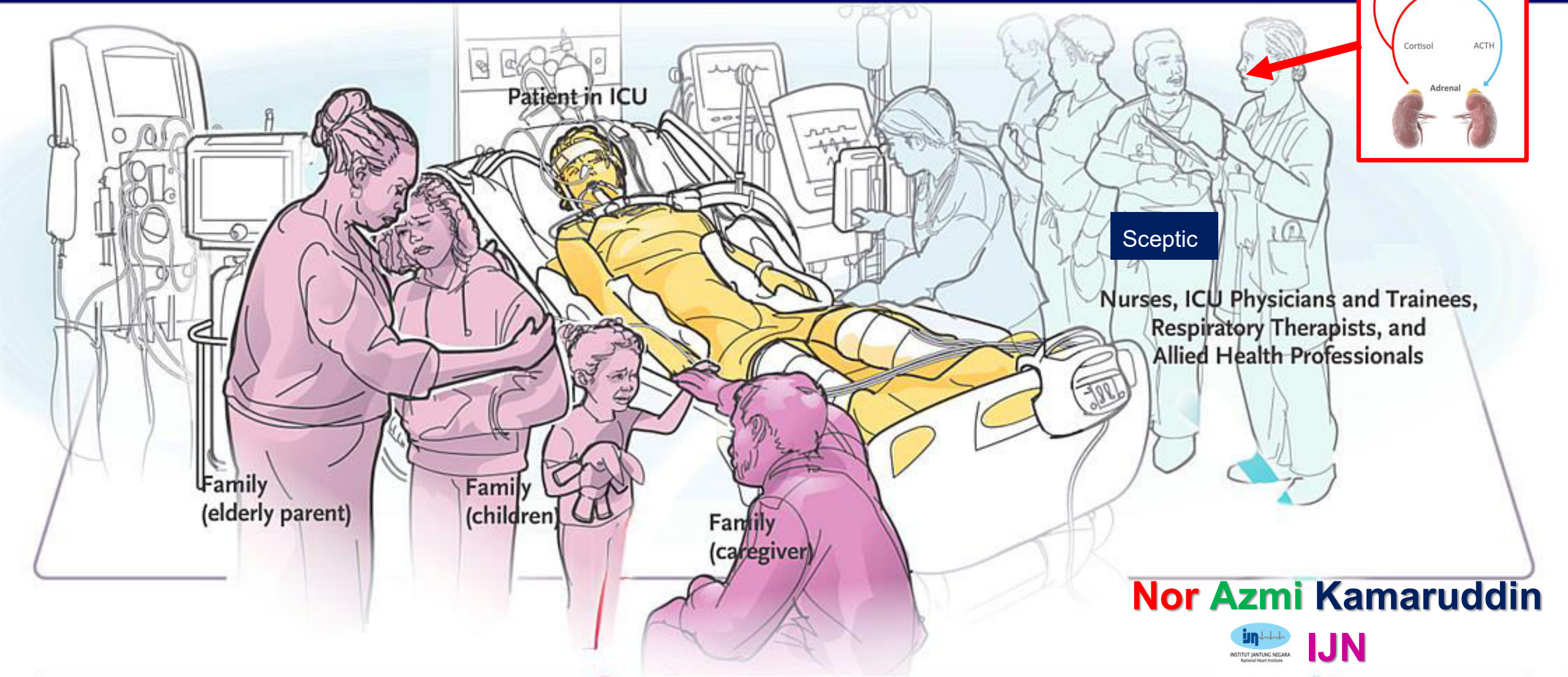
HPA Axis Evaluation in Critical Illness

On the occasion of the **Launch of the Practical Guide To Endocrine Dynamic Tests**

Academy of Medicine Malaysia Putrajaya

5th December 2024



Nor Azmi Kamaruddin

IJN

INSTITUT JANTUNG NEGARA
National Heart Institute

Disclosure of Financial Relationships with Pharmaceutical Companies (Conflict of Interest Declaration)

Nor Azmi Kamaruddin
MBBS, MMed, DIS, FACE, FAMM, FCPM(Endocrinology)

Nothing To Declare

Ten False Beliefs About Cortisol In Critically Ill Patients

1. A lower plasma total cortisol value is associated with a worse outcome.
2. A single measurement of plasma cortisol gives a valid estimation of the 24 h average cortisol level
3. Total cortisol assays are interchangeable
4. The incremental response of total plasma cortisol to cosyntropin stimulation is a reliable indicator of adrenal function and a predictor of outcome
5. A high increment on the cosyntropin test rules out adrenal insufficiency
6. Total plasma cortisol concentrations accurately reflect the bioavailable fraction - plasma free cortisol
7. Calculation of PFC concentrations is an acceptable alternative to direct measurement
8. Plasma cortisol concentrations accurately reflect intracellular concentrations
9. Elevated cortisol concentrations are primarily due to increased glucocorticoid production
10. Treatment with ‘stress doses’ of hydrocortisone in critically ill patients with suspected hypoadrenalism results in physiological cortisol levels

Intensive Care Med (2015) 41:1817–1819

Contents:

1. What happens to serum cortisol in critically-ill patients ?
    A. Levels of free cortisol, total cortisol and ACTH
    B. Production of cortisol, ACTH
    C. Variability of cortisol levels (cf post-stimulation with ACTH)
    D. Cortisol Binding Proteins esp CBG , albumin
    E. Cortisol Binding Affinity
    F. Enzymes that breakdown cortisol
    G. Half-life of cortisol
    H. Dissociation of ACTH from Cortisol

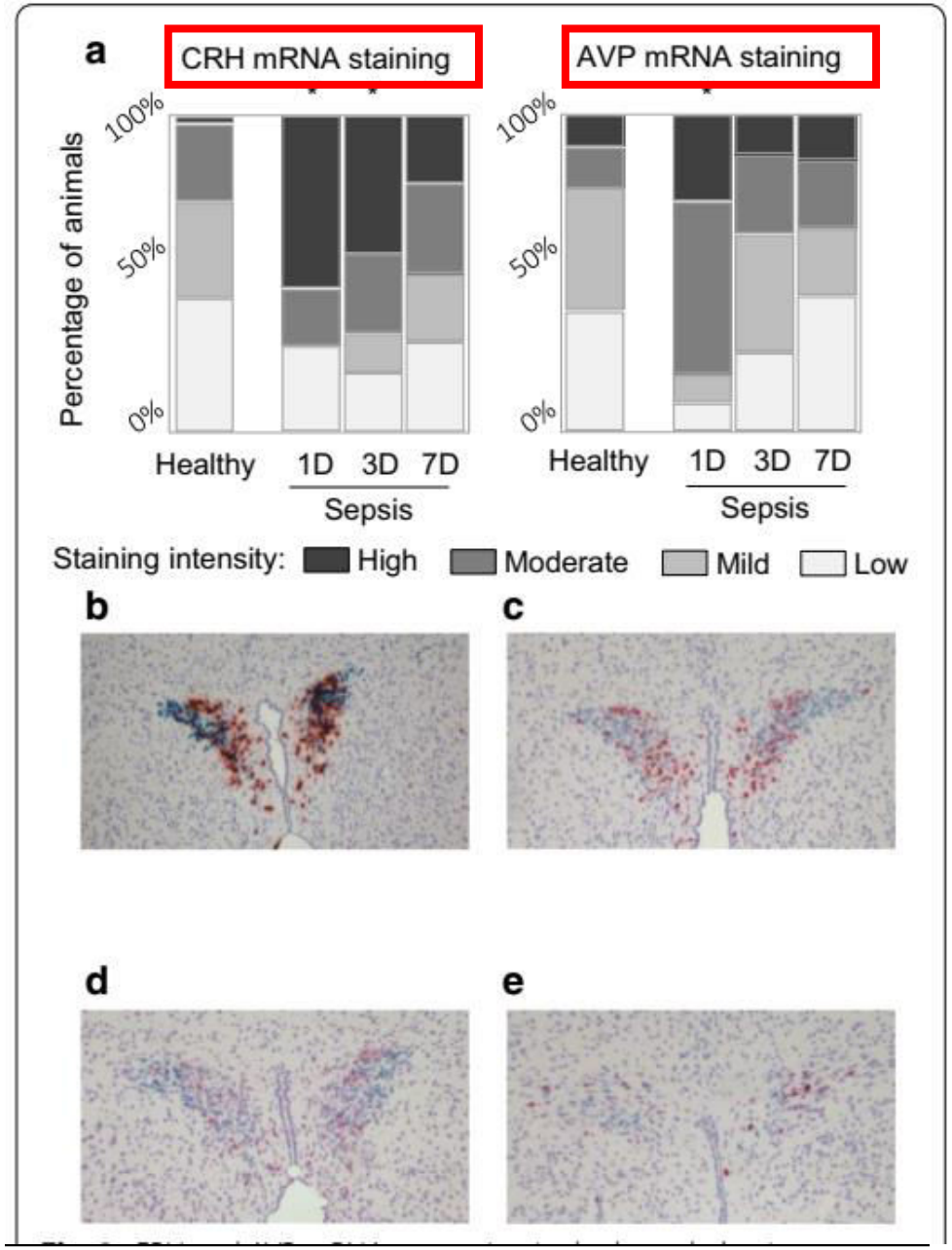
2. What are the responses of adrenals and pituitary (HPA axis) in critically-ill patients
    A. Standard & Low Dose ACTH Stimulation Test
    B. CRH Stimulation Test

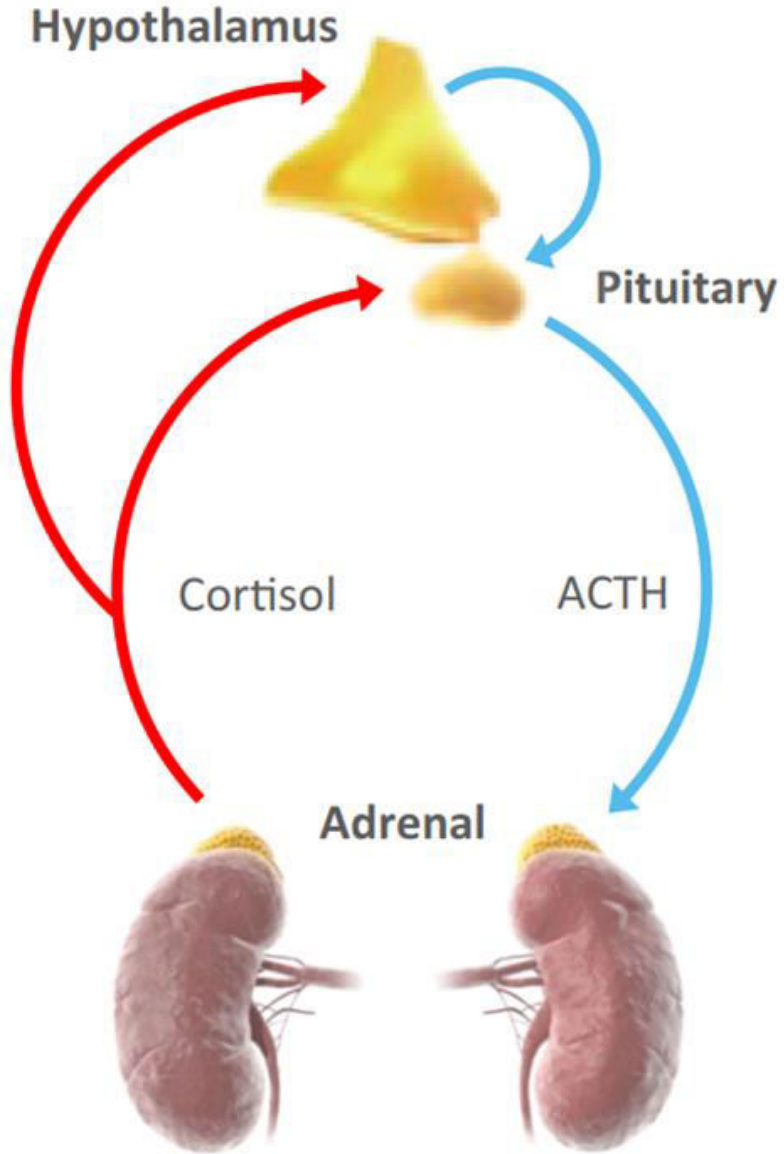
3. Fate of HPA Axis beyond 4-weeks in critically-ill patients
    A. Three phases / timelines of HPA responses in critical illness

4. New recommendations that have not made it into the guidelines.
    A. Traditional lab tests eg serum cortisol, SSST, LDSST
    B. Safest high / supraphysiological steroid “replacement” dose

5. Conclusion & Recommendations
    A. What to look for in the first 4 weeks of critical illness
    B. Transition into the new steroid replacement dose

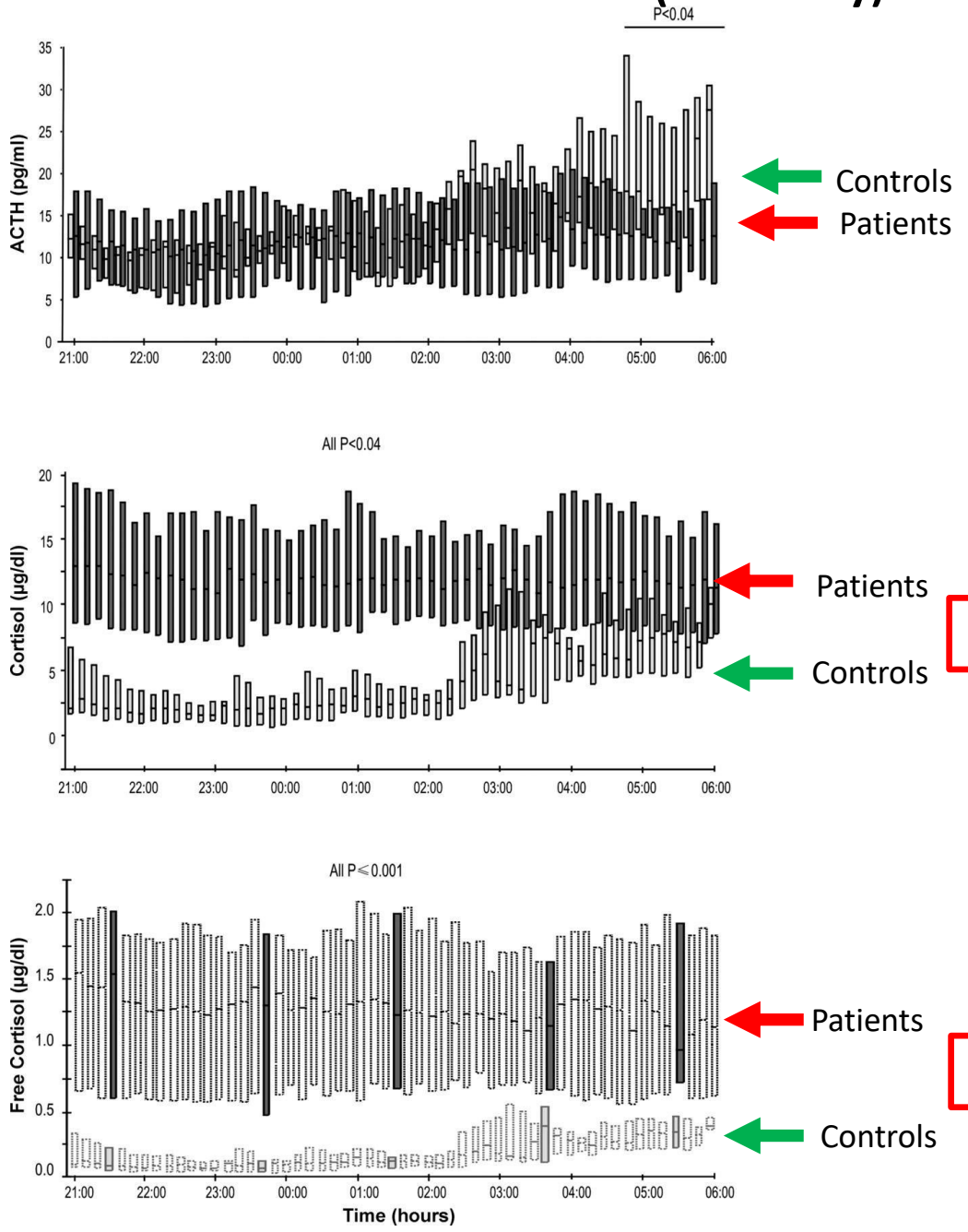
CRH and AVP mRNA Expression In The Hypothalamic Paraventricular Nucleus.





