Adrenal Insufficiency: Current Practice 2012

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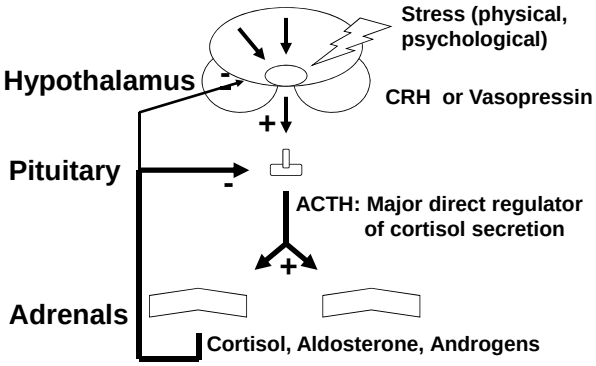
Division of Endocrinology, Diabetes, and Metabolism
The Ohio State University's Wexner Medical Center

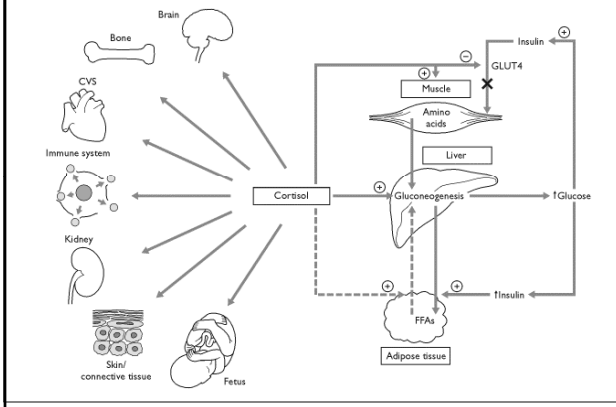
Hypothalamus-Pituitary-Adrenal Axis



Overview

- A *very* brief review of adrenal function
- What is adrenal insufficiency?
- Adrenal insufficiency in the outpatient setting
- Adrenal insufficiency during critical illness
- Therapy for adrenal insufficiency

Actions of cortisol



- Actions of Aldosterone
  - Promotes sodium/water retention
  - Promotes potassium excretion
  - May be involved in tissue remodeling (e.g. in the heart)
- Actions of adrenal androgens
  - Responsible for initiation of puberty
    - Secondary sex characteristics in women

What is Adrenal insufficiency?

- When discussing adrenal insufficiency (Addison disease), we are almost always talking about ***glucocorticoid (cortisol) insufficiency***
- However, other adrenal hormones can also be affected in *primary* adrenal failure

Adrenal Insufficiency (Addison disease)

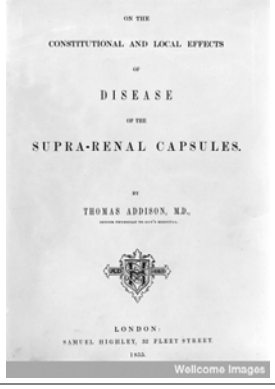

ON THE
CONSTITUTIONAL AND LOCAL EFFECTS
OF
DISEASE
OF THE
SUPRA-RENAL CAPSULES.
BY
THOMAS ADDISON, M.D.,
LONDON:
SAMUEL HIGHLEY, 32 FLEET STREET.
1855.

Image courtesy of Wellcome Images http://images.wellcome.ac.uk/

Clinical Addison disease

Clinical Features of Chronic Adrenocortical Insufficiency

•Weakness, fatigue	100%
•Weight loss	100%
•Anorexia	100%
•Hyperpigmentation	92%
•Hypotension	88%
•Nausea, abdominal pain	56%
•Salt craving	19%
•Hypoglycemia	??

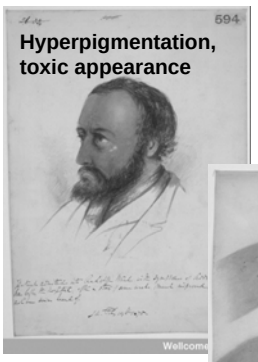
»more common in children and women

Features of Acute Adrenocortical Insufficiency (Adrenal Crisis)

- Hypotension
- Weakness (prox. muscle), confusion
- Nausea, vomiting, abdominal pain
- Dehydration, hypovolemia
- Hyperthermia
- Hypoglycemia

TREAT FIRST, AND DIAGNOSE LATER!!

