775–1.827)	0.48		
CS therapy versus no CS therapy in PICU			2.307 (1.125–4.731)	0.02

^a Long-stay patients are patients who needed intensive care for at least 3 days. Patients who received corticosteroids within the three days prior to PICU admission were excluded from these analyses. ^bFor the model on the association of CS administration in PICU with new infections, only infections occurring beyond the first day of CS administration were considered ("left-truncation"). ^cInfants are patients younger than 1 year. ^dEvaluated with the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) with scores ranging from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4–5 indicating high risk. ^eScores range from 0 to 71, with higher scores indicating more severe illness. ^fHigher scores indicate a higher risk of mortality. ACTH: adrenocorticotropic hormone, CI confidence interval, CS corticosteroids, HPA axis hypothalamus–pituitary–adrenal axis, HR hazard ratio, OR odds ratio, PeLOD pediatric logistic organ dysfunction score first 24 h in PICU, PICU pediatric intensive care unit, PIM2 pediatric index of mortality 2 score, PN parenteral nutrition

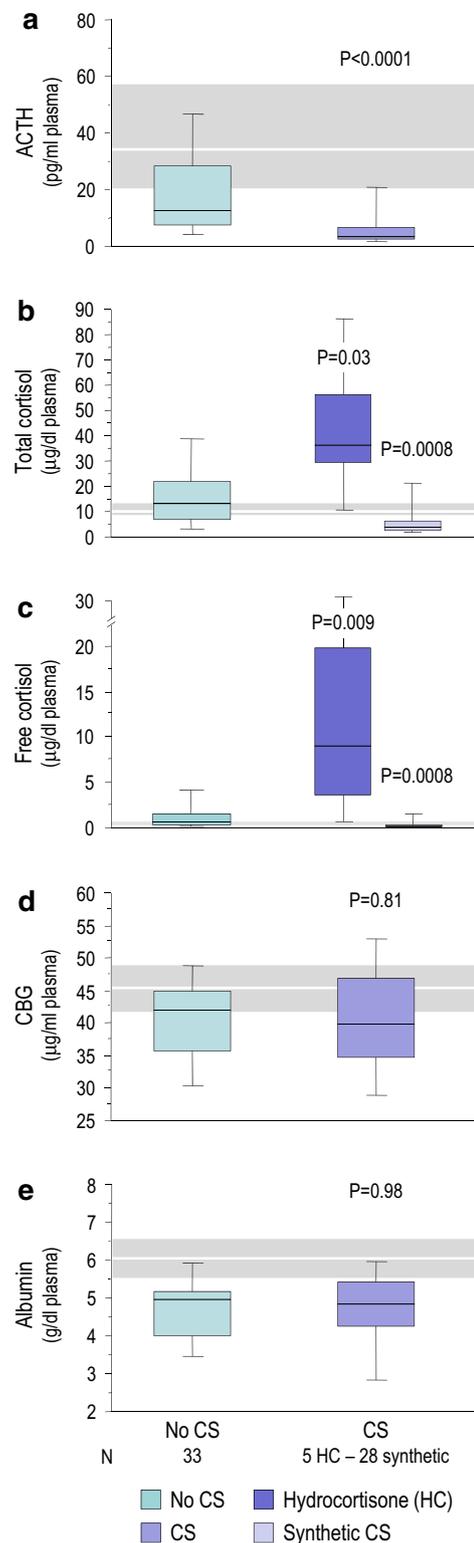
Fig. 3 Association between treatment with corticosteroids initiated in the PICU and plasma concentrations of ACTH, total cortisol, free cortisol, CBG, and albumin. Plasma concentrations of ACTH (a), total cortisol (b), free cortisol (c), CBG (d) and albumin (e) were quantified on the morning after the first day of CS administration and on equivalent days for patients who did not receive corticosteroids, manually matched 1:1 with the patients who received CS. To evaluate the association between CS administration and total and free cortisol, a distinction was made between hydrocortisone and synthetic CS, since the radioimmunoassay for cortisol does not measure synthetic CS. Box plots show medians, interquartile ranges, and 10th and 90th percentiles. The grey bars represent the interquartile range obtained for the healthy control children, with the white lines indicating the medians. *P* values represent the comparison of CS (or type of CS) versus no CS administration. ACTH: adrenocorticotropic hormone, CBG: cortisol-binding globulin, CS: corticosteroids, PICU: pediatric intensive care unit, PN: parenteral nutrition

admission. Adjusted for baseline risk factors, the use of corticosteroids during PICU stay was independently associated with a lower likelihood of an earlier live discharge from ICU and with a higher risk of 90-day mortality for all patients (Online Resource Table_6) and for long-stay patients alike (Table 2). There was no independent association between use of corticosteroids and the risk of new infections.