Téblick et al. Crit Care (2021) 25:65

Plasma ACTH, Total Cortisol and Free Cortisol Levels In 40 Patients (Dark Gray) And 8 Controls (Light Gray)

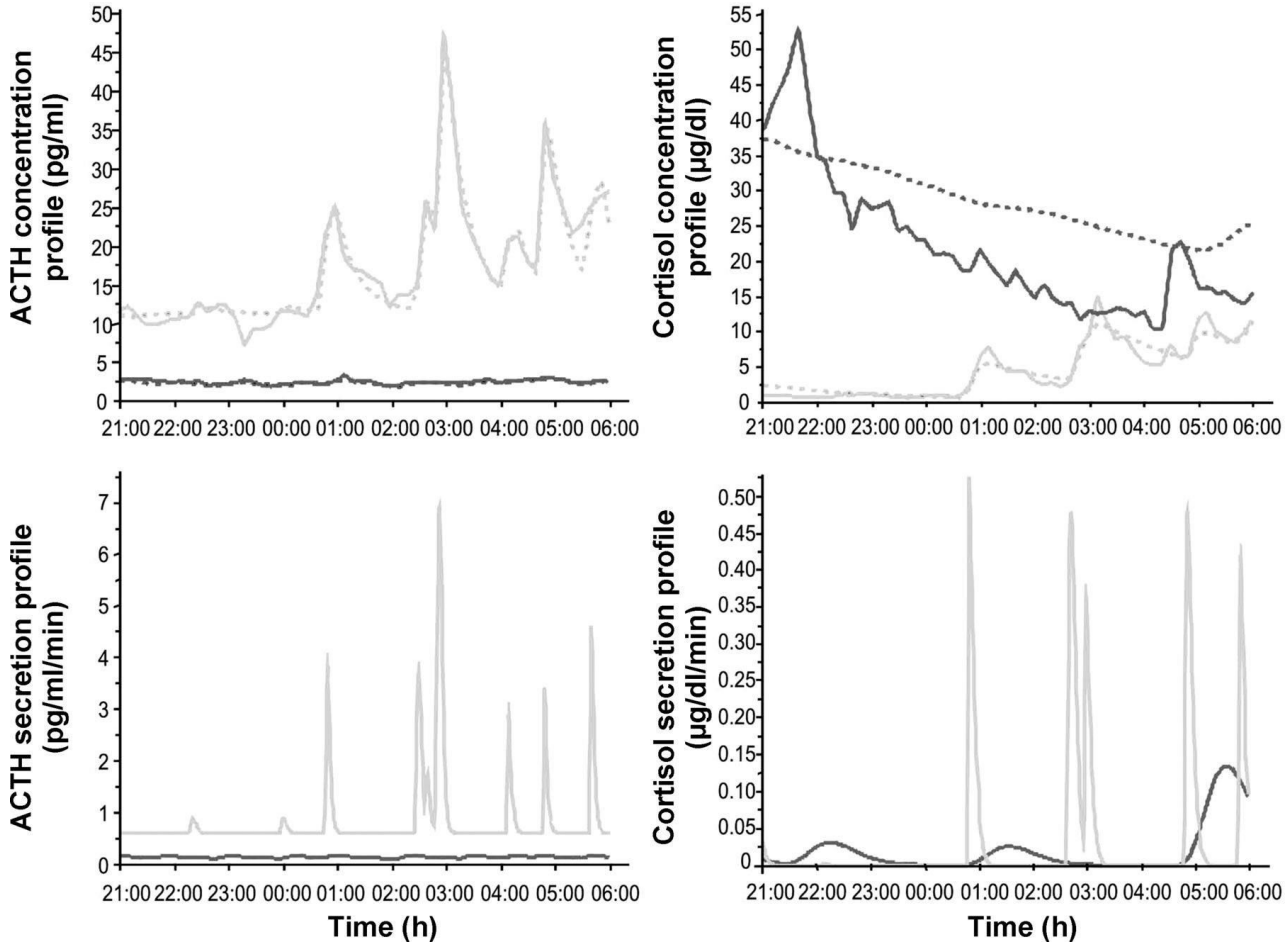


Plasma ACTH concentrations were lower in patients than controls from 0450 hours onward

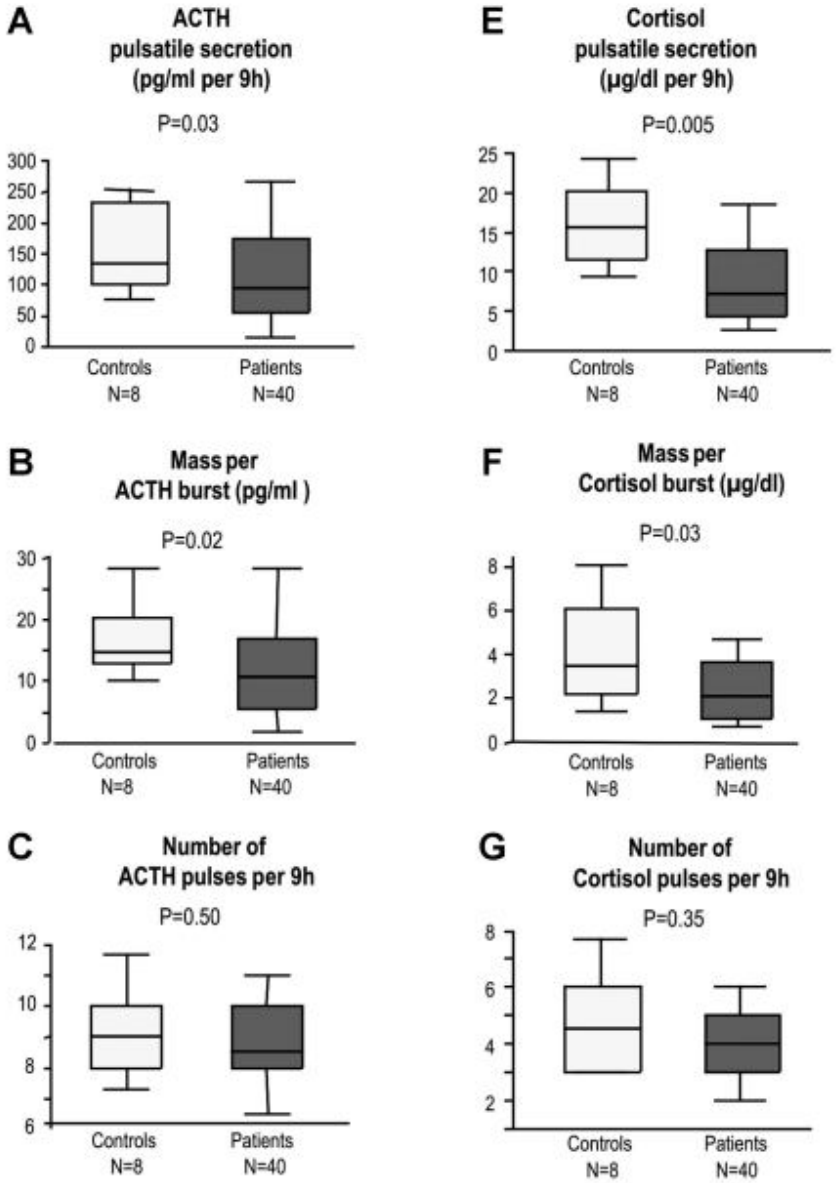
Plasma total and free cortisol concentrations (bottom) were always higher in patients than controls.

American Journal of Physiology-Endocrinology and Metabolism Vol. 306, No. 8, 2014

Illustrative ACTH and Cortisol Profiles



Steady release, less bursts !



Amplitude & Frequency of the pulses of ACTH & Cortisol in Patients vs Controls

American Journal of Physiology-Endocrinology and Metabolism Vol. 306, No. 8, 2014

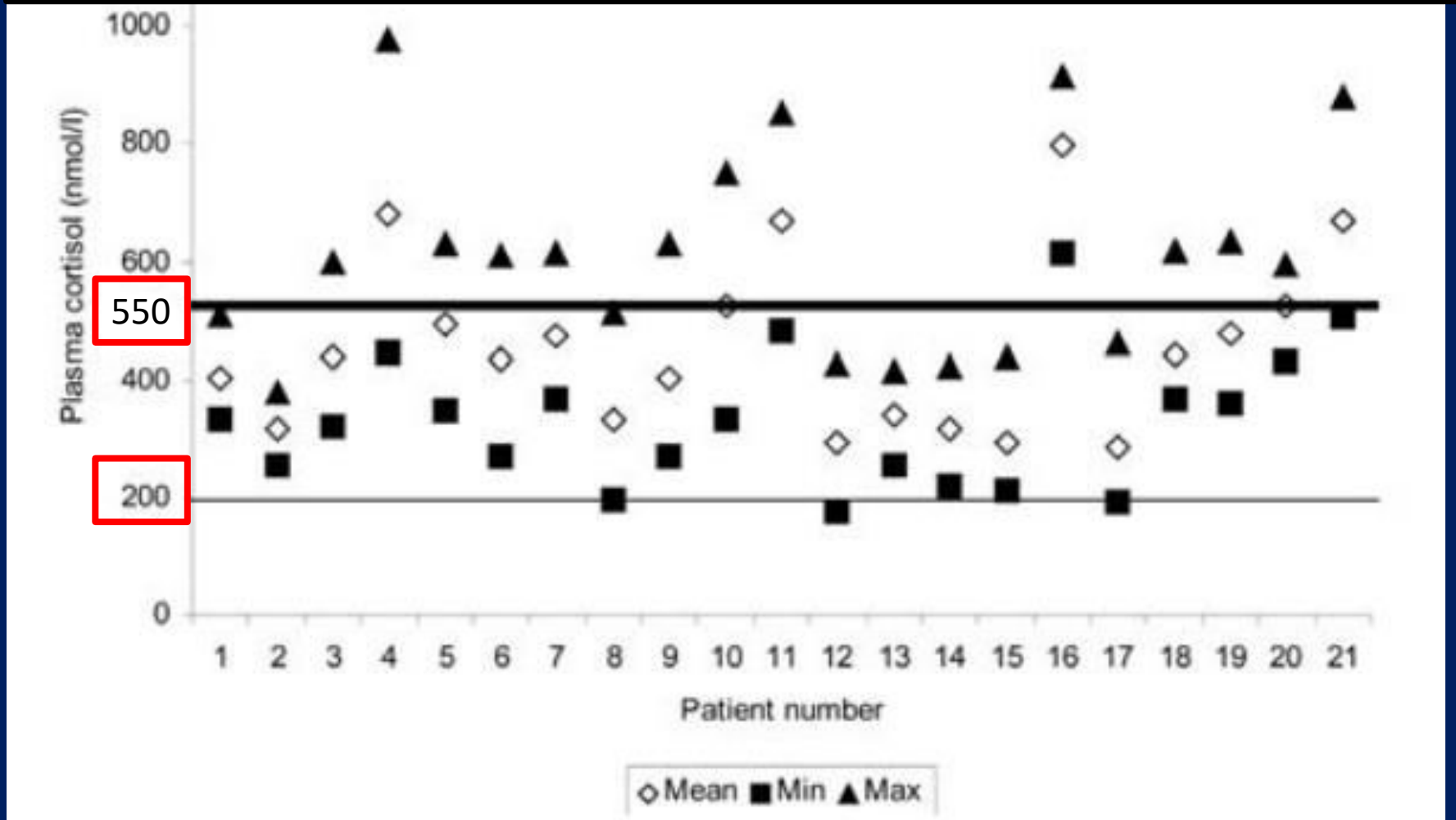
The Plasma Cortisol Profile Of Individual Patients

Plasma cortisol levels were performed on arterial blood samples hourly for 24 hours from 0500 on Day 1

When is the optimum sampling times for cortisol ?
Variability is driven by individual variability not by hour/ time of the day mesurements.

The thick horizontal line corresponding to a random Cortisol value of 550 nmol/l relates to the threshold value of stress cortisol in critically ill patients

The thin horizontal line corresponding to a random cortisol value of 200 nmol/l relates to the threshold value below which adrenal insufficiency would be diagnosed in the general medical population.



Anaesthesia and Intensive Care, Vol. 33, No. 2, April 2005

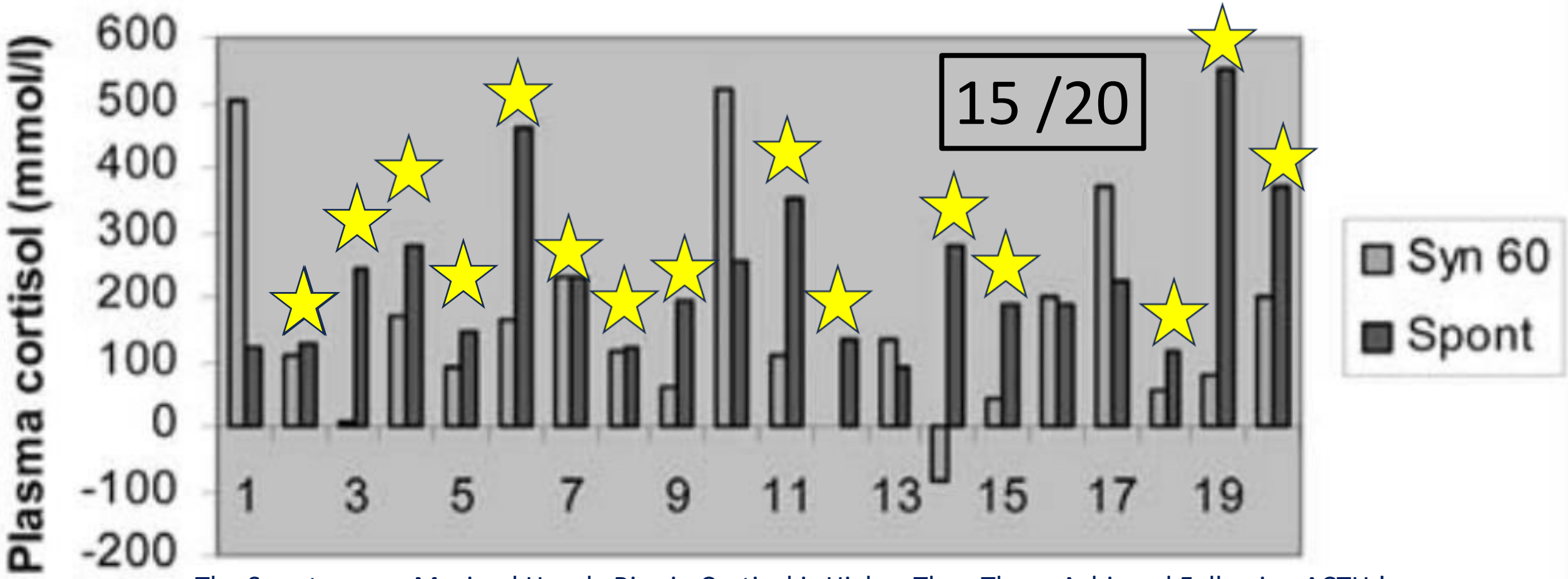
There was hour to hour variability (coefficient of variation 8-30%) in plasma cortisol concentrations.

No circadian rhythm was demonstrable

A single Cortisol level in ICU is NOT Representative !

A Bar Diagram Comparing The Spontaneous Maximal Hourly Rise In Plasma Cortisol With That Induced By Corticotropin.

Purple bars represent spontaneous rises and the grey bars corti-cotropin-induced rises.



The Spontaneous Maximal Hourly Rise in Cortisol is Higher Than Those Achieved Following ACTH !

Anaesthesia and Intensive Care, Vol. 33, No. 2, April 2005

A Bar Diagram Comparing The Spontaneous Maximal Hourly Rise In Plasma Cortisol With That Induced By Corticotropin.

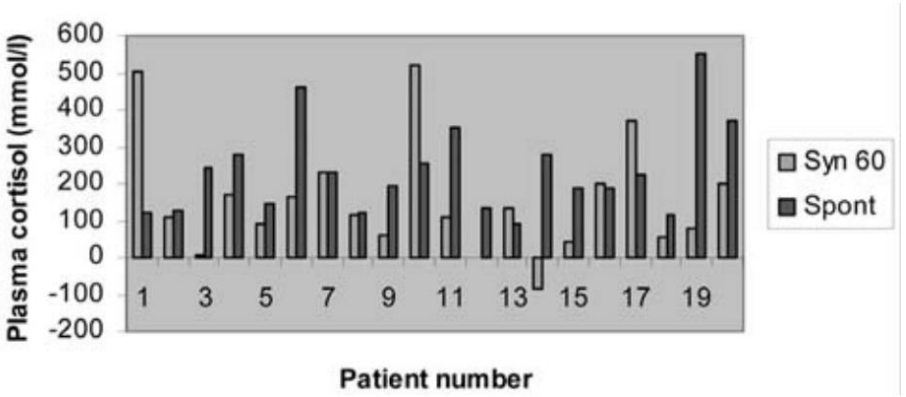
Purple bars represent spontaneous rises and the grey bars corti-cotropin-induced rises.

TABLE 1

Demographic data

Total number of patients	21
Sex	M14, F7
Mean age in years	44 (14)
Mean APACHE II score	21 (7)
Mean SOFA score	7 (3)
Hospital mortality	10%

Figures in brackets represent standard deviation.



Only four patients demonstrated an increase >200 nmol/l at 30 minutes (the criterion for adrenal insufficiency after 1 µg corticotropin.

A plasma cortisol increase of >250 nmol/l at 60 minutes after corticotropin was found in only two (9%) subjects

The mean maximal spontaneous hourly rise in cortisol was 233±121 nmol/l,
significantly greater than the corticotropin-induced rise 136±133 nmol/l ($P<0.001$).

In 15 patients the maximal spontaneous hourly increase in plasma cortisol was greater than that induced by corticotropin

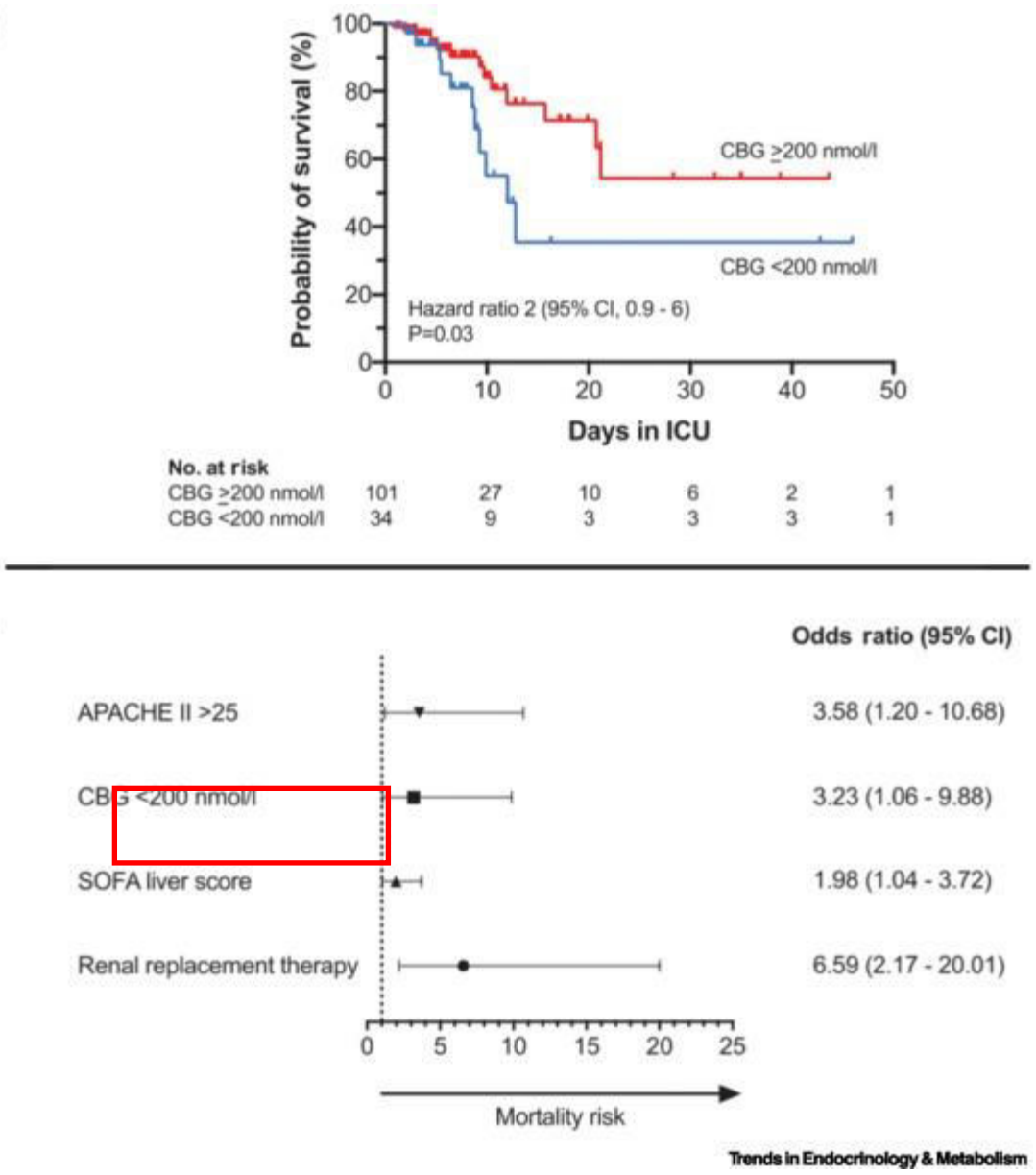
There was no significant difference in the mean plasma cortisol concentrations between responders (423±284 nmol/l) and non responders to corticotropin (474±207 nmol/l) ($P=0.66$)

Anaesthesia and Intensive Care, Vol. 33, No. 2, April 2005

CBG Depletion And Septic Shock Survival.

