77 year old male with hypoglycemia

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HPI:

- 77 y.o. male with a PMH of hypothyroidism, CHF (LVEF 20%), A-fib, CKD stage 3, who presented to the hospital with AMS, which was felt to be secondary to a syncopal episode. He was admitted to the medical floor.
- While on the floor the pt was found to be unresponsive by the nurse with T 95.7, HR 60-70s, BP 82/52, O2 sat 71%, BS 44 mg/dl.
- The pt was transferred to ICU for further management.

HPI:

- While in the ICU the pt continued to have recurrent episodes of hypoglycemia with blood sugars dropping to as low as 32 several times a day.
- Endocrinology consulted for the work up of hypoglycemia.

HPI:

- The pt did not have any hx of DM and his family denied any access to insulin or diabetic medications.
- He had a hx of hypothyroidism for about 8 years after RAI treatment, however his family or PCP were not aware of the underlying etiology of his thyroid problem in the past.

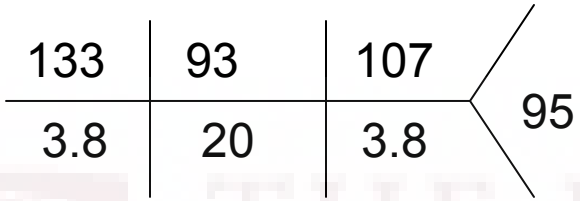
Meds:

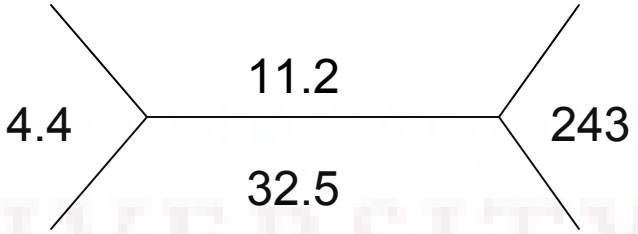
- Coreg 3.125mg BID
- Lasix 40mg BID
- Bidil 20-37.5mg Q24H
- Levothyroxine 88mcg Q24H
- Metolazone 2.5mg QAM
- K-dur 20meq Q24H
- Aldactone 12.mg Q24H
- Amiodarone 200mg Q24H

Physical exam:

- General: not in acute distress, well-nourished
- Eyes: PERRLA
- Neck: no thyromegaly
- Heart: RRR, grade 2 systolic murmur at the apex
- Lungs: CTAB
- Abdomen: BS+, nontender, nondistended
- LE: no edema, extremities are cold and clammy
- Neuro: alert, AAOx0, did not follow commands

Labs:





Ca 8.6 (8.4-10.2 mg/dL)
Mg 3.6 (1.6-2.5 mg/dL)
Phos 5.8 (2.5-4.4 mg/dL)

BNP 42311(<450 pg/mL)

Lactic acid 6.7 (0.7-2.1 mEq/L)

PT 14.8 (11.8-14.5s)
PTT 34.1 (24-34s)
INR 1.2 (0.9-1.1)

TSH 0.03 (0.3-4.0 mcU/ml)

Free T4 0.94 (0.9-1.7 ng/dL)

Total T3 38 (80-195 ng/dL)

Reverse T3 1780 (160-353 pg/mL)

TG antibodies 17.3 (<0.4 KU/mL)

Anti-TPO antibodies 26 (<0.4 KU/mL)

Hypoglycemia:

TABLE 1. Causes of hypoglycemia in adults

Ill or medicated individual

1. Drugs
   - Insulin or insulin secretagogue
   - Alcohol
   - Others (Table 2)
2. Critical illnesses
   - Hepatic, renal, or cardiac failure
   - Sepsis (including malaria)
   - Inanition
3. Hormone deficiency
   - Cortisol
   - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
4. Nonislet cell tumor