Addison disease



Images courtesy of Wellcome Images http://images.wellcome.ac.uk/

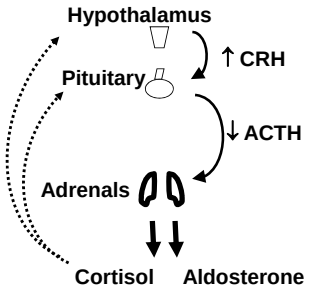
Adrenal Crisis

- Acute loss of adrenal function
  - Acute loss of adrenals
    - Surgery
    - Hemorrhage/thrombosis
  - Acute loss of pituitary function
  - Acute loss of steroid replacement

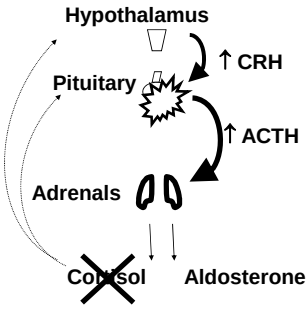
OR

- Acute stress in the setting of compensated chronic adrenal failure
  - Precipitating event (e.g., like DKA)

Normal Adrenal Function



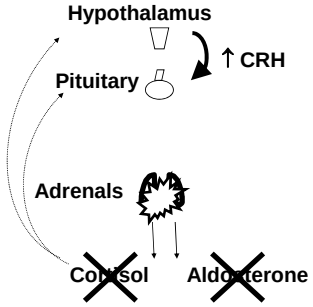
Secondary Adrenal Insufficiency



- Primary
  - Adrenal gland
  - Destruction of glands
- Secondary
  - Pituitary
  - Inadequate ACTH
  - NO increased pigment
  - Fewer electrolyte imbalances

(regulated by Renin/Angiotension system)

Primary Adrenal Insufficiency



- Primary
  - Adrenal gland
  - Destruction of glands

Causes of adrenal failure

- Like CS, iatrogenic causes are probably most common
- Inherited forms of adrenal failure
  - Typically presenting early in life (<1 yr)
    - CAH, especially salt-wasters (steroid biosynthesis defect)
    - Other rare genetic diseases (lipoid CAH, AHC)
  - Typically presenting in childhood, and dx should be "obvious"
    - AAA
      - Alacrima, Achalasia, Adrenal failure
    - Autoimmune Polyendocrine Syndrome (APS), Type I (APECED)
      - Ectodermal dysplasia, mucocutaneous candidiasis

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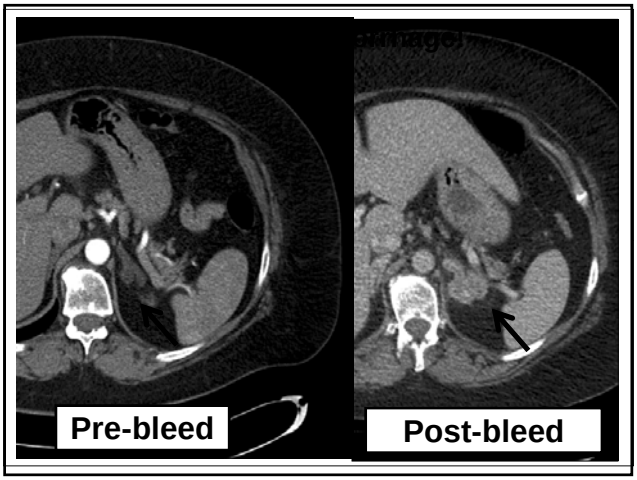
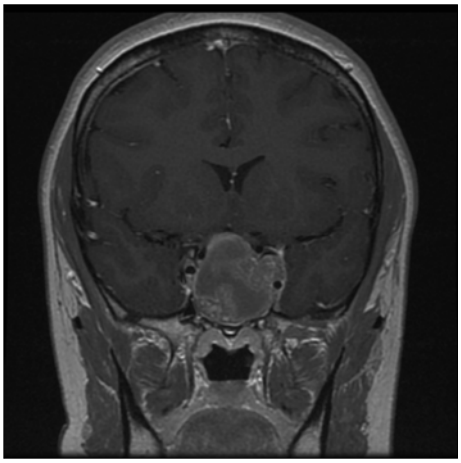
- Presenting later in life
  - Autoimmune Polyendocrine Syndrome (APS), Type II
    - Type I DM, thyroid disease
    - May occur as sole autoimmune feature (although rare)
  - Adrenal hemorrhage
    - Resulting from sepsis
  - HIV, other viral diseases
  - Adrenalectomy
- Note that non-classical CAH rarely causes adrenal insufficiency