Low circulating CBG could be partially attributed to a downregulation of the glucocorticoid receptor-α (GRα) in the liver

Albumin, the other important cortisol binding protein is also reduced in critically ill patients



In critically ill patients, cortisol binding globulin (CBG) levels significantly decreased, dropping by around 50% compared to healthy individuals,

Cortisol binding by CBG is also reduced reversibly by pyrexia and acidemia

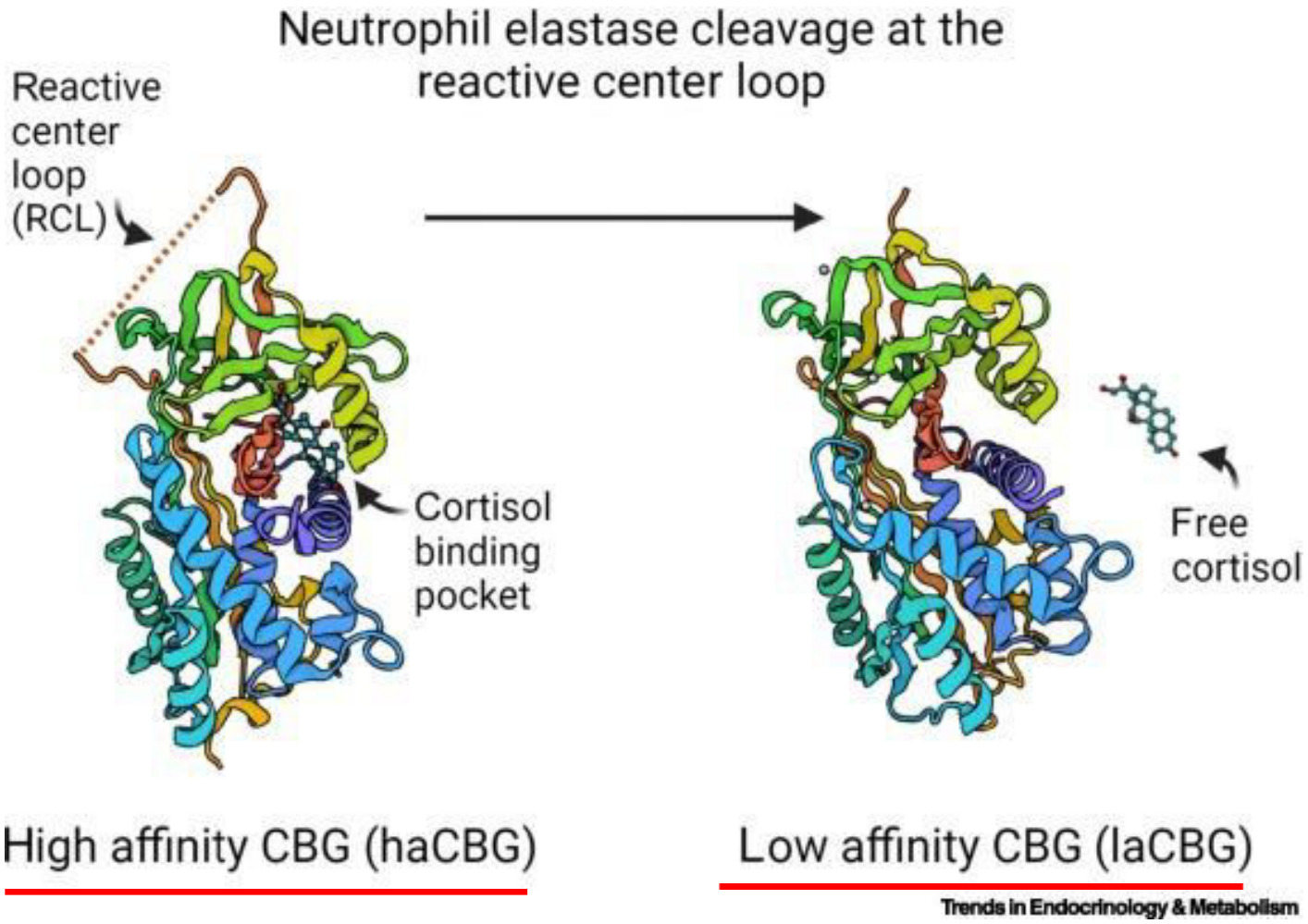
Plasma clearance of cortisol is substantially reduced and cortisol half-life is on average 8-fold longer in these patients compared with healthy subjects

Trends in Endocrinology & Metabolism, Volume 34, Issue 3, 181 – 190, 2023

Cleavage Of The Exposed Reactive Center Loop At The Neutrophil Elastase (NE) Cleavage Site By NE Produces Conformational Change Of CBG,

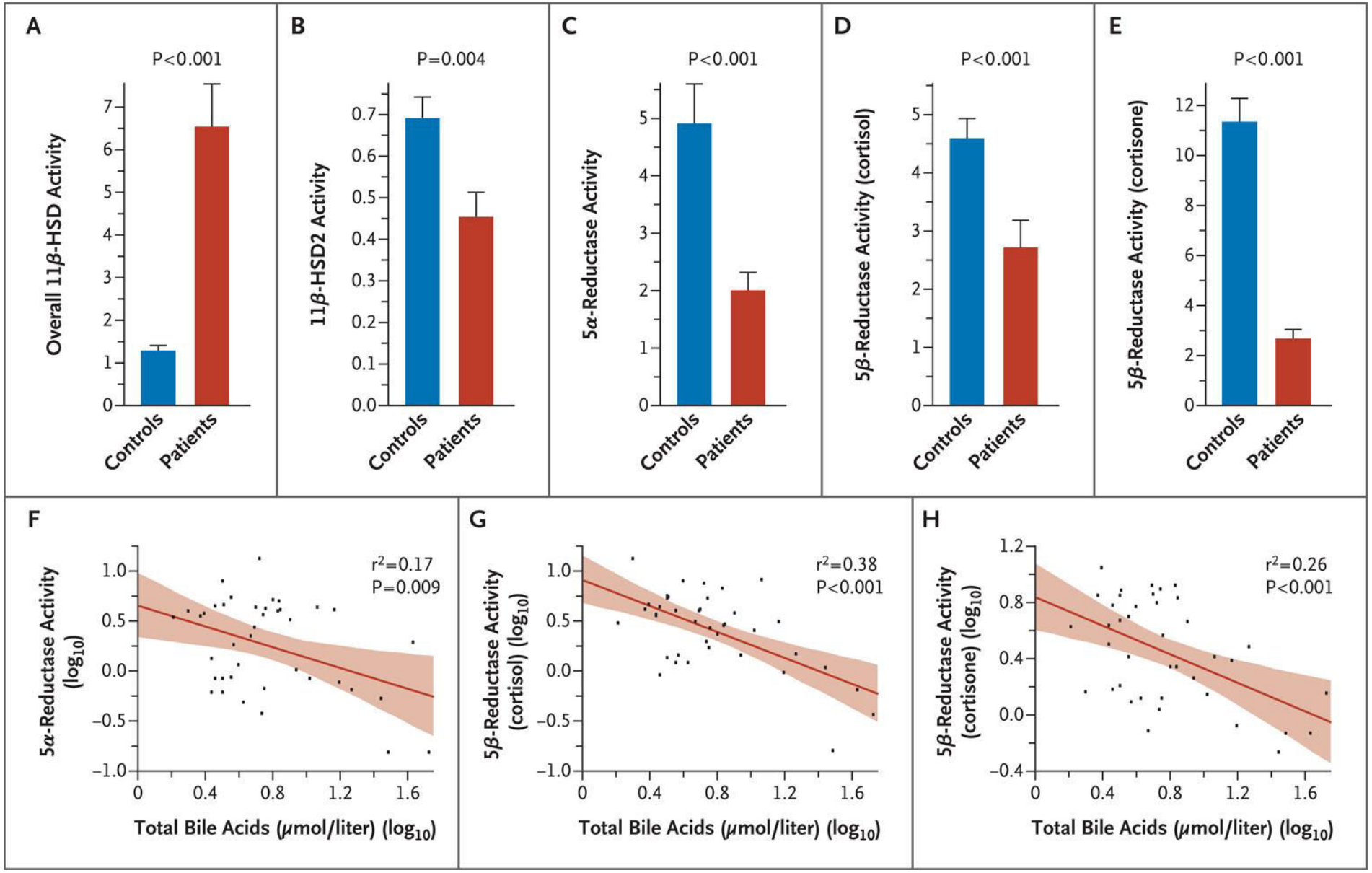
Resulting In 90% Reduction In Cortisol-binding Affinity

Increases free Cortisol by 4 X



Trends in Endocrinology & Metabolism, Volume 34, Issue 3, 181 – 190, 2023

Activity of Cortisol-Metabolizing Enzymes, as Estimated from Ratios of Cortisol Metabolites in 24-Hour Urine Samples.



N Engl J Med 2013;368:1477-1488

Plasma Half-life Of A Therapeutic Dose Of Cortisol.

12. Table S3: Main results for ICU survivors and non-survivors versus controls.

	Controls mean±SD	ICU survivor mean±SD	ICU non-survivor mean±SD	P-value Control vs ICU-survivor	P-value ICU-survivor vs non-survivor
Plasma ACTH and cortisol time course					
Mean Plasma ACTH (pg/ml)	49.6±37.9	16.9±9.7	17.1±9.1	<0.001	0.83
Mean Plasma Total Cortisol (µg/dl)	11.9±2.3	16.8±7.8	17.3±8.7	0.01	0.73
Free Cortisol day 1 (µg/dl)	0.4±0.1	1.8±2.1	2.8±4.0	0.001	0.93
Free Cortisol day 7 (µg/dl)	0.4±0.1	1.3±1.3	1.4±0.8	<0.001	0.28
Cortisol kinetics during stable isotope tracer infusions					
Plasma Cortisol at steady state (µg/dl)	2.9±1.3	9.1±4.1	14.7±2.7	0.002	0.07
Rate of Appearance of Cortisol (mg/h)	1.5±1.5	2.6±1.4	3.7±0.4	0.05	0.28
Plasma Clearance of D4-cortisol (liter/min)	0.5±0.3	0.3±0.1	0.26±0.06	0.03	0.83
Plasma D4-cortisol (µg/dl)	1.7±1.1	2.7±1.0	2.3 0.6	0.03	0.83
Net rate of appearance Cortisone (mg/h per µg/dl)	0.14±0.07	0.07±0.02	0.07±0.0006	0.008	0.90
Rate of appearance of D3-cortisol (mg/h)	0.5±0.1	0.4±0.1	0.4±0.1	0.42	0.28
Plasma clearance of a therapeutic dose of cortisol					
Plasma Clearance of Cortisol (liter/min)	0.10±0.02	0.05±0.03	0.02±0.01	0.001	0.03
Cortisol Half-life (h)	1.8±0.3	9.4±10.0	17.9±13.0	<0.001	0.03
Activity of cortisol metabolizing enzymes estimated by ratios of urinary cortisol metabolites					
11β-HSD2 (E/F)	0.7±0.2	0.5±0.3	0.3±0.3	0.01	0.13
overall-11β-HSD (THF+allo/THE)	1.3±0.4	6.9±6.3	4.1±2.6	<0.001	0.35
5α-reductase (alloTHF/F)	4.9±2.6	2.3±1.8	0.5±0.3	0.002	0.01
5β-reductase (THF/F)	4.6±1.3	3.0±2.9	1.3±1.4	0.001	0.14
5β-reductase (THE/E)	11.4±3.7	2.6±2.2	2.9±2.5	<0.001	1.00
Tissue expression of cortisol metabolizing enzymes					
		NA			NA

N Engl J Med 2013;368:1477-1488

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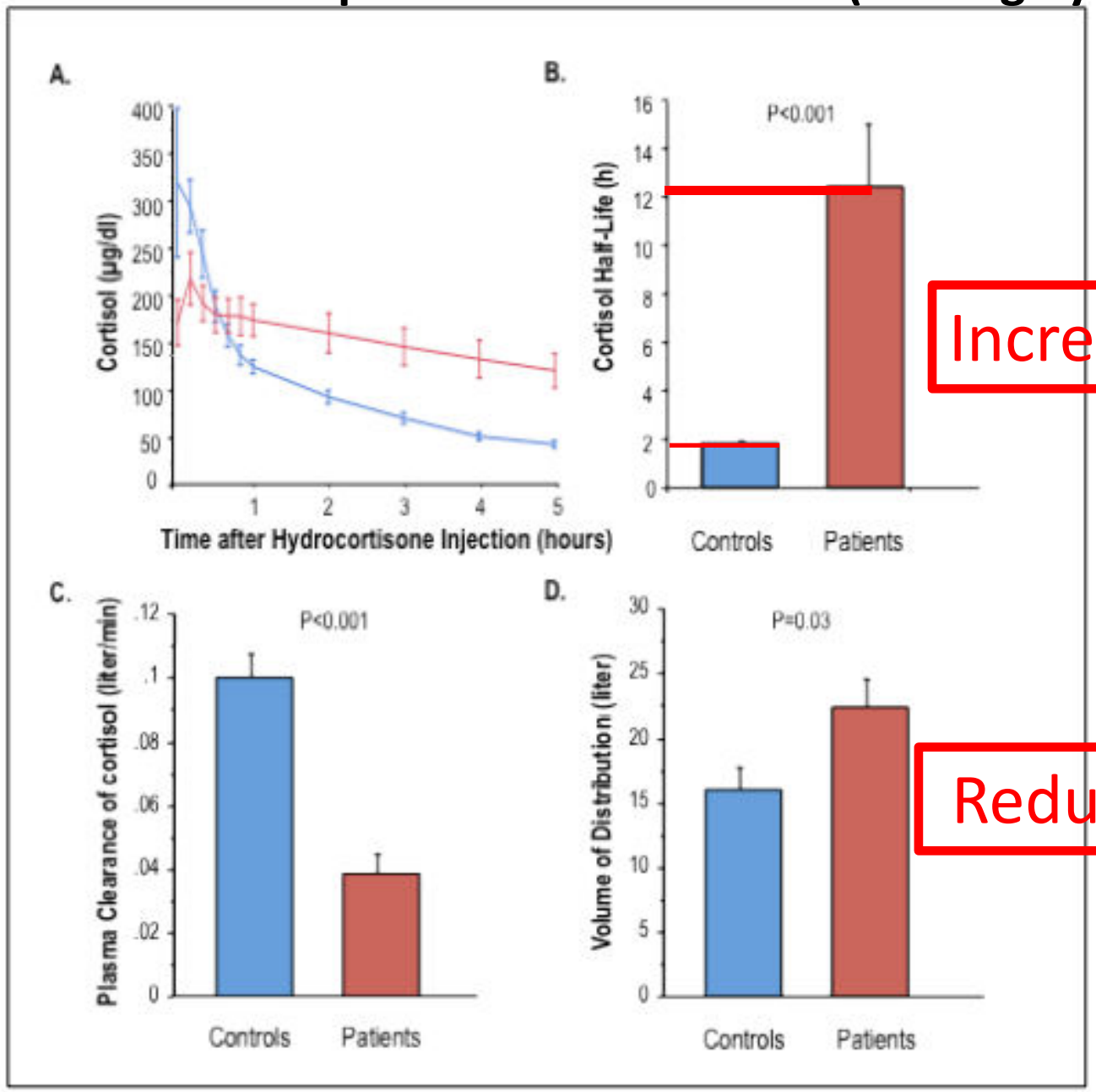
Tissue expression of cortisol metabolizing enzymes					
		NA		NA	

Basis for the NEW 60 mg hydrocortisone Dose for critically ill patients.
(40 mg AM 20 mg PM)

N Engl J Med 2013;368:1477-1488

Plasma half-life of a therapeutic dose of cortisol (100 mg hydrocortisone).