Seemingly well individual

5. Endogenous hyperinsulinism
   - Insulinoma
   - Functional β-cell disorders (nesidioblastosis)
     - Noninsulinoma pancreatogenous hypoglycemia
     - Post gastric bypass hypoglycemia
   - Insulin autoimmune hypoglycemia
     - Antibody to insulin
     - Antibody to insulin receptor
   - Insulin secretagogue
   - Other
6. Accidental, surreptitious, or malicious hypoglycemia

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

Moderate quality of evidence (⊕⊕⊕◯)
- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

Low quality of evidence (⊕⊕◯◯)
- Chloroquineoxaline sulfonamide
- Artesunate/artemisin/artemether
- IGF-I
- Lithium
- Propoxyphene/dextropropoxyphene

Very low quality of evidence (⊕◯◯◯)
- Drugs with >25 cases of hypoglycemia identified
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor antagonists
  - β-Adrenergic receptor antagonists
  - Levofloxacin
  - Mifepristone
  - Disopyramide
  - Trimethoprim-sulfamethoxazole
  - Heparin
  - 6-Mercaptopurine

Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709.

Labs:

Glucose 38 (60-1-9 mg/dL)
C-peptide 3.48 (0.3-2.35 pmol/mL)
Insulin 9.1 (<28.5 uIU/mL)
Proinsulin 100 (3-20 pmol/L)
Cortisol 161.3 mcg/dL

IGF II 249 (288-736 ng/mL)

Random cortisol and ACTH:
Cortisol 162.4 mcg/dL, ACTH 50.8 pg/mL at 8.30PM

Stim test:
Cortisol 164.8 mcg/dL -> 170 mcg/dL

Serum free cortisol
11.48 (0.04-0.45 mcg/dL 4-6 PM)

Chlorpropamide:
Negative

Tolazamide:
Unable to assess

Tolbutamide:
Negative

Glyburide:
Negative

Glipizide:
Negative

Repaglinide:
Negative

Glimepiride:
Negative

Acetohexamide:
Negative

Hypoglycemia

TABLE 3. Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (*i.e.* Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms.

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/ml	C-peptide (nmol/liter)	Proinsulin (pmol/liter)	β-Hydroxy -butyrate (mmol/liter)	Glucose increase after glucagon (mg/dl)	Circulating oral hypo-glycemic	Antibody to insulin	Diagnostic inter-pretation
No	< 55	< 3	< 0.2	< 5	> 2.7	< 25	No	No	Normal
Yes	< 55	» 3	< 0.2	< 5	≤ 2.7	> 25	No	Neg (Pos)	Exogenous insulin
Yes	< 55	≥ 3	≥ 0.2	≥ 5	≤ 2.7	> 25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	< 55	≥ 3	≥ 0.2	≥ 5	≤ 2.7	> 25	Yes	Neg	Oral hypo-glycemic agent
Yes	< 55	» 3	» 0.2[a]	» 5[a]	≤ 2.7	> 25	No	Pos	Insulin autoimmune
Yes	< 55	< 3	< 0.2	< 5	≤ 2.7	> 25	No	Neg	IGF[b]
Yes	< 55	< 3	< 0.2	< 5	> 2.7	< 25	No	Neg	Not insulin (or IGF)-mediated

Neg, negative; Pos, positive; PGBH, post gastric bypass hypoglycemia.
a Free C-peptide and proinsulin concentrations are low.
b Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709.

Clinical course:

- In the ICU the pt was started on dobutamine and levo gtt
- Continuous tube feeding were started and the pt did not have any episodes of hypoglycemia while on tube feeds
- CVVH was started
- Empirically started on vanco, cefepime, flagyl
- Blood cx grew Strep. Gallolyticus x 2
- On day 5 of the ICU admission abx were changed to ceftriaxone