Discussion

In this study of critically ill children admitted to the PICU, plasma ACTH concentrations were either normal or low and were further lowered by the use of exogenous corticosteroids. Total and free plasma cortisol levels were elevated only briefly, thereafter lowering to normal levels despite persistently low circulating levels of cortisol binding-proteins and despite suppressed cortisol metabolism throughout PICU stay. Withholding supplemental PN during the first week in PICU did not affect this phenotype. Adjusted for risk factors, upon admission plasma concentrations of ACTH or free cortisol did not hold prognostic value for patient-centered clinical outcomes whereas on day 3 in the PICU, a *high* free cortisol and a *low* plasma ACTH level independently predicted worse outcome. Also, treatment with systemic corticosteroids initiated during the first few days in the PICU, which further suppressed ACTH, was found to independently associate with poor outcomes, adjusted for other risk factors.

Systemic cortisol availability in critically ill children treated in the PICU was found to be elevated only transiently and to a much lesser extent than was previously reported for adults [3, 5, 30]. The finding that plasma



ACTH in patients was never significantly higher than in matched healthy children, not even in the presence of elevated plasma cortisol upon PICU-admission, was in line with previous adult data [3, 5, 30]. These findings suggest that peripheral mechanisms, such as low plasma binding and suppressed cortisol breakdown, are active to increase and maintain cortisol availability also in the pediatric critically ill population [3, 9]. The observation that exogenous corticosteroids further suppressed plasma ACTH suggests that ACTH is not fully endogenously suppressed during pediatric critical illness and thus that central activators balance against suppressors in exogenous corticosteroid-naïve patients but that pituitary feedback inhibition remains responsive to a further increase of glucocorticoid signaling.

The low plasma ACTH observed beyond the PICU-admission day in the critically ill children cannot be brought about by feedback-inhibition through free cortisol, given that free cortisol was no longer elevated, unless the set-point for feedback inhibition would be lower in this context. A lower set-point for feedback inhibition by thyroid hormones has also been suggested as an explanation for the low T3 syndrome of critical illness [31–33]. Absence of elevated free cortisol concentrations after a few days in the PICU, while cortisol binding-proteins were low and cortisol metabolism was suppressed, suggests that the concomitantly low ACTH must have played a role. Endogenous or iatrogenic suppressors of ACTH may be involved. Candidate endogenous suppressors of ACTH are elevated levels of bile acids as these have shown to be able to cross the blood–brain barrier and act as ligands for the glucocorticoid receptor, hereby potentially suppressing corticotropin-releasing hormone and hereby suppressing ACTH [34–36]. The use of opioids and other drugs in the PICU may have added suppressive effects on the HPA axis [30, 37, 38].

Admission levels of plasma ACTH and cortisol did not hold prognostic value for clinical outcome when adjusted for type and severity of illness and other risk factors. Hence, they appeared to be merely a correlate of the type and severity of illness. However, it was striking to observe that among long-stay patients, after extensive adjustment for risk factors including type and severity of illness, a high plasma free cortisol and a low plasma ACTH on day 3, a time point where both cortisol and ACTH levels were lowered as compared with PICU admission, together were independently predictive of poor outcome. Also, exogenous steroid treatment initiated during the first few days in the PICU, which further lowered plasma ACTH, was predictive of poor outcome after extensive adjustment for risk factors. Together these findings may suggest that the amount of cortisol availability required for

an effective struggle for survival and recovery from critical illness in children may not be as high as previously assumed and lower than in adults. Excessive amounts of cortisol could indeed also be harmful [18, 19]. Alternatively, a direct role of endogenous and/or exogenous ACTH suppressors in mediating the independent association between low plasma ACTH and adverse outcome is possible and cannot be excluded from this study.

The strengths of this study are the large sample size of a heterogeneous cohort of critically ill children and the use of samples and data from a well-documented RCT which allowed to carefully adjust for prospectively registered confounders and which allowed case-by-case matching. A weakness of the study is that data were predominantly gathered during the first week in the PICU so that no conclusions can be drawn on a more prolonged phase of pediatric critical illness. Another weakness is the observational nature of our analyses of the associations with patient-centered clinical outcomes, which (although adjusted for baseline risk factors) cannot fully take into account potential confounding factors such as disease course. Lastly, free cortisol concentrations were not directly measured but calculated.

In conclusion, cortisol availability during pediatric critical illness is only briefly elevated, driven by peripheral rather than central mechanisms, and is followed by low ACTH and normal free cortisol levels until PICU-discharge. Low ACTH is further lowered by treatment with corticosteroids suggesting active feedback inhibition at the pituitary level. Beyond PICU-admission day, a high circulating cortisol as well as the administration of systemic corticosteroids appeared independent predictors of adverse outcome. These findings raise the hypothesis that increasing cortisol availability during the first days after onset of critical illness in children may be inappropriate. Studies investigating the effect of treatment with corticosteroids in critically ill children should thus carefully plan interim safety analyses to avoid possible harm.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-019-05854-0>) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees (Medical Ethical Committee University Hospitals Leuven: ML8052, Medical Ethical Review Committee Erasmus Medical Center Rotterdam: NL38772.000.12, Health Research Ethics Board Stollery Children's Hospital Edmonton: Pro00038098) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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