Increased by 6 X

Reduced by 50%

N Engl J Med 2013;368:1477-1488

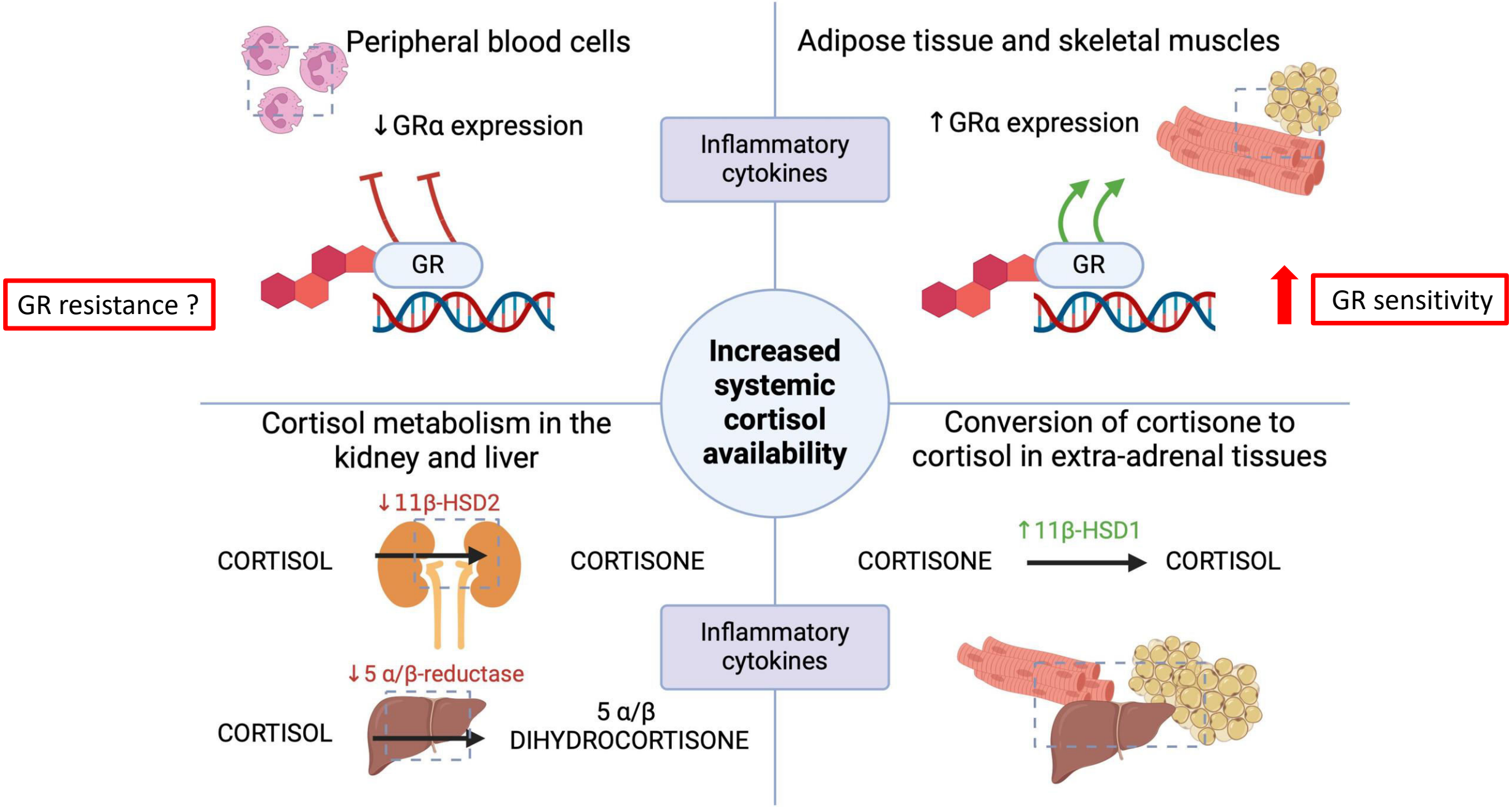
Baseline and Cosyntropin-Stimulated Serum Total Cortisol and Free Cortisol Concentrations in Critically Ill Patients and Healthy Volunteers

Table 2. Base-Line and Cosyntropin-Stimulated Serum Total Cortisol and Free Cortisol Concentrations in Critically Ill Patients and Healthy Volunteers.* **Group 1** had serum albumin values less than or equal to 2.5 g per deciliter; **Group 2** had serum albumin values higher than 2.5 g per deciliter.

Variable	Group 1 (N=36)	Group 2 (N=30)	Healthy Volunteers (N=33)
Total cortisol			
Base line (μg/dl)	15.8±7.4†‡§	22.6±8.9†‡	8.6±4.2
Range	5.3–35.4	9.6–54.0	3.8–23.7
Median	13.3	21.5	7.9
After cosyntropin stimulation (μg/dl)	23.4±9.5§¶	34.4±10.3‖	27.8±5.3
Range	10.0–50.2	20.0–59.8	19.1–43.3
Median	21.2	31.6	27.2
Subjects with a maximal response <18.5 μg per deciliter after cosyntropin stimulation — no./total no. (%)	14/36 (39)†§	0/30	0/33
Free cortisol			
Base line (μg/dl)	5.1±4.1†‡**	5.2±3.5†‡	0.6±0.3
Range	1.3–12.8	1.5–13.0	0.2–1.4
Median	4.0	4.7	0.6
After cosyntropin stimulation (μg/dl)	9.3±6.3†‡**	10.1±5.9†‡	2.8±0.7
Range	3.1–29.4	4.0–29.1	1.9–4.5
Median	8.6	9.2	2.7
As a percentage of total cortisol			
At base line	31.1±14.4†‡††	22.6±10.2†‡	8.0±2.1
After cosyntropin stimulation	38.6±18.9†‡‡‡	29.5±11.2†‡	10.1±2.0

N Engl J Med 2004;350:1629-38

The Mechanisms Leading To The Increased Systemic Availability Of Cortisol In Acute Conditions



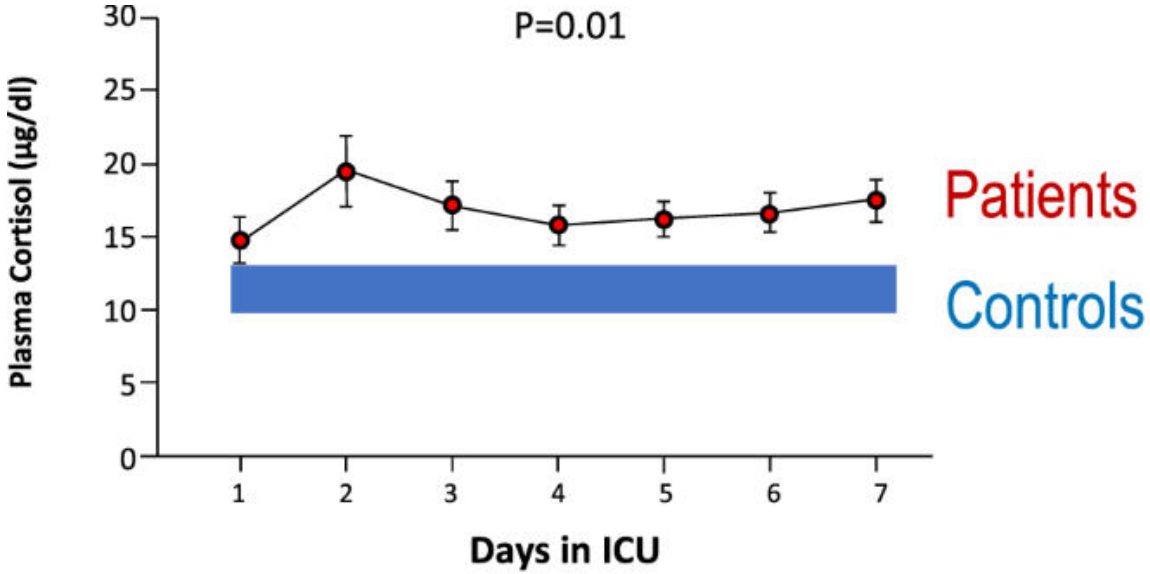
Front. Endocrinol, Sec. Adrenal Endocrinology, Volume 15, 06 November 2024

Dissociation between ACTH and Cortisol Levels among Patients in the Intensive Care Unit (ICU)

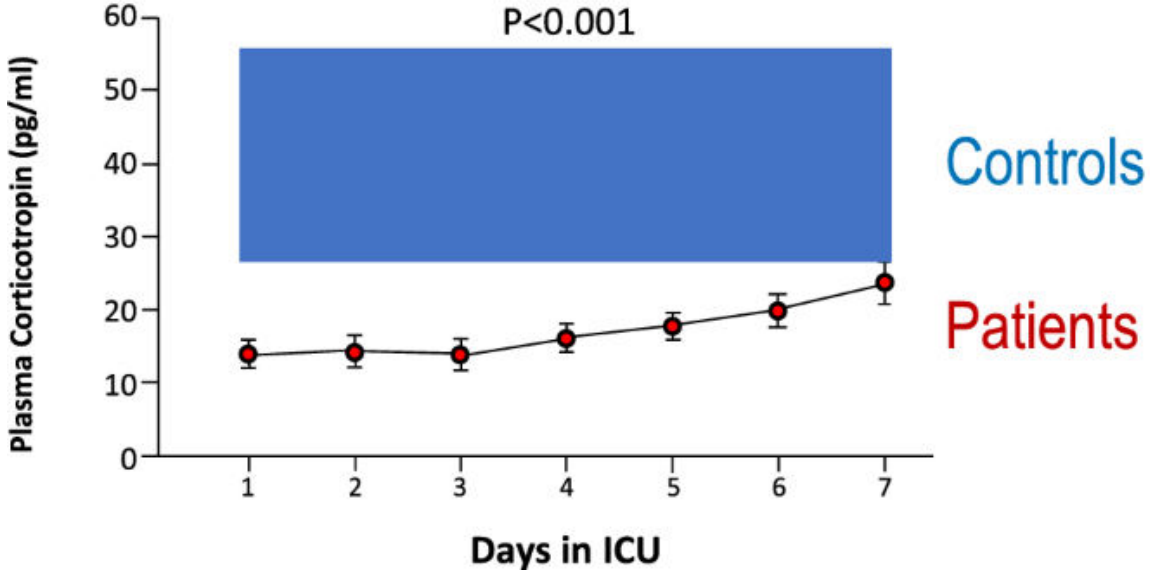
In the patients, as compared with the controls, endogenous cortisol levels are increased by a factor of 3.5 (P<0.001),

The rate of appearance of cortisol (cortisol production) is increased by 83% (P=0.02)

There was no significant difference in cortisol production between patients who were treated with inotropes and those who were not treated (2.7±1.3 mg per hour and 2.9±1.4 mg per hour, respectively; P=0.86).



Cortisol clearance is even more suppressed in non-survivors (0.02±0.01 liters per minute) than in survivors (0.05±0.03 liters per minute, P=0.03).



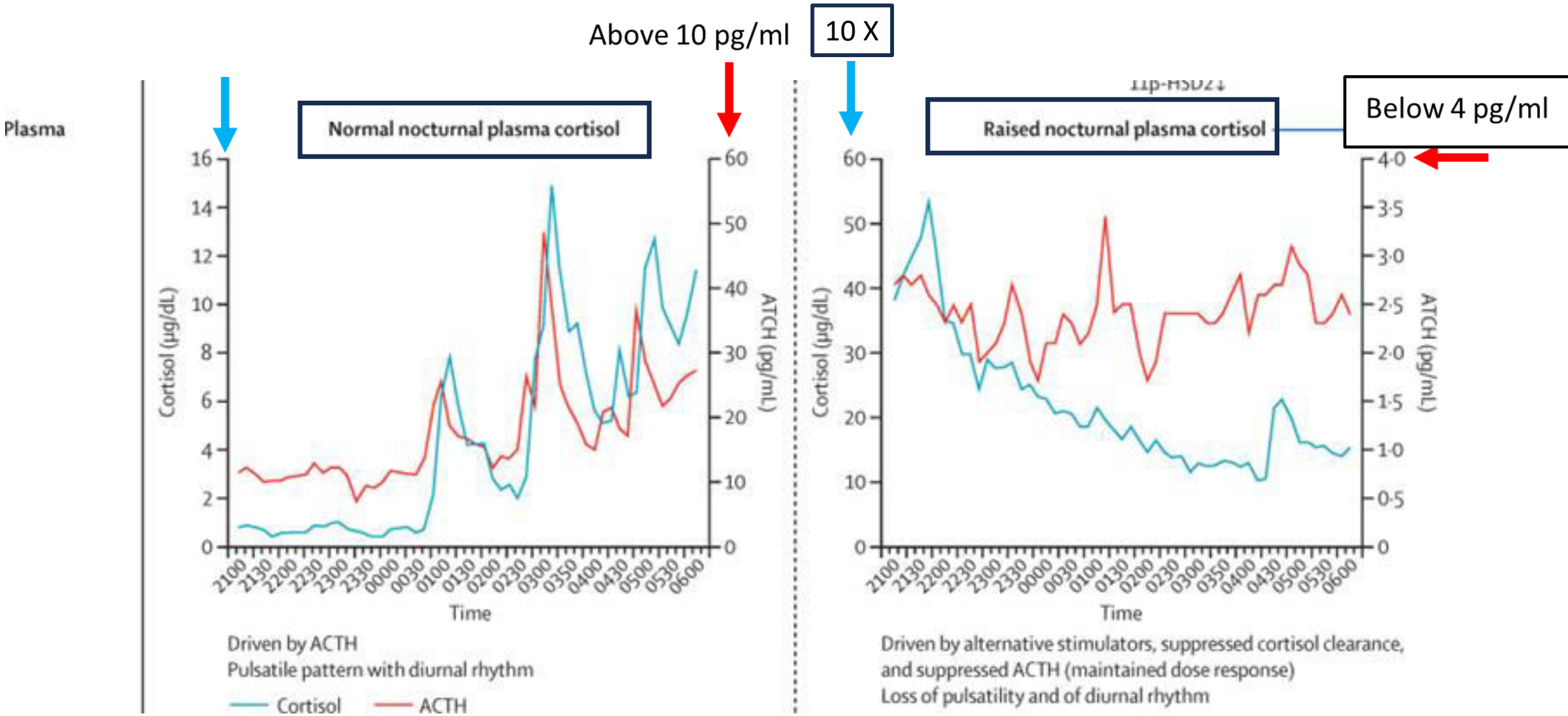
Day 1 of 31.6±10.4 mg per liter (P=0.001) and on

Day 7 of 47.4±11.6 mg per liter (P<0.001), as compared with

A single measure of 67.8±8.7 mg per liter in the controls.

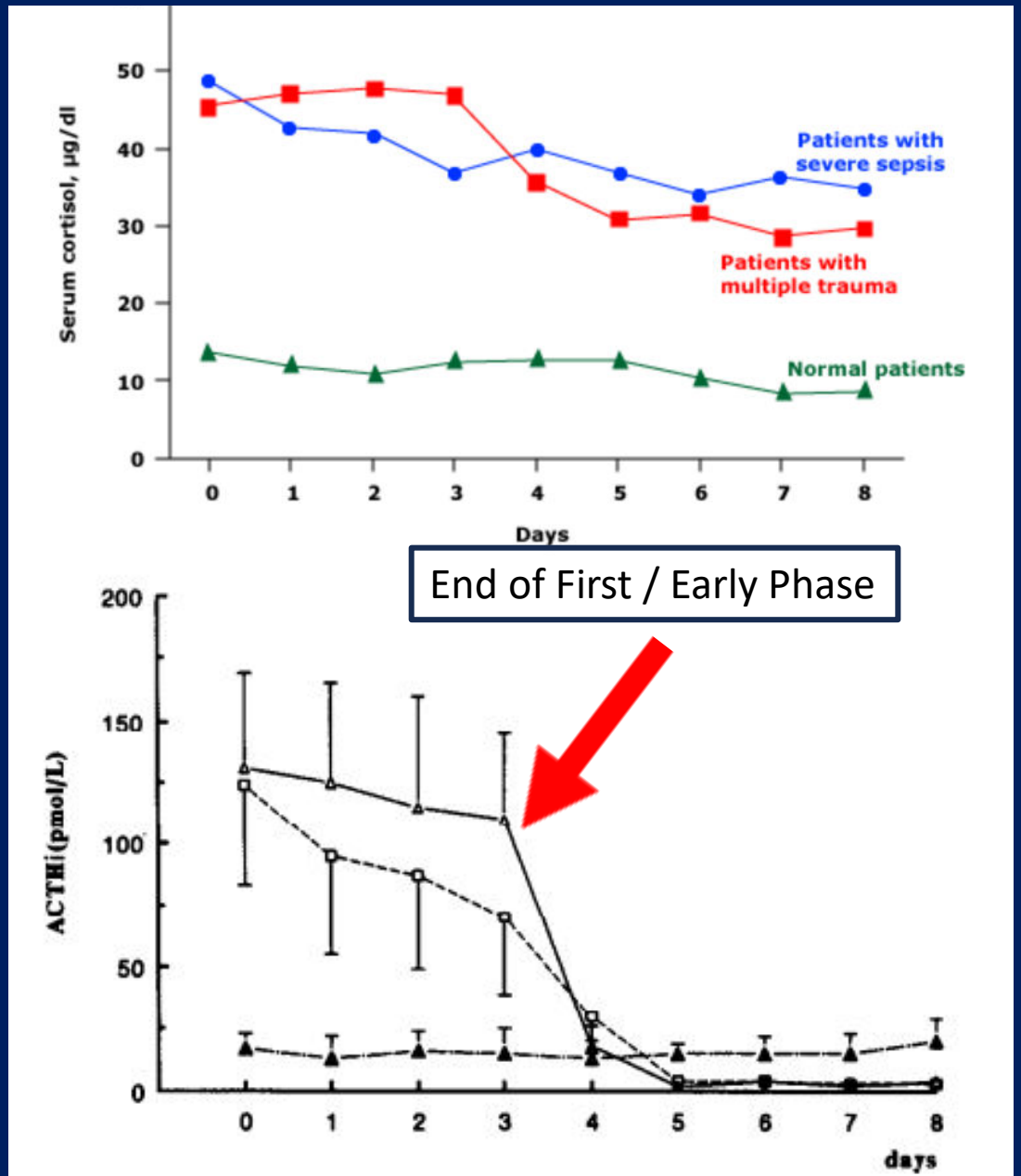
J Anesth. 2021 Dec;35(6):903-910.