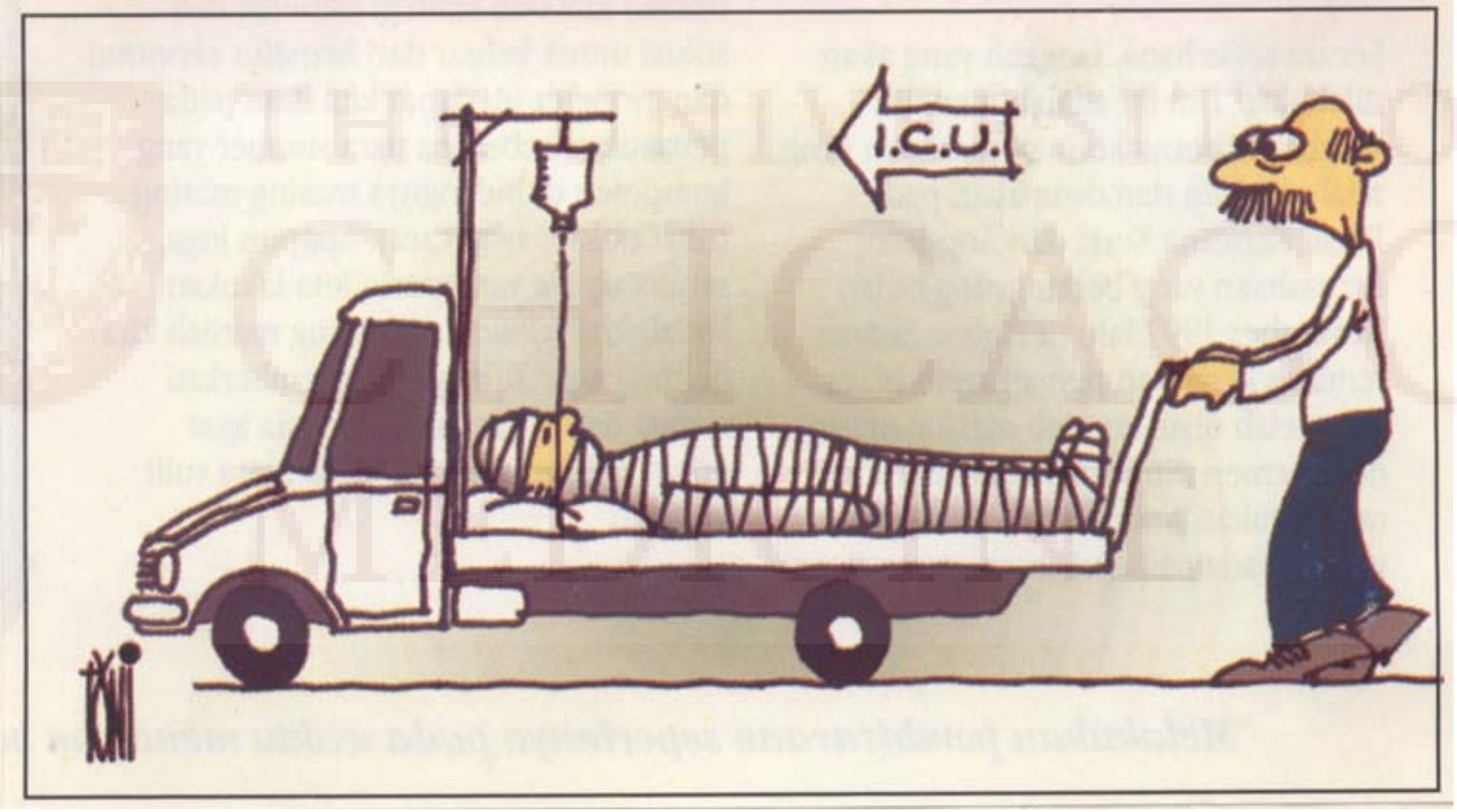
Clinical course:

- On day 6 vasopressin gtt was added due to worsening hypotension
- On day 7 phenylephrine and epinephrine gtt were added
- On day 8 goals of care were addressed with the family and the pt was made DNI/DNR
- On day 12 the pt was made comfort care only, CVVH, inotropes and pressors were d/c, fentanyl gtt was started
- On day 12 the pt died
- Autopsy was declined by the family