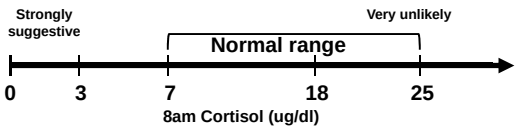


Secondary adrenal failure

- Pituitary malfunction
  - Tumor destroying normal cells
  - Autoimmune hypophysitis
    - May be quite specific for loss of ACTH-producing cells
  - Infiltrative diseases of pituitary
    - Histiocytosis X
    - Sarcoidosis
    - Metastatic disease

Diagnosis of Adrenal Insufficiency in the Outpatient setting: Static Testing

- A GOOD HISTORY IS ESSENTIAL!
  - History of steroid use, including nasal steroids or injected steroids (e.g., back injections)
- 8 AM cortisol (probably NOT reliable in hospitalized patients)



Diagnosis of Adrenal Insufficiency in the Outpatient setting: Static Testing - 2

- ACTH measurements
  - Generally not helpful, particularly low values
  - Elevated values may suggest primary Adrenal Insufficiency in the right clinical setting
- "Suggestive" findings:
  - Eosinophilia, hyperchloremia, acidosis, hypercalcemia, azotemia, hyponatremia/hyperkalemia and fasting hypoglycemia

Adrenal Insufficiency: Current Practice 2012

Rami N. Khayat, MD
Associate Professor
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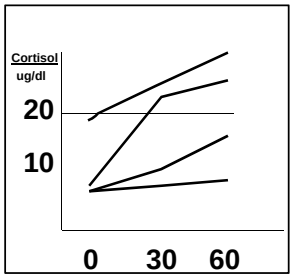
The Ohio State University's Wexner Medical Center

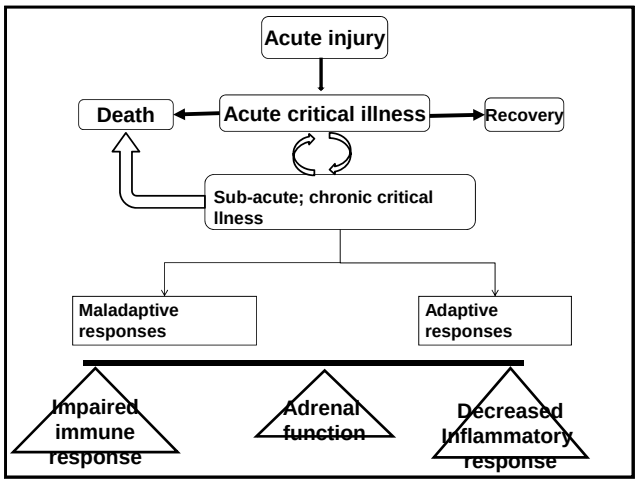
Diagnosis of Adrenal Insufficiency: ACTH stim test

- Give IV/IM bolus of 250 mcg ACTH, measure blood at 0, 30, 60 min
- Normal response is for cortisol to reach >18 mcg/dl
- Caveat : ACTH stim test will be "normal" in early pituitary failure. Once adrenal atrophy sets in, test becomes subnormal



Adrenal Insufficiency during Critical Illness

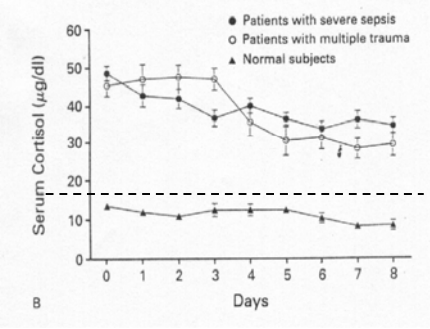
- Adrenal function during critical illness
- Relative adrenal insufficiency
- Overview of Corticosteroid therapy in the ICU
- Conclusions



Adrenal Function in Critical Illness

- Adrenal Gland
  - Synthetic inhibition
    - Drugs
      - Etomidate
      - Ketoconazole
      - » Corticosteroids
    - Cytokines
  - Destruction
    - Pre-existing
      - Autoimmune
      - Infection
        - HIV • CMV
        - TB • Fungal
      - Metastasis
    - Acute
      - Hemorrhage
      - Infection