Nocturnal Cortisol (Blue) and ACTH (Red) Responses in Healthy vs Critically-Ill Patients



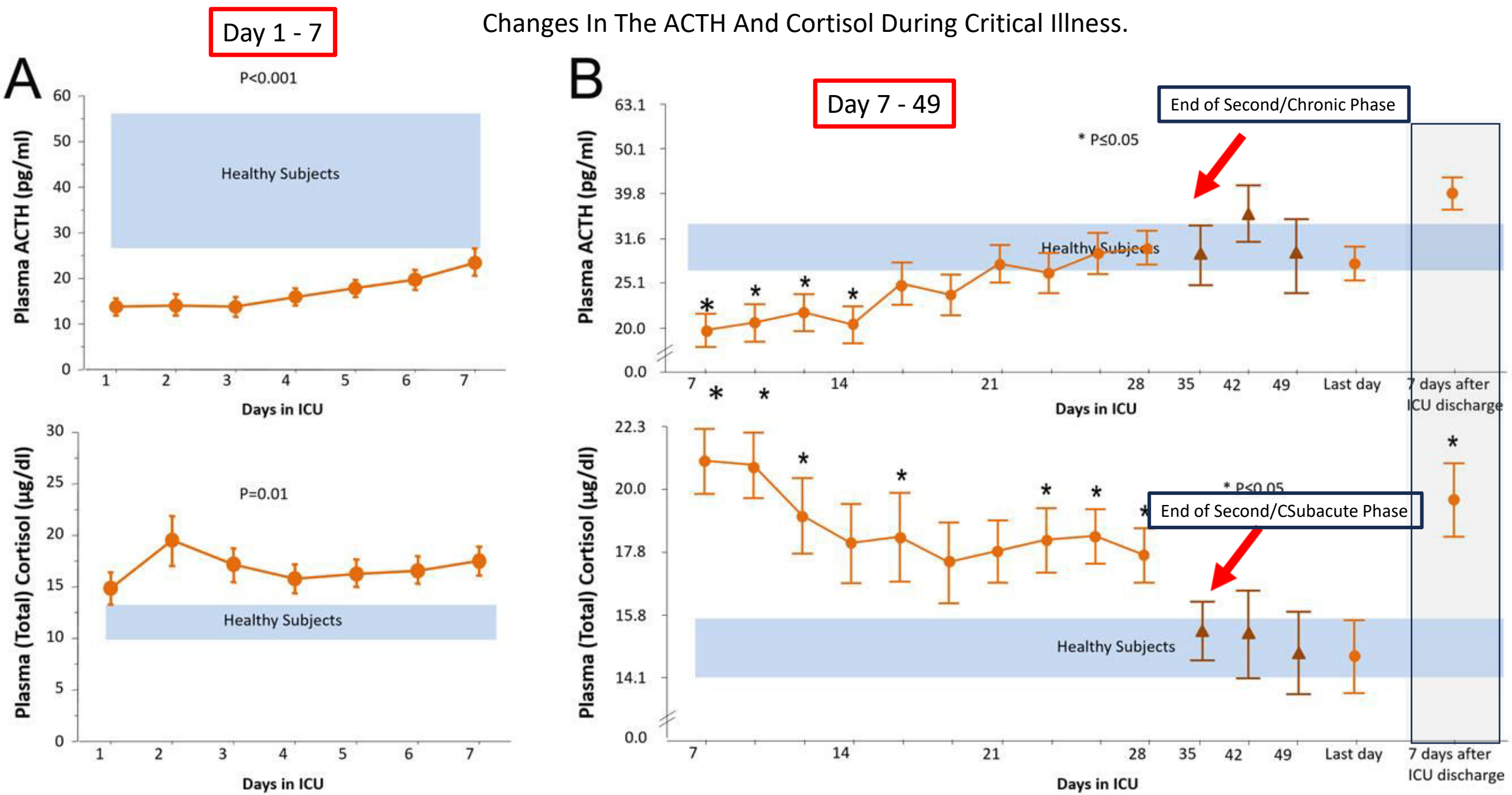
The Lancet Diabetes & Endocrinology Volume 3, Issue 10, October 2015, Pages 805-815

Plasma Cortisol & ACTH In Patients With Sepsis And Multiple Trauma And In Control Subjects During The First 8 Days After Admission Into ICU.



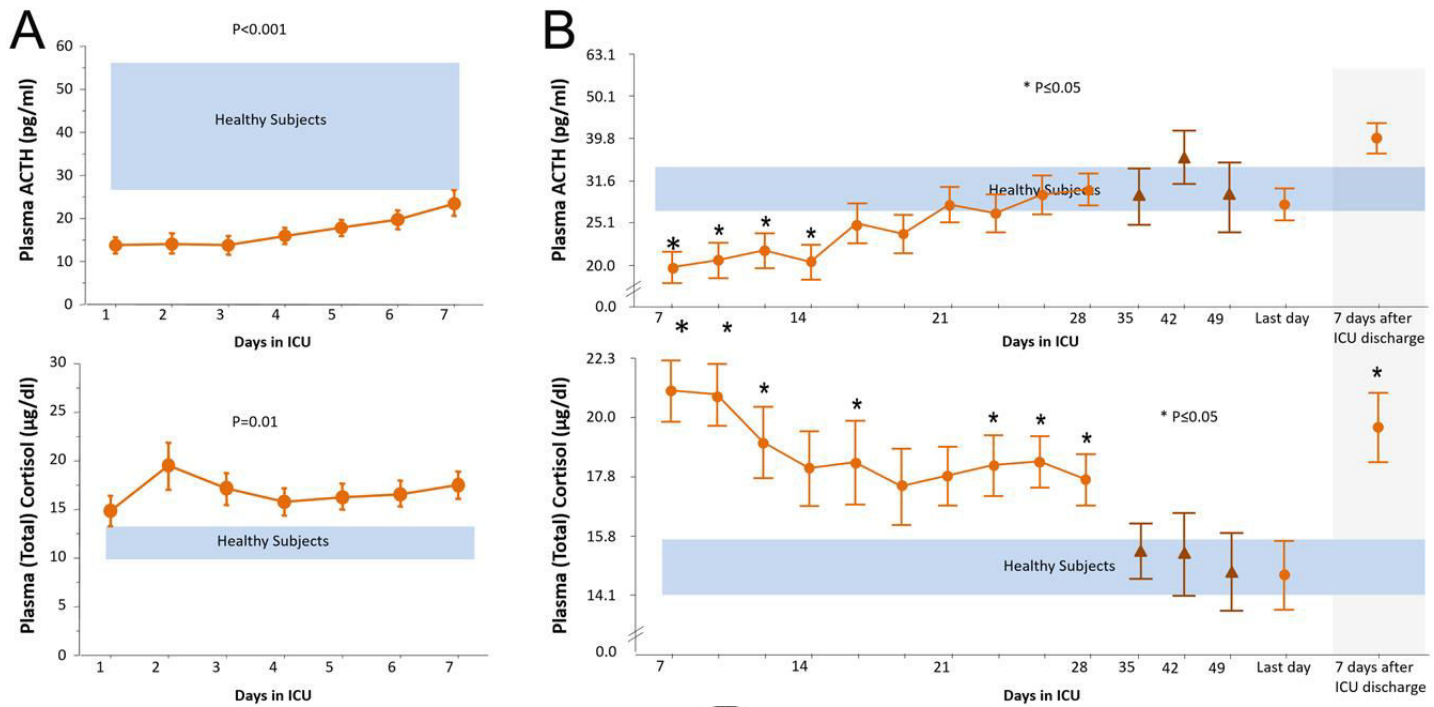
J Clin Endocrinol Metab. 1995;80(4):1238-1242.

Changes In The ACTH And Cortisol During Critical Illness.



Endocrine Connections Volume 8: Issue 8 , R131–R143, 2019

Changes in The ACTH And Cortisol During Critical Illness.



HPA Axis In Critical Illness

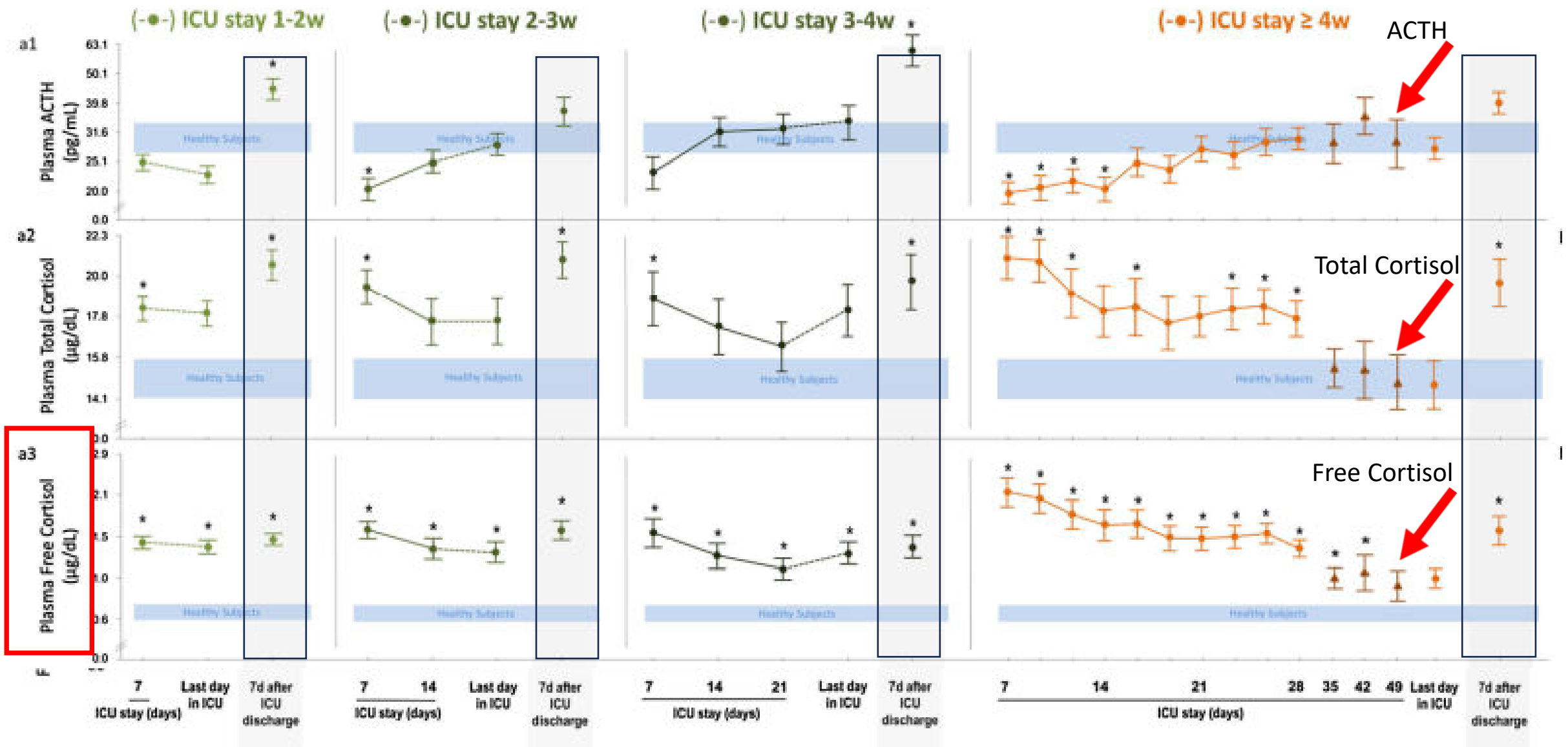
an acute phase (a few minutes after the initial damage)

a subacute phase (a few hours to several days after the initial damage)

chronic phase (more than a few weeks after the initial damage)

Endocrine Connections Volume 8: Issue 8 , R131–R143, 2019

Adrenocortical Function Parameters From Day 7 In ICU Until ICU Discharge Or Death - and 7 Days After ICU Discharge - For Patients Who Did Not Receive Glucocorticoids



Intensive Care Med. 2018 Oct;44(10):1720-1729.

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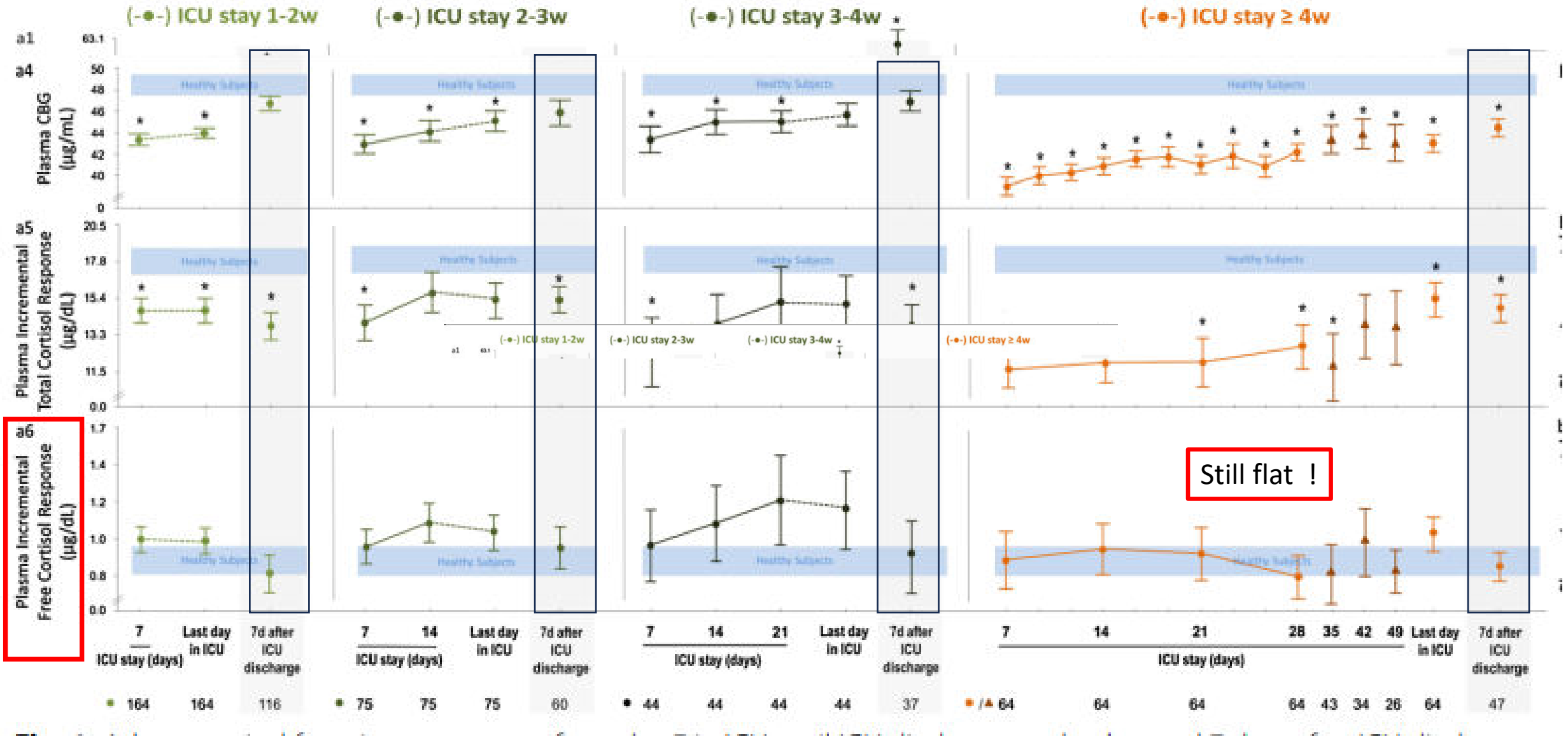
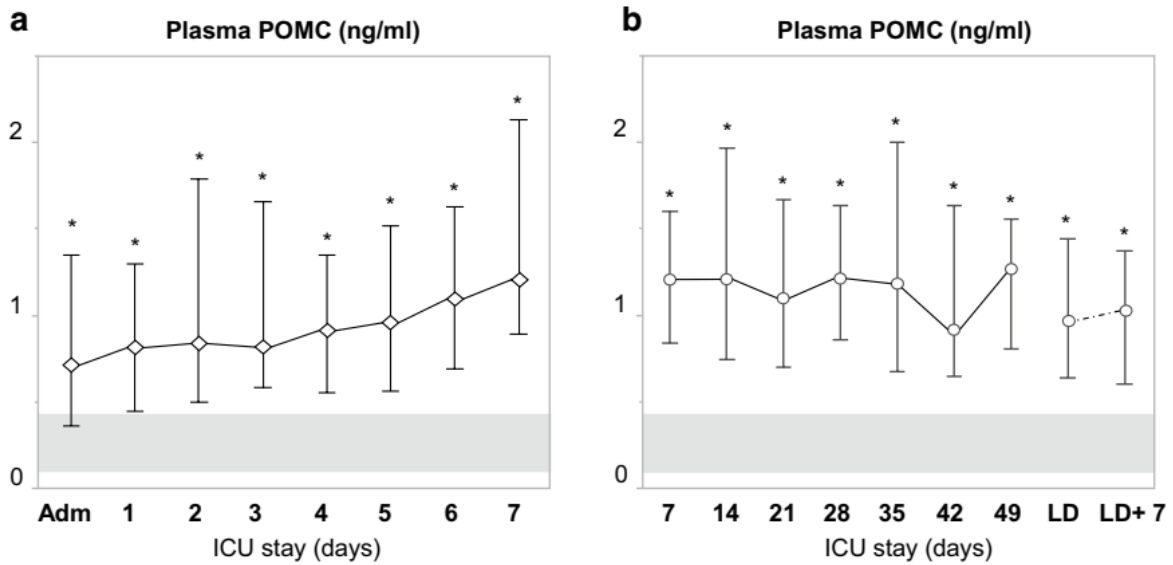
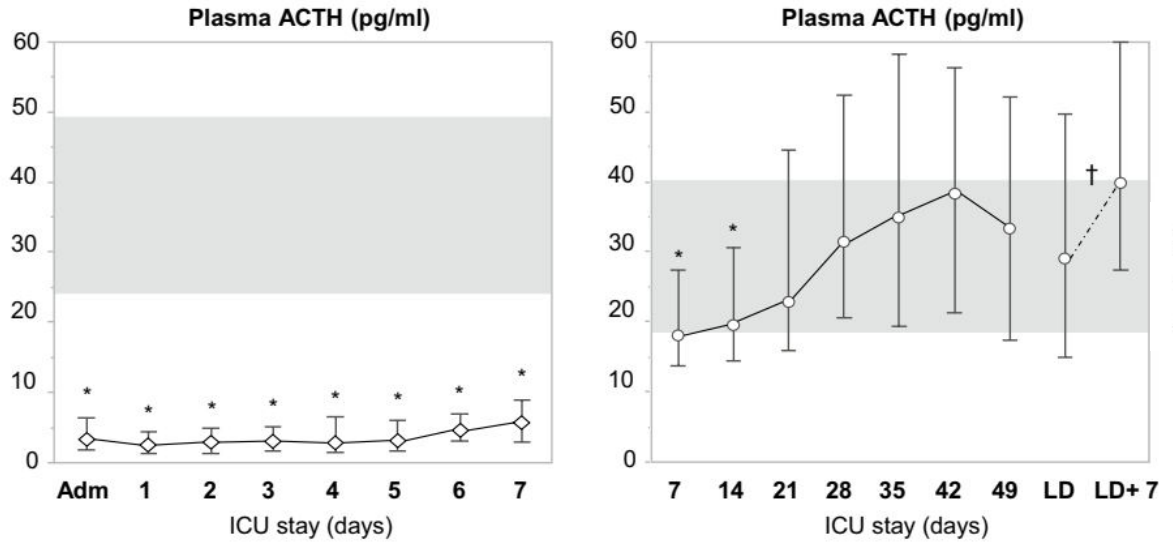


Intensive Care Med. 2018 Oct;44(10):1720-1729.