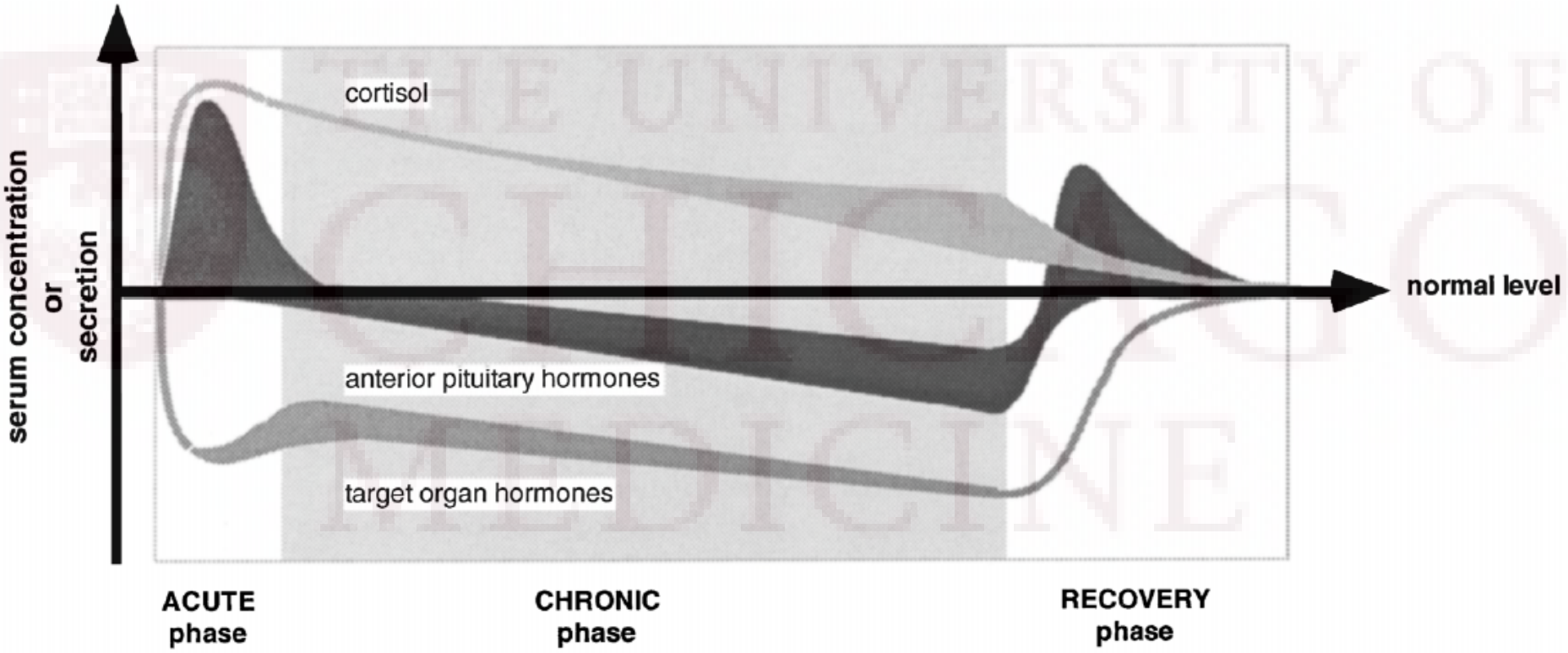
Questions:

- HPA axis in critical illness
- How high can cortisol rise in a situation of severe shock/stress?
- Cortisol levels in critical illness as a prognostic factor
- Can high cortisol levels in critical illness be suppressed with dexamethasone?

HPA axis in critical illness



HPA axis in critical illness



Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. Van den Berghe G, de Zegher F, Bouillon R. J Clin Endocrinol Metab. 1998 Jun;83(6):1827-34.