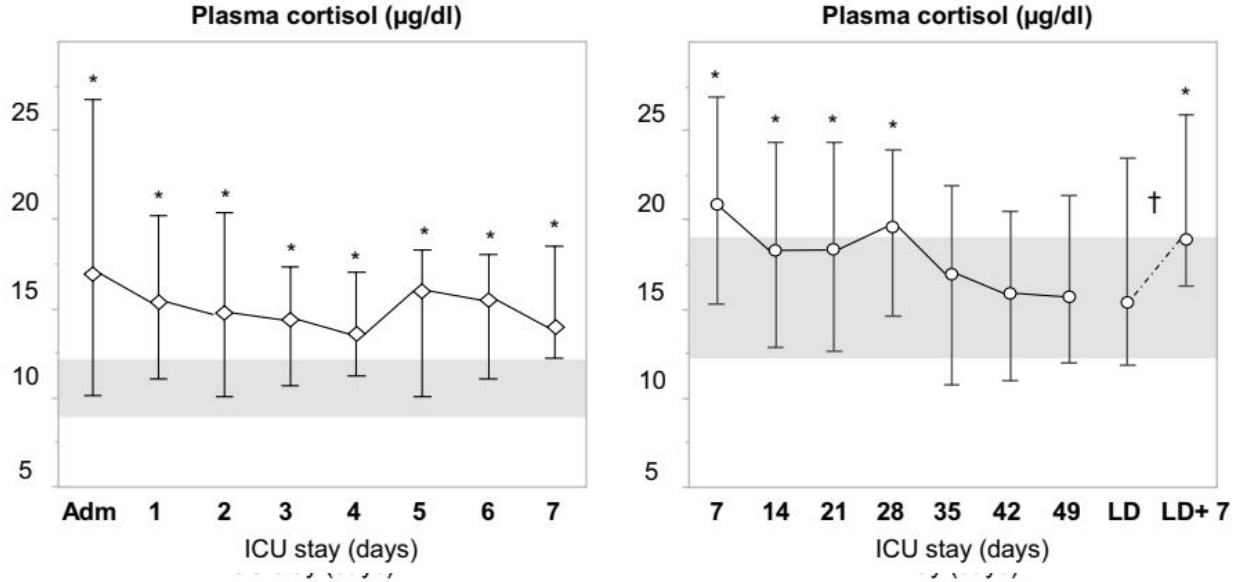
Plasma Cortisol, ACTH and POMC Concentrations In Critically Ill Patients.



POMC where ACTH dissociation occurs



From ICU day 35 and ICU day 21 onwards,
plasma concentrations of total cortisol and ACTH, respectively,
were no longer different from those in healthy control subjects

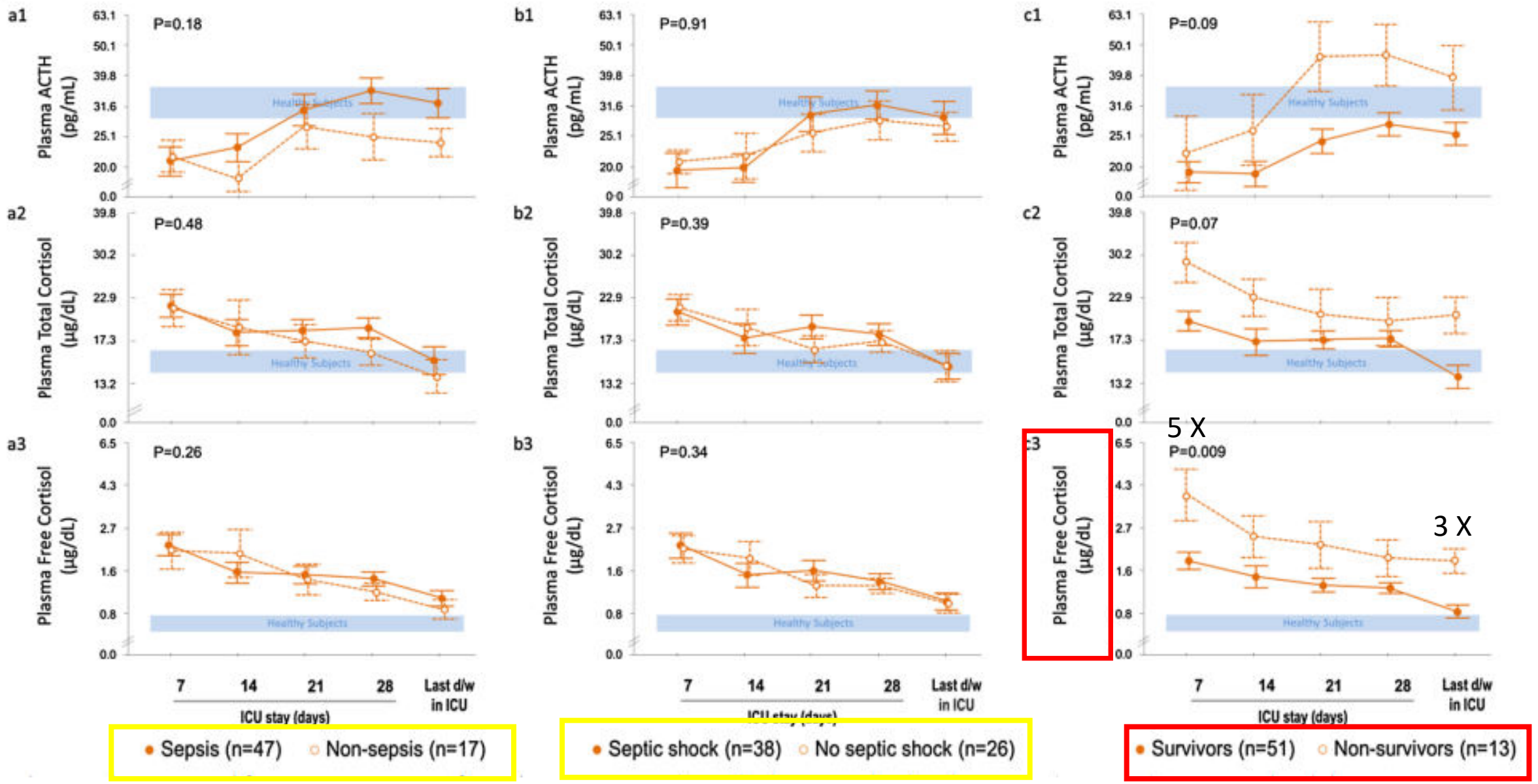


Per time point (n):

Patients:	51	51	51	51	43	38	30	25	45	45	45	45	29	22	15	45	27
Healthy controls:	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20

Téblick et al. Crit Care (2021) 25:65

Adrenocortical Function Parameters From Day 7 In ICU Until ICU Discharge Or Death In Long-stay (ICU≥4w) Patients Who Did Not Receive Glucocorticoids



Intensive Care Med. 2018 Oct;44(10):1720-1729.

ACTH and Cortisol Responses To CRH In Acute, Subacute, And Prolonged Critical Illness: A Randomized, Double-blind, Placebo-controlled, Crossover Cohort Study

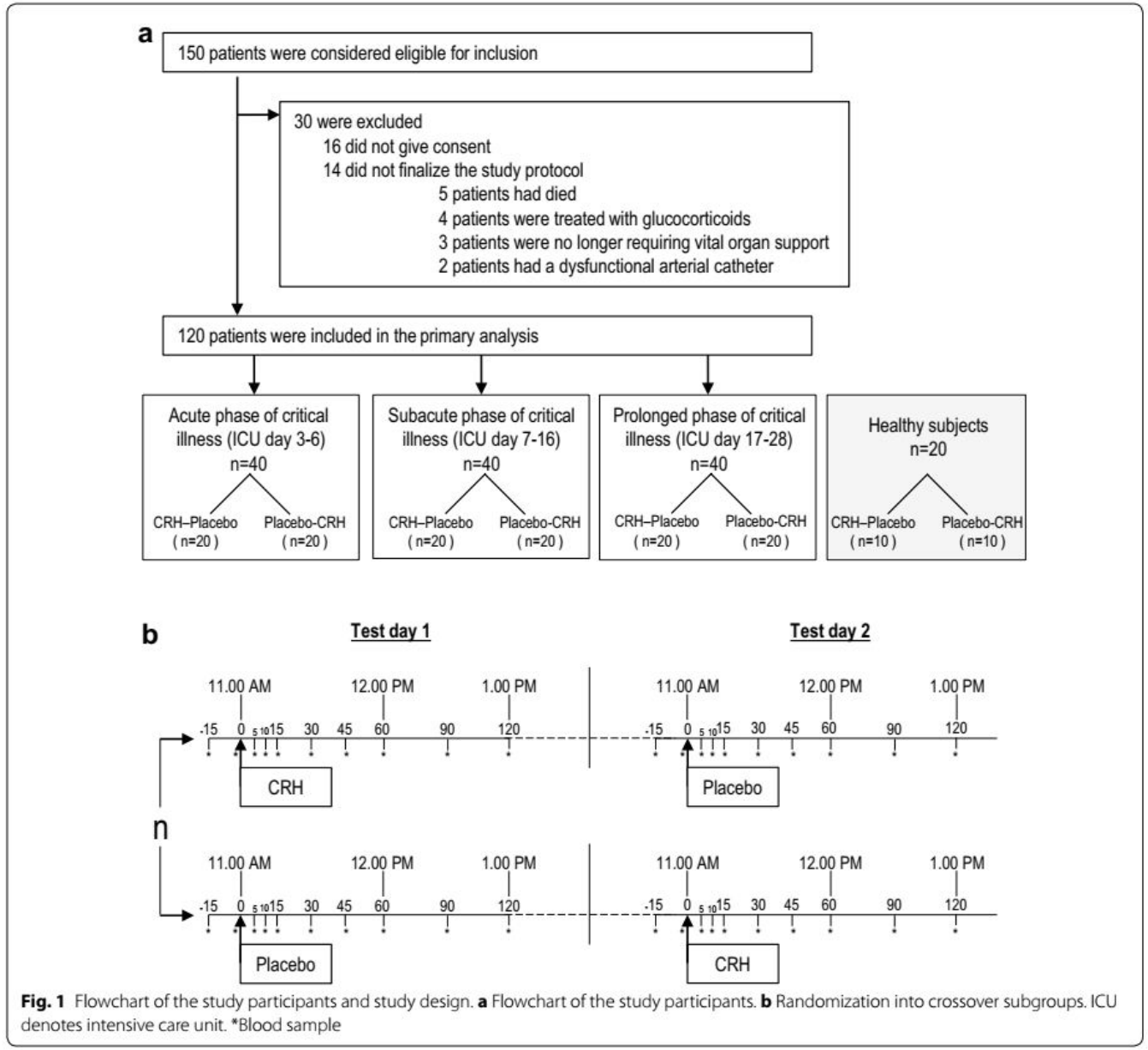


Fig. 1 Flowchart of the study participants and study design. **a** Flowchart of the study participants. **b** Randomization into crossover subgroups. ICU denotes intensive care unit. *Blood sample

Intensive Care Med (2018) 44:2048–2058

Plasma ACTH, total and free cortisol concentrations after CRH or placebo injection over time in ICU.

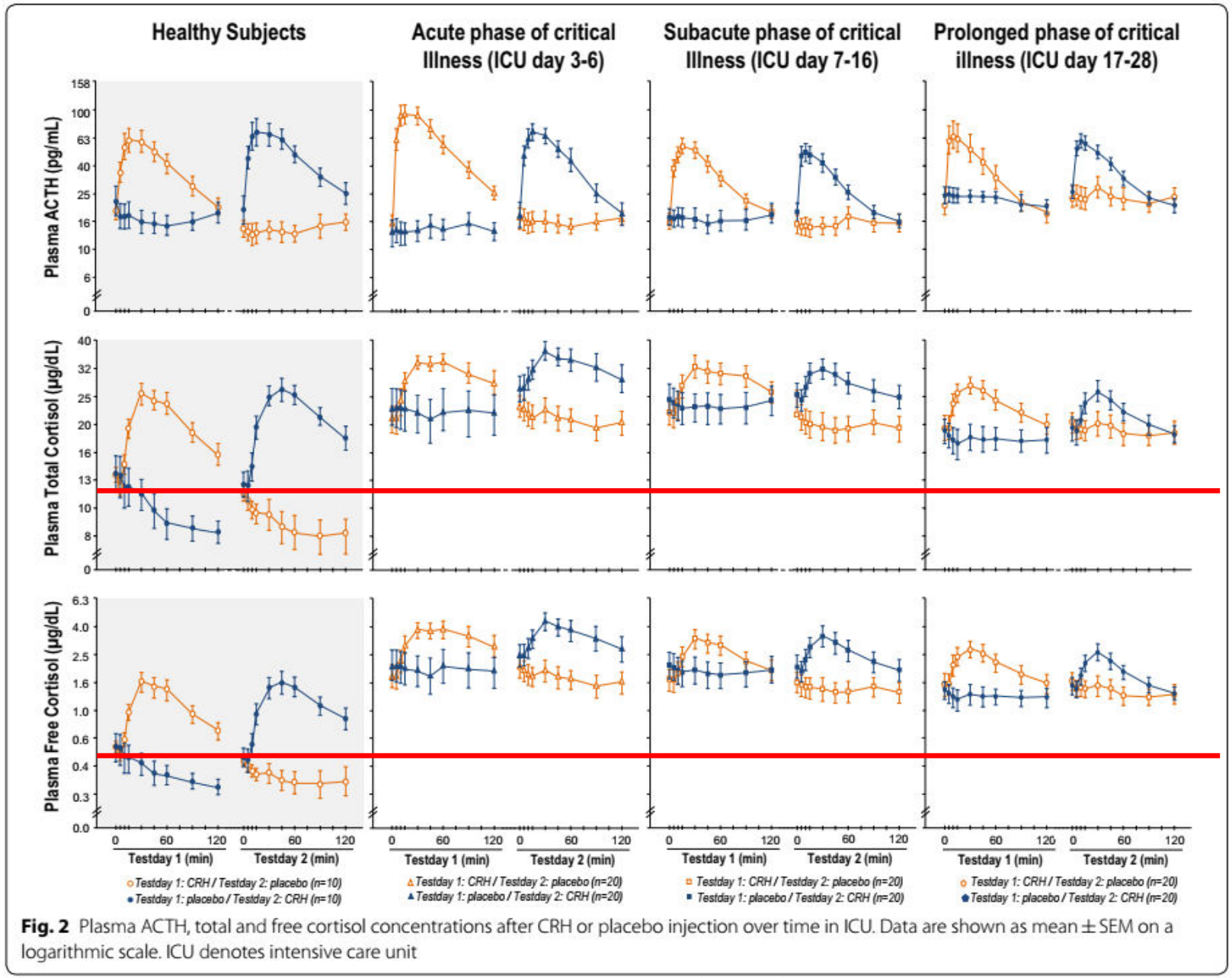
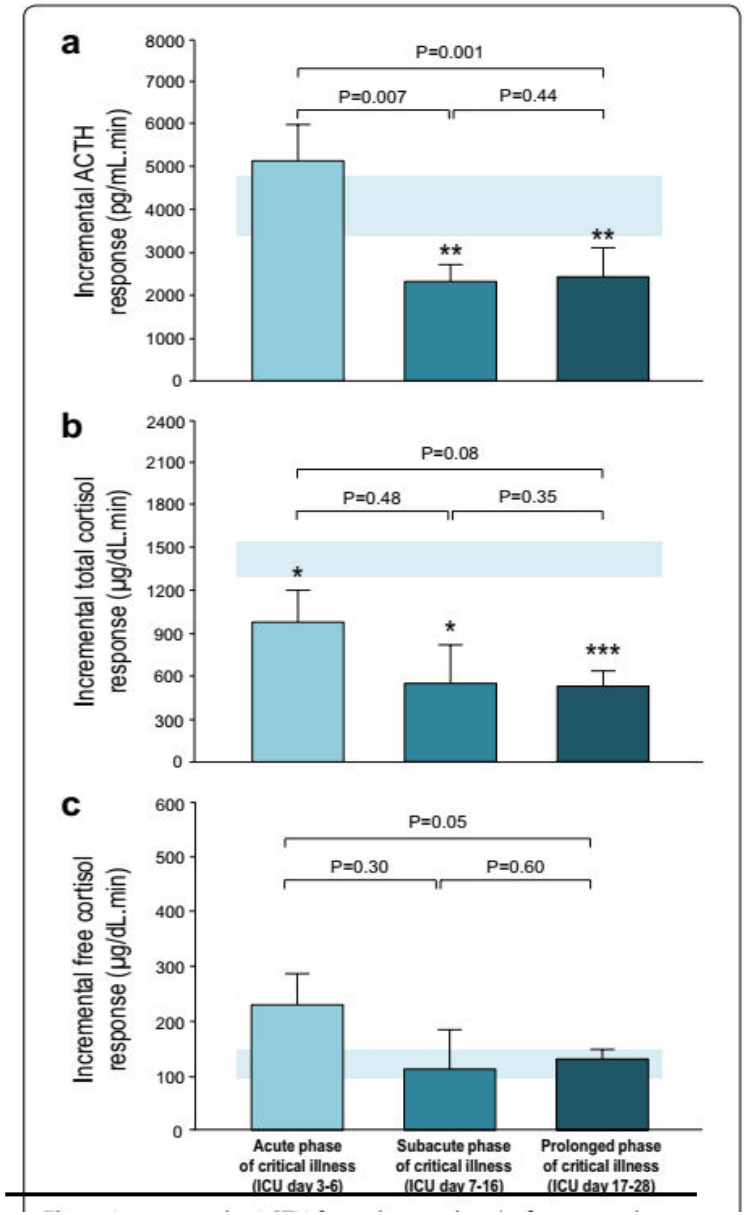


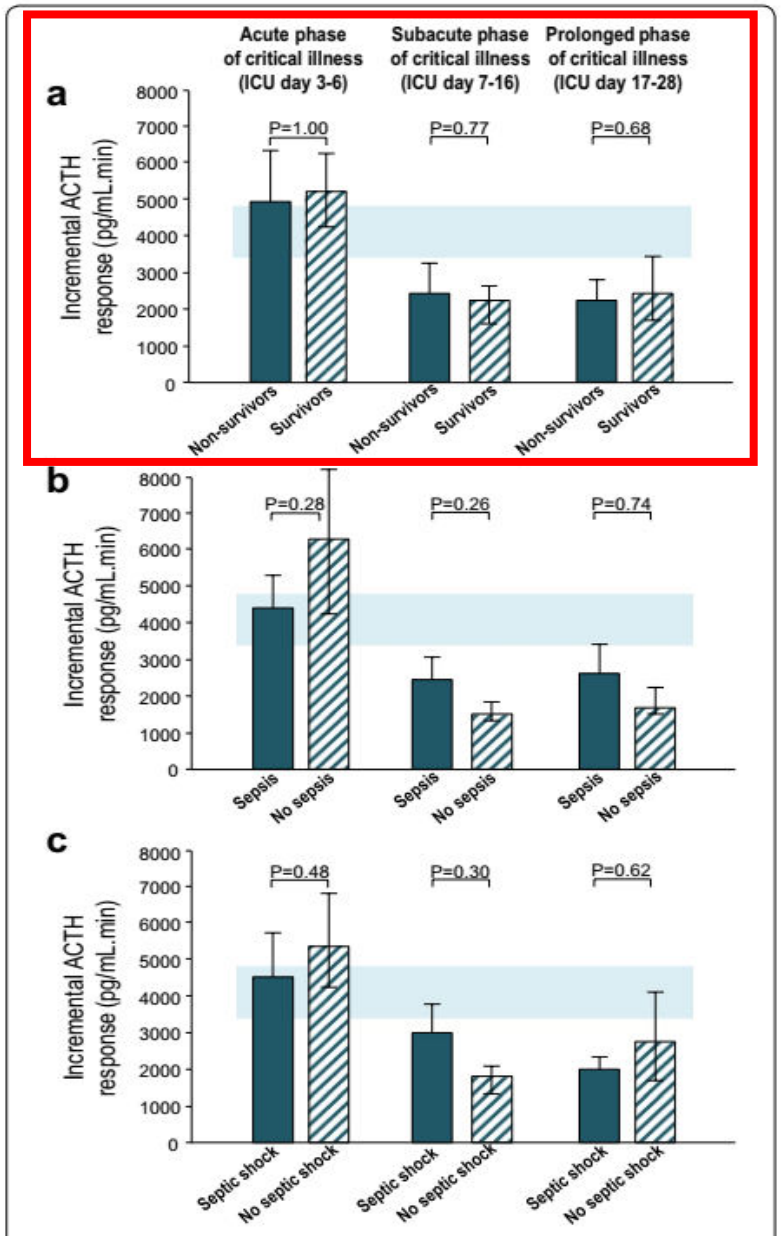
Fig. 2 Plasma ACTH, total and free cortisol concentrations after CRH or placebo injection over time in ICU. Data are shown as mean ± SEM on a logarithmic scale. ICU denotes intensive care unit

Intensive Care Med (2018) 44:2048–2058

Incremental A ACTH, B Total Cortisol And C Free Cortisol Responses To CRH And Placebo In 3 Patient Cohorts.



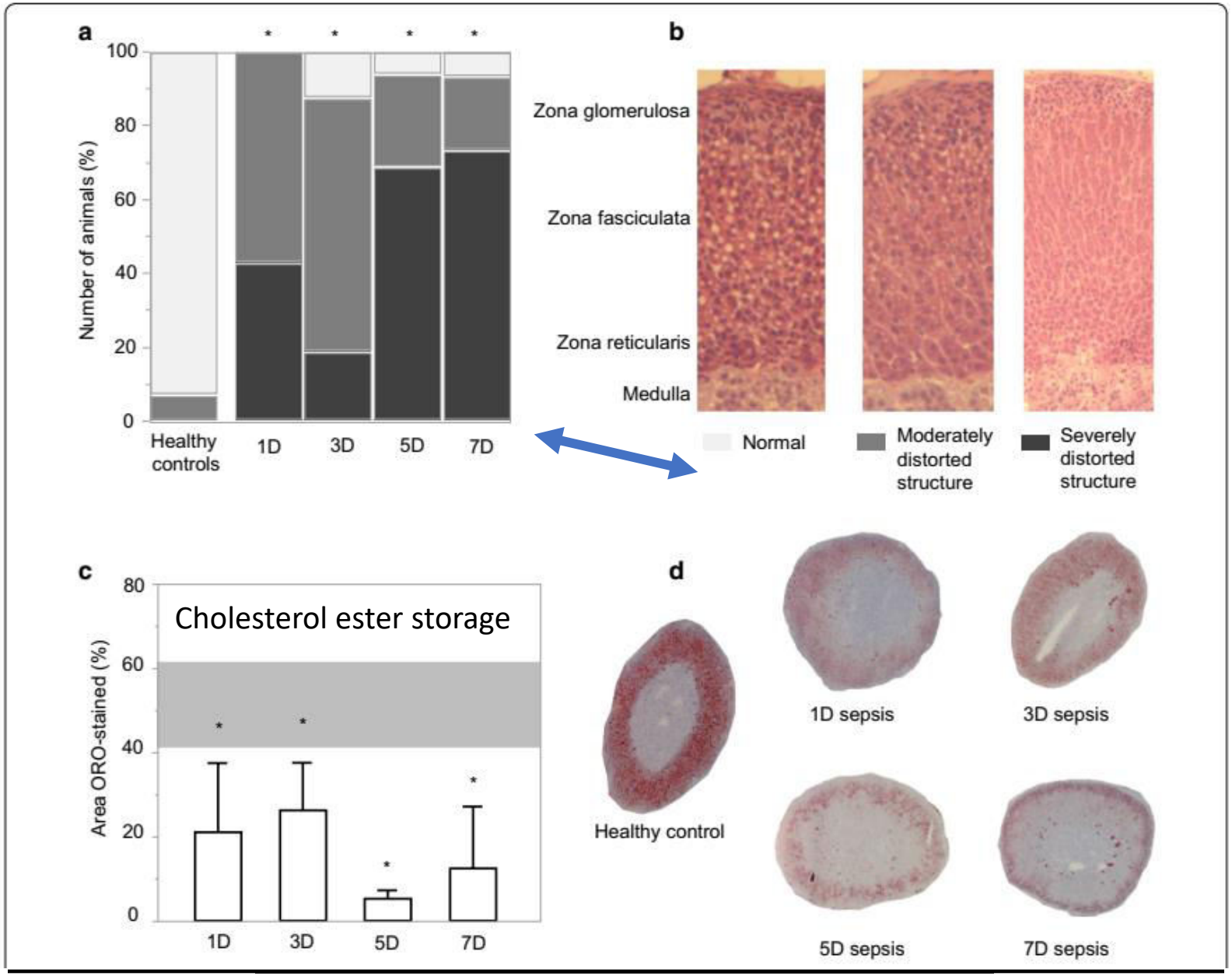
Incremental ACTH responses to CRH and placebo in 3 patient cohorts.



Non-survivors vs Survivors

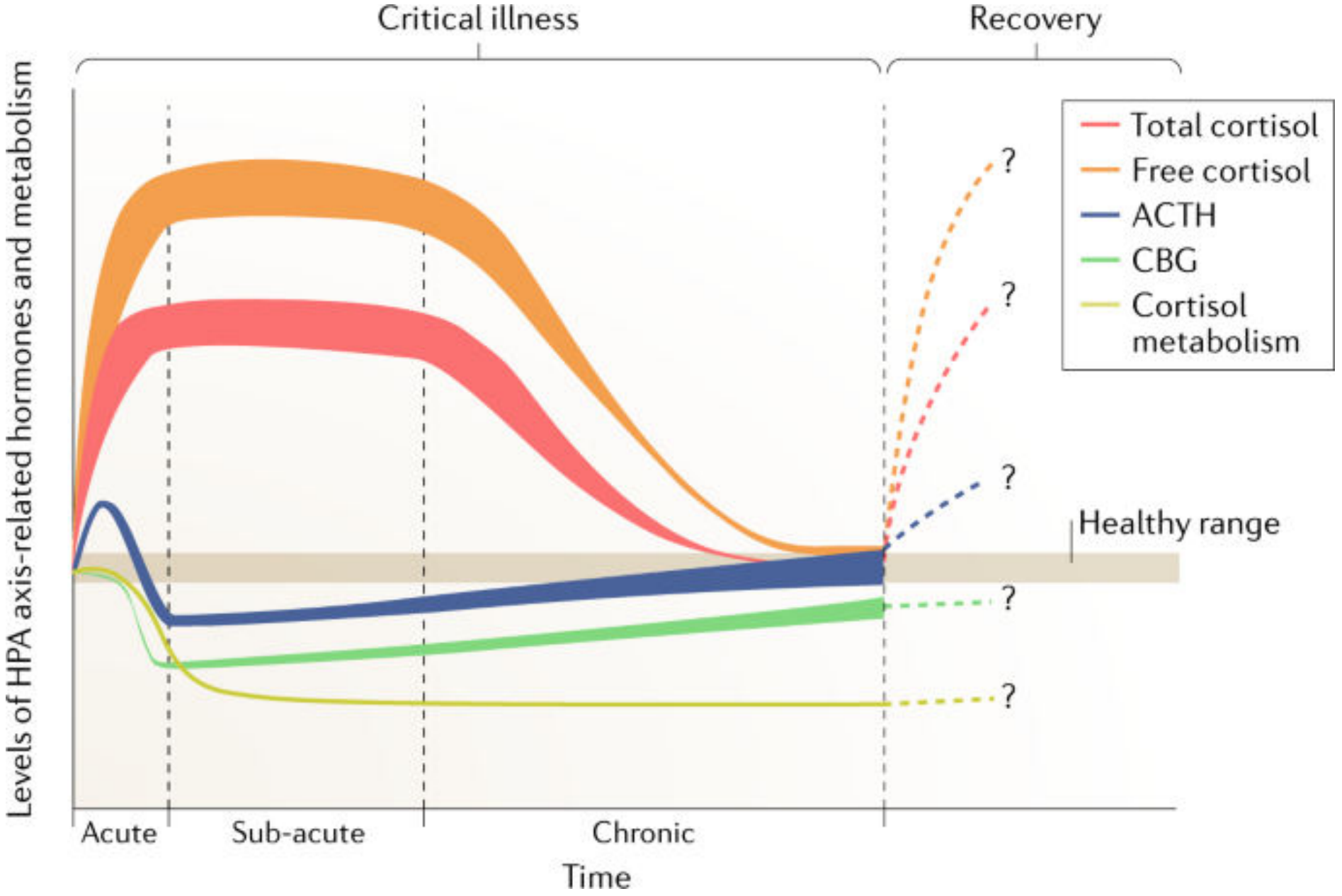
Intensive Care Med (2018) 44:2048–2058

Adrenocortical Architecture and Adrenal Cholesterol Ester Storage.



Téblick et al. Crit Care (2021) 25:65

Time and Dose Dependent Changes In Plasma Concentrations Of Key Components During Critical Illness.



Nature Reviews Endocrinology volume 15, pages417–427 (2019)

Higher Cortisol Values In Non-Survivors !

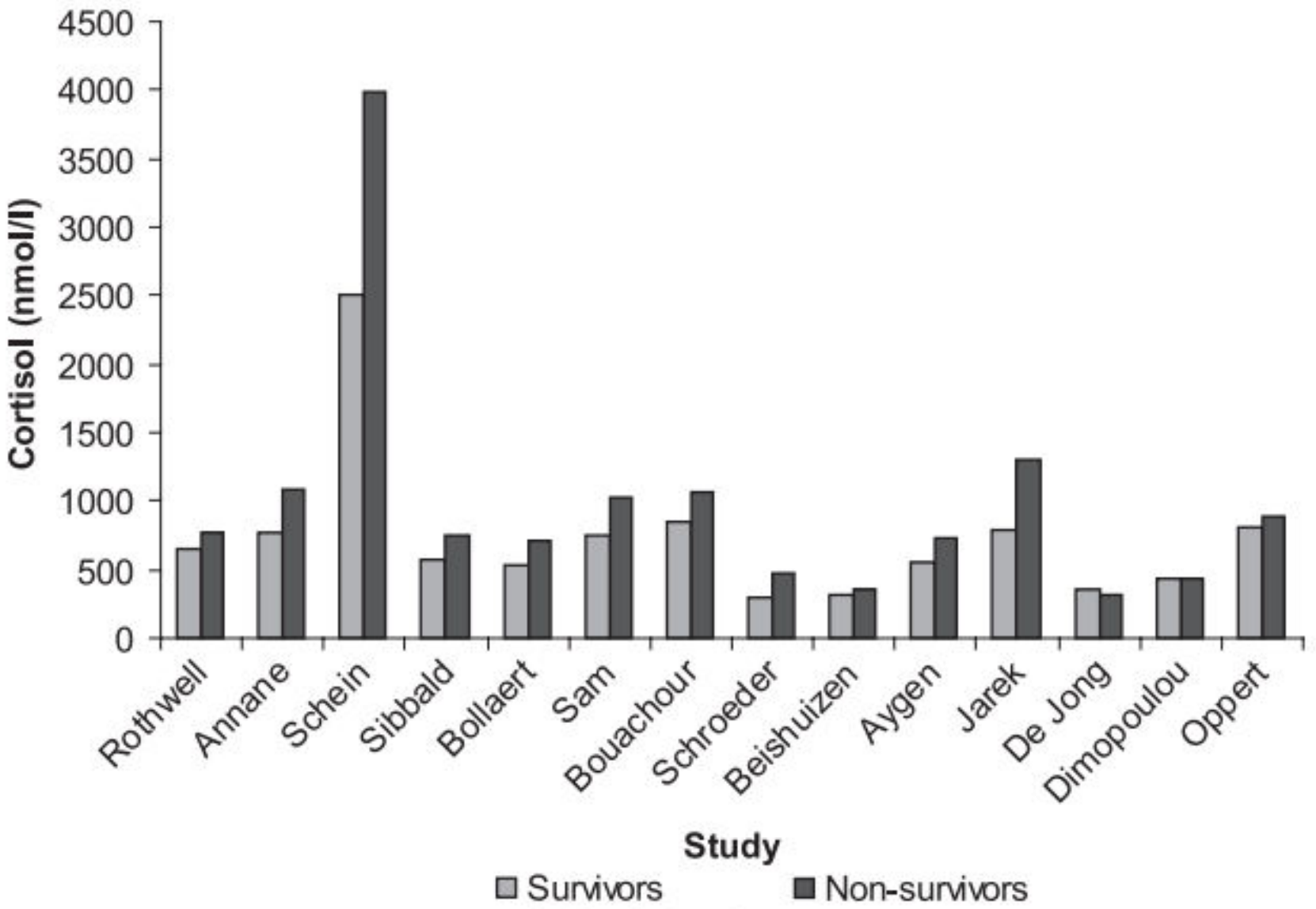


FIGURE 2: Cortisol and outcome.

Anaesthesia and Intensive Care, Vol. 38, No. 3, May 2010

Arguments For And Against Hydrocortisone Treatment For Suspected Insufficient Systemic Cortisol Availability In ICU

Condition	Arguments for	Arguments against
Preexisting HPA disorders	To prevent/treat adrenal crisis	—
Acquired bilateral adrenal hemorrhage (eg, Waterhouse-Friderichsen)	To prevent/treat adrenal crisis	—
Chronic treatment with glucocorticoids	To prevent/treat adrenal crisis	—
Acute septic shock	Annane studies reported vasopressor effect and reduced mortality with stress dose hydrocortisone in combination with fludrocortisone.	Other large RCTs with stress hydrocortisone did not confirm outcome benefit, except vasopressor effect. Direct comparison of hydrocortisone with combination hydrocortisone/fludrocortisone showed no difference. Recent preclinical research not supportive.
ICU patient with a low incremental total cortisol response to ACTH stimulation test	RCT suggesting heterogeneity of treatment effect in patients with septic shock, with benefit of hydrocortisone restricted to patients with low incremental total cortisol response to ACTH.	Other RCTs did not confirm benefit of hydrocortisone in patients with septic shock and low incremental cortisol response to ACTH. The ACTH stimulation test is flawed in critical illness due to reduced cortisol binding and increased cortisol distribution volume.
Patients with prolonged (weeks) critical illness showing symptoms/signs of adrenal insufficiency in the absence of elevated plasma ACTH/(free) cortisol	Acquired central HPA suppression represents an indication for substitution doses of hydrocortisone.	Further research is needed regarding diagnostic tests. RCTs are needed to assess outcome benefit of substitution doses of hydrocortisone in patients with prolonged critical illness.