Adrenocortical function in critical illness:

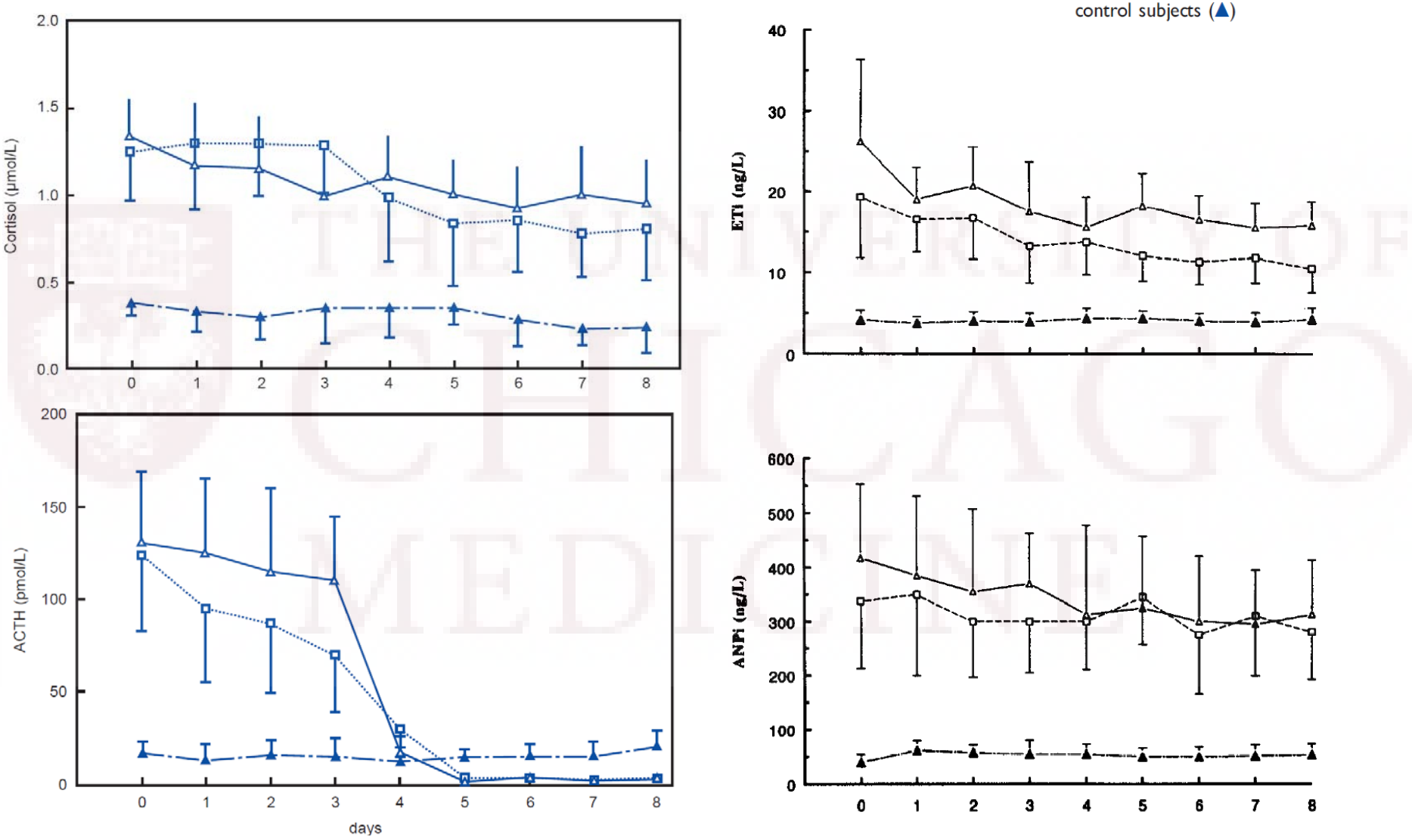
- Shift away from mineralocorticoid to a 6-fold increase in glucocorticoid production
- Decreased levels of CBG
- Increased receptor responsiveness (inflammatory cytokines IL-4 and IL-10 may increase cortisol receptor binding affinity)
- Decreased levels of DHEAS, which has immunostimulatory properties on Th1 helper cells

Adrenocortical function in critical illness:

High cortisol in critical illness

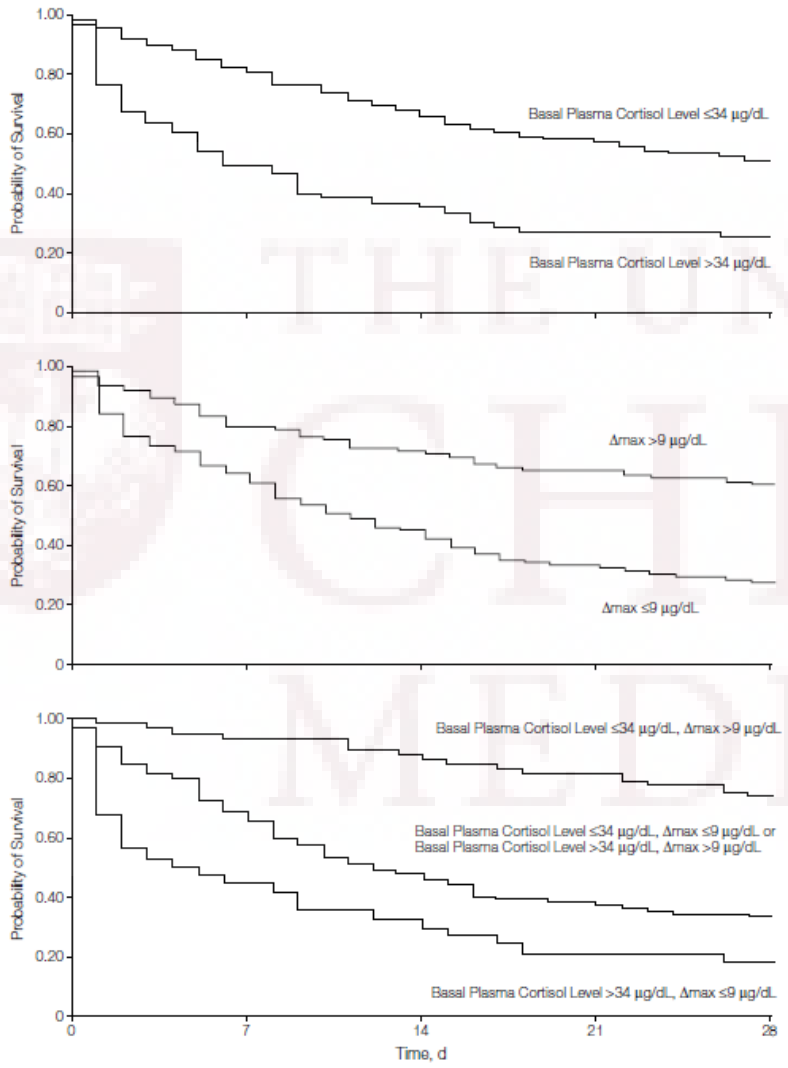
- Shifts carbohydrate, fat, and protein metabolism - energy is instantly and selectively available to vital organs
- Overall utilization of substrates is reduced, anabolism is postponed
- Intravascular fluid retention
- Enhanced inotropic and vasotropic response to catecholamines and angiotensin II
- Reduced immune response (self muting), however prolonged imbalance between immunosuppressive and immunostimulatory hormones of adrenocortical origin may participate in the increased susceptibility for infectious complications

HPA axis in critical illness



Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. Vermes I, Beishuizen A, Hampsink RM, Haanen C. J Clin Endocrinol Metab. 1995 Apr;80(4):1238-42.