Abbreviations: HPA, hypothalamus-pituitary-adrenocortical; ICU, intensive care unit; RCT, randomized controlled trial.

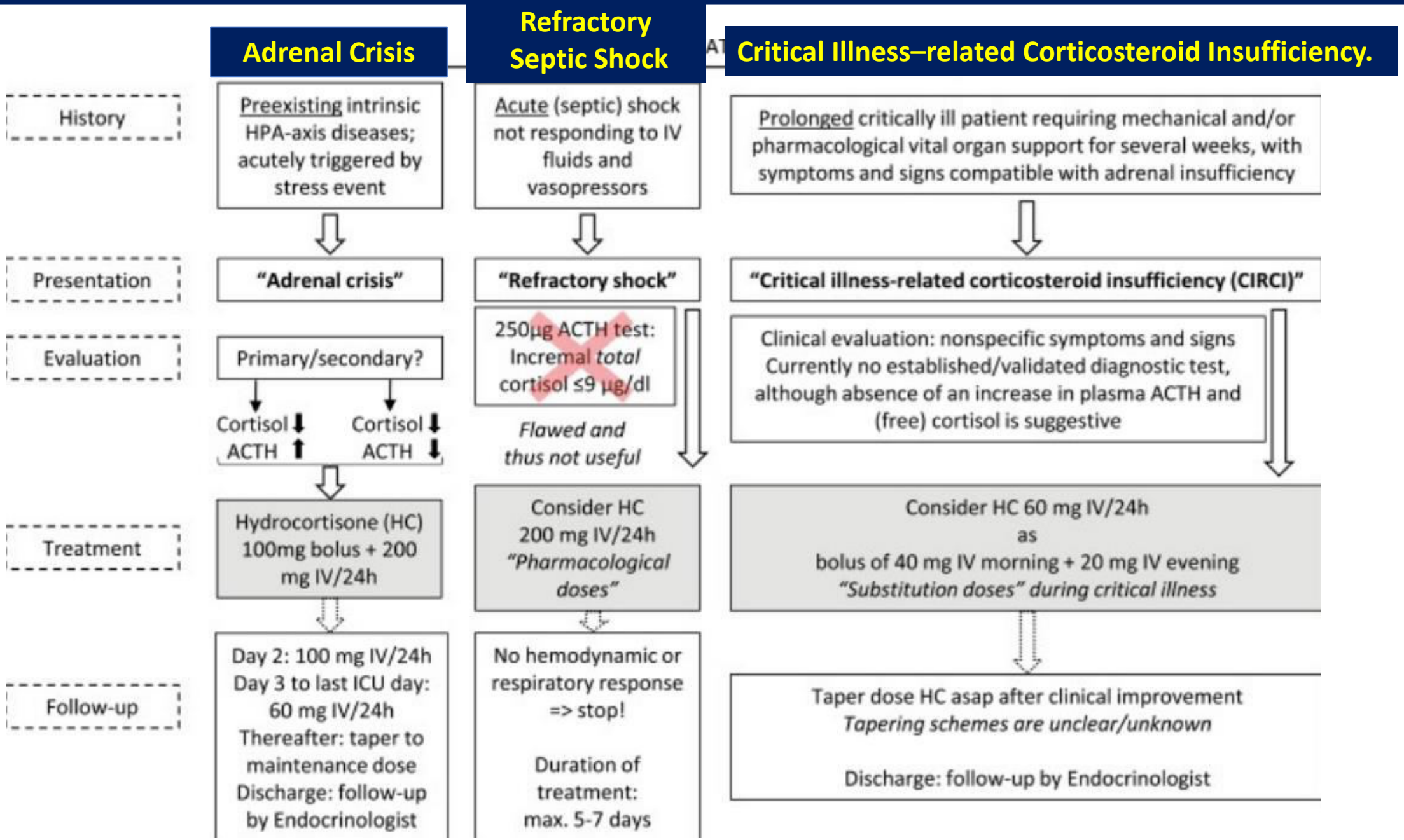
Endocrine Reviews, 2023, 44, 1096–1106

Major RCTs Investigating The Effect Of Glucocorticoid Treatment In Critical Illness

Principal investigator, year, study acronym[a]	Number of participants; main inclusion criteria	Drug dose, posology and treatment duration; tapering	Primary outcome	Predictive value of 250 µg ACTH stimulation test result	Major secondary outcomes	Major adverse effects
Annane, 2002 (REF.[113])	299 mechanically ventilated patients with septic shock	Hydrocortisone 50 mg IV bolus every 6 h + fludrocortisone 50 µg PO every 24 h during 7 days; not tapered	28-day mortality: lower in GC group	Benefit only in non-responders (incremental cortisol <9 µg/dl), potential harm in responders	Time to shock reversal: shorter in GC group	None reported
Sprung, 2008, CORTICUS[116]	499 participants, predominantly patients with septic shock; various inclusion and exclusion criteria	Hydrocortisone 50 mg IV bolus every 6 h during 5 days; tapered over 6 days	28-day mortality: no difference	No difference between responders and non-responders	Time to shock reversal: shorter in GC group	Hyperglycaemia, hypernatraemia and superinfections (new sepsis and new septic shock): more in GC group
Annane, 2018, APROCCHSS[114]	1,241 patients with probable or proven septic shock; various inclusion and exclusion criteria	Hydrocortisone 50 mg IV bolus every 6 h + fludrocortisone 50 µg PO every 24 h during 7 days; not tapered	90-day all-cause mortality: lower in GC group	No difference between responders and non-responders	Time to shock reversal and time to weaning from mechanical ventilation: shorter in GC group	Hyperglycaemia: more in GC group
Venkatesh, 2018, ADRENAL[115]	3,658 mechanically ventilated patients with septic shock; various inclusion and exclusion criteria	Hydrocortisone 200 mg IV, continuous infusion during 7 days or shorter if earlier ICU discharge; not tapered	90-day mortality: no difference	Test not performed	Time to shock reversal and time to weaning from initial mechanical ventilation: shorter in GC group	All adverse events combined: more in GC group

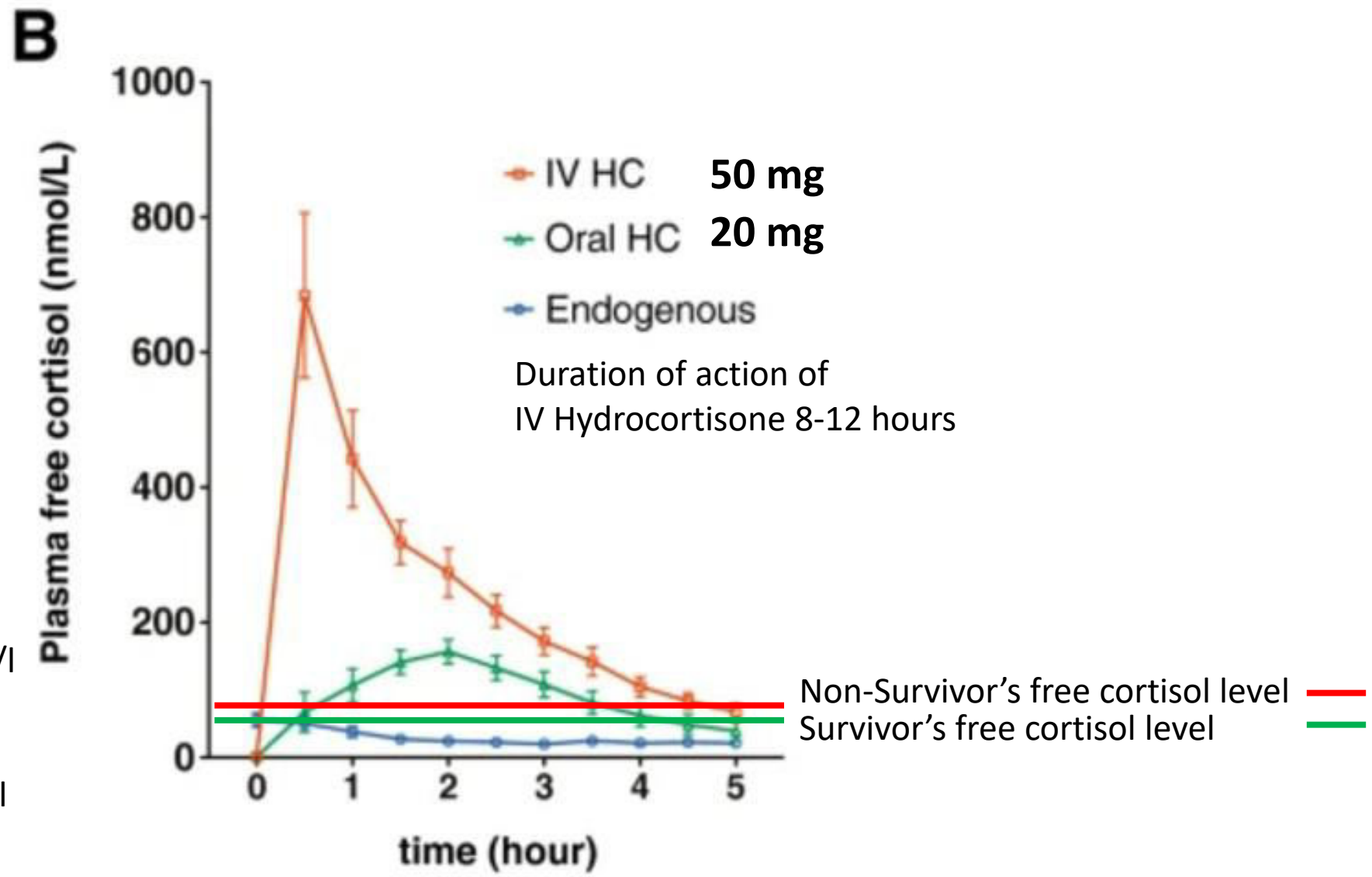
Nature Reviews Endocrinology volume 15, pages417–427 (2019)

Diagnostic Approach And Steroid Treatment



J Clin Endocrinol Metab. 2022 Jun 16;107(7):2057-2064

Total Plasma Cortisol Concentrations After Oral And Intravenous Hydrocortisone

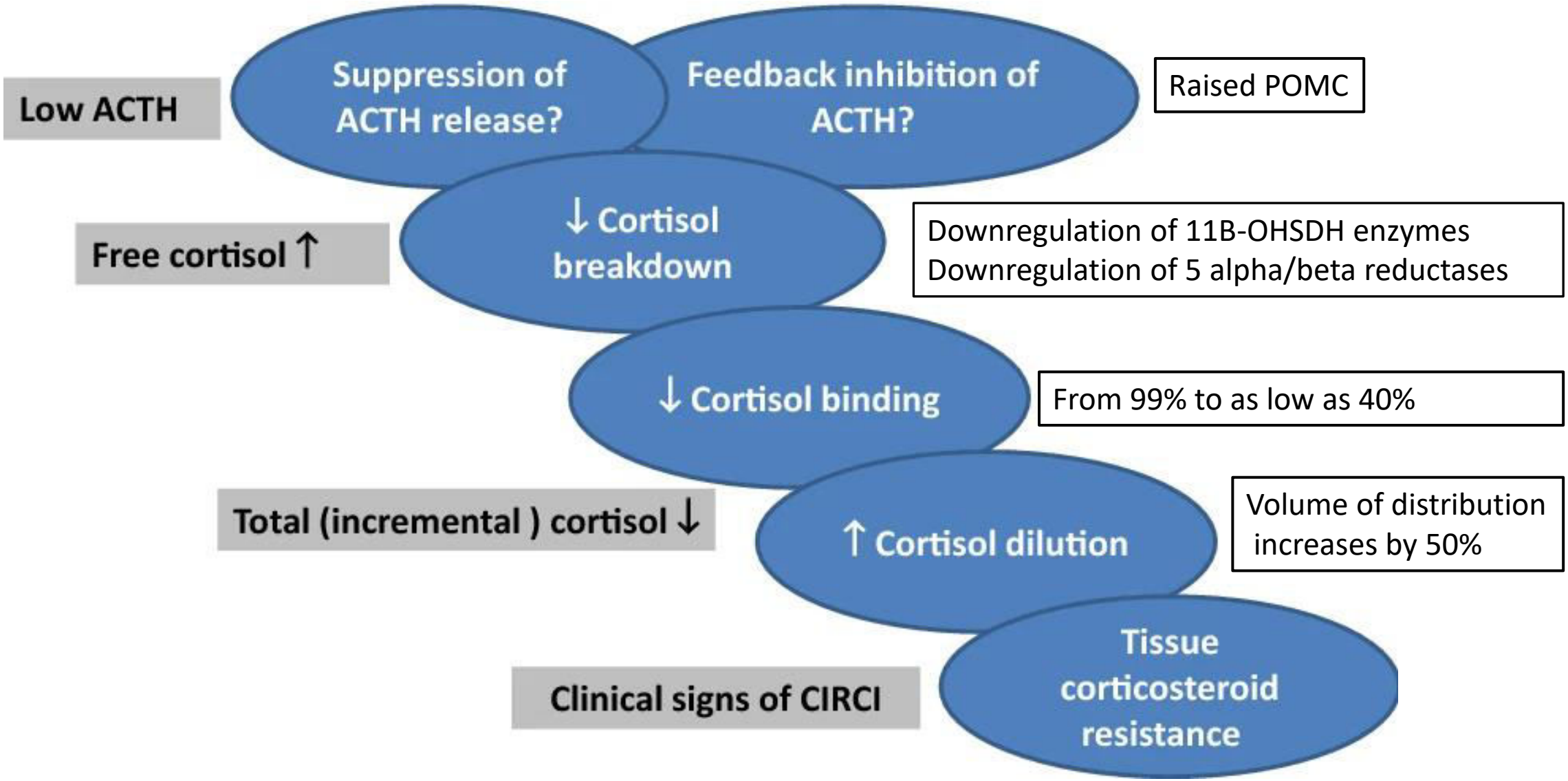


ICU Non-Survivor
2.8 ug/dl X 27.59 = 77.25 nmol/l

ICU Survivor
1.8 ug/dl X 27.59 = 49.66 nmo/l

BMC Endocrine Disorders volume 14, Article number: 91 (2014)

Pitfalls In The Assessment Of Adrenocortical Activity During Prolonged Critical Illness



Intensive Care Med 44, 1976–1978 (2018).

Summary

1. Serum (total) cortisol in critical illness are influenced by numerous factors;
   - Reduction in CBG level and binding capacity – more free cortisol released
   - Variability in hour to hour serum cortisol levels .Majority higher than if stimulated by ACTH
   - Modest production of cortisol (max 60 mg daily)
   - Reduce activity of enzymes in the kidneys and liver that breakdown cortisol

   All the above invalidates the use of serum cortisol, alone or following ACTH stimulation

   If you opted for free cortisol (cumbersome!) or plasma free cortisol measurements they were always high in critically ill (non-survivors higher than survivors)

2. ACTH is low in the first 4 weeks of critical illness and using it to stimulate cortisol resulted in blunted response.
   - Behaviour is similar to cases of exogenous steroid administration.
   - Even when CRH is employed the cortisol is still blunted

3. The above are in seen in non-survivors vs survivors, those given glucocorticoids vs those not given glucocorticoids

4. There are suggestions to limit steroid replacement in critically ill to merely 60 mg iv hydrocortisone. Has not made it's way into any guidelines

5. Critically ill that responded to high dose glucocorticoids haemodynamically benefitted from the positive effect of glucocorticoids on vasculature sensitivity to vasopressors. This had no bearing on the behaviour of the HPA axis in critically illness

Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

RECOMMENDATIONS FOR DIAGNOSIS OF CIRCI

1. Is total cortisol response to synthetic adrenocorticotropic hormone (ACTH; cosyntropin) superior to random plasma or serum total cortisol for the diagnosis of CIRCI?

Recommendation: The task force makes no recommendation regarding whether to use delta cortisol (change in baseline cortisol at 60 min of < 9 μg/dL) after cosyntropin (250 μg) administration or a random plasma cortisol of < 10 μg/dL for the diagnosis of CIRCI.

2. Is plasma or serum free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using plasma free cortisol level rather than plasma total cortisol for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

3. Is salivary free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using salivary rather than serum cortisol for diagnosing CIRCI (conditional recommendation, very low quality of evidence).

4. Is the 1-μg ACTH stimulation test superior to the 250-μg ACTH test for the diagnosis of CIRCI?

Recommendation: We suggest that the high-dose (250-μg) rather than the low-dose (1-μg) ACTH stimulation test be used for the diagnosis of CIRCI (conditional recommendation, low quality of evidence).

5. Is hemodynamic response to hydrocortisone (50–300 mg) superior to the 250-μg ACTH stimulation test for the diagnosis of CIRCI?

Recommendation: We suggest the use of the 250-μg ACTH stimulation test rather than the hemodynamic response to hydrocortisone (50–300 mg) for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

6. Is corticotropin level superior to the 250-μg ACTH stimulation test for the diagnosis of CIRCI?

Recommendation: We suggest against using corticotropin levels for the routine diagnosis of CIRCI (conditional recommendation, low quality of evidence).

Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Sepsis

A. Should corticosteroids be administered among hospitalized adult patients with sepsis without shock?

Recommendation: We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence).

B. Should corticosteroids be administered among hospitalized adult patients with septic shock?

Recommendation: We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).

C. What is the recommended dose and duration of treatment among hospitalized adult patients with septic shock treated with corticosteroids?

Recommendation: If using corticosteroids for septic shock, we suggest using long course and low dose (e.g., IV hydrocortisone < 400 mg/day for at ≥ 3 days at full dose) rather than high dose and short course in adult patients with septic shock (conditional recommendation, low quality of evidence).

Acute Respiratory Distress Syndrome

Should corticosteroids be administered among hospitalized adult patients with acute respiratory distress syndrome?

Recommendation: We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO_2/FiO_2 of < 200 and within 14 days of onset) (conditional recommendation, moderate quality of evidence).

Major Trauma

Should corticosteroids be administered among hospitalized adult patients with major trauma?

Recommendation: We suggest against the use of corticosteroids in major trauma (conditional recommendation, low quality of evidence).

Critical Care Medicine , December 2017 • Volume 45 • Number 12