Cortisol as a prognostic factor



- **good**

cortisol level at T0 < or = 34 microg/dL and delta max > 9 microg/dL - 28-day mortality rate 26%

- **intermediate**

cortisol level at T0 34 microg/dL and delta max < or = 9 microg/dL or cortisol level at T0 > 34 microg/dL and delta max > 9 microg/dL - 28-day mortality rate 67%

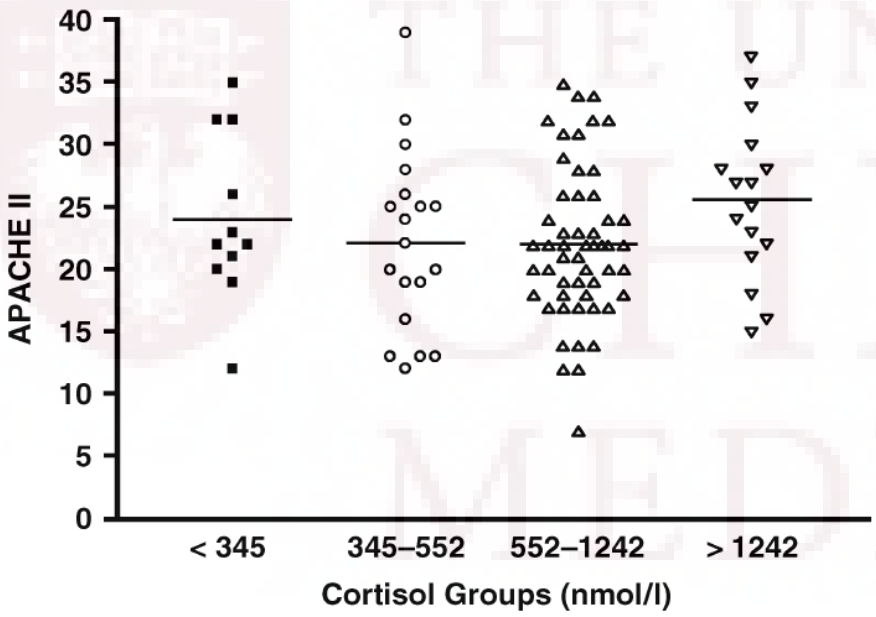
- **poor**

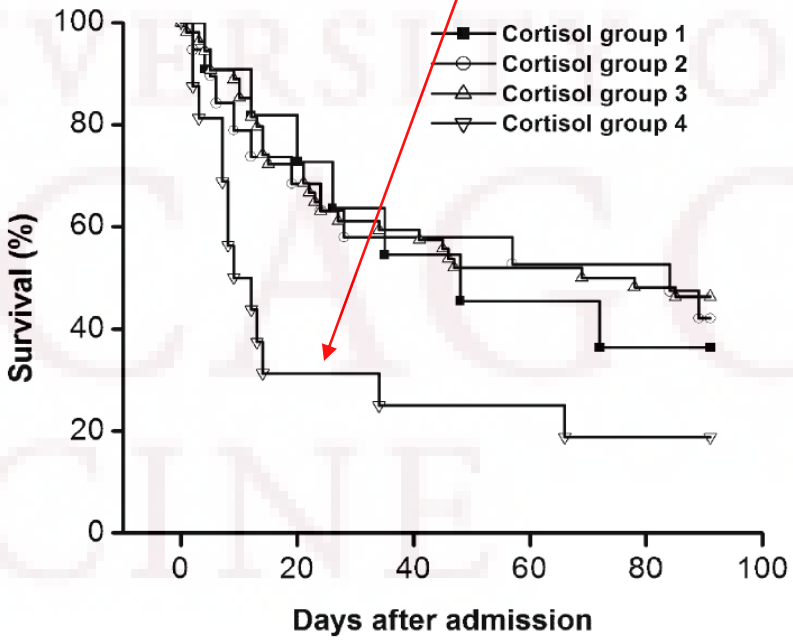
cortisol level at T0 > 34 microg/dL and delta max < or = 9 microg/dL - 28-day mortality rate 82%

A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. JAMA. 2000 Feb 23;283(8):1038-45.

Cortisol as a prognostic factor

4480.616 nmol/l = 162.4 µg/dl





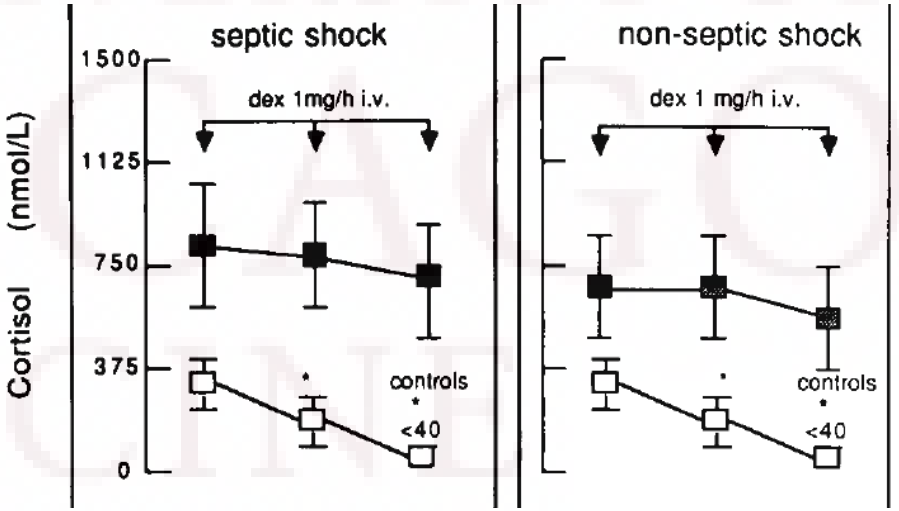
	Group 1	Group 2	Group 3	Group 4
% In-hospital mortality	54%	53%	41%	81%*
% 90-day mortality	64%	55%	52%	87%†

Cortisol levels and mortality in severe sepsis. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Clin Endocrinol (Oxf). 2004 Jan;60(1):29-35.

Can dexamethasone suppress relative hypercortisolism in critical illness?

Table 1. Characteristics of study patients

Pt.	Sex	Age (yr)	SAPS	Diagnosis	Outcom
Group 1 (Septic Shock)					
1	M	60	17	Uremigenic cholangiolitis	D
2	M	80	25	Urinary infection	S
3	F	47	24	Gram-negative septicemia	S
4	F	83	28	Uremigenic cholangiolitis	D
5	M	62	24	Abdominal sepsis	D
6	M	49	25	Peritonitis	D
7	M	77	35	Gram-positive septicemia	D
8	F	67	32	Postoperative sepsis (strangulated hernia)	D
9	F	36	17	Salpingitis	S
10	F	57	17	Uremigenic cholangiolitis	D
11	M	55	26	Pneumococcia (ARDS)	D
Group 2 (Nonseptic Shock)					
12	F	51	27	Digestive hemorrhage (ethylic cirrhosis)	D
13	M	65	21	Digestive hemorrhage (gastric cancer)	D
14	F	37	13	Cardiogenic shock	S
15	M	33	26	Cardiogenic shock	D
16	F	34	17	Cardiogenic shock	S
17	M	38	34	Hemorrhagic shock (multiple trauma)	D
18	M	71	18	Hemorrhagic shock (esophageal cancer)	S



Hypercortisolism in septic shock is not suppressible by dexamethasone infusion. Perrot D, Bonneton A, Dechaud H, Motin J, Pugeat M. Crit Care Med. 1993 Mar;21(3):396-401.

Take home points:

- There is a relative hypercortisolism related to severe illness, which could play a protective role and accelerate fight-or-flight response
- Levels of cortisol could be used as a predictor of mortality in critically ill patients
- Relative hypercortisolism is not supressed by dexamethasone in critical illness

References:

- Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. Cryer PE, Axelrod L, Grossman AB, et al. J Clin Endocrinol Metab 2009; 94:709.
- Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. Van den Berghe G, de Zegher F, Bouillon R. J Clin Endocrinol Metab. 1998 Jun;83(6):1827-34.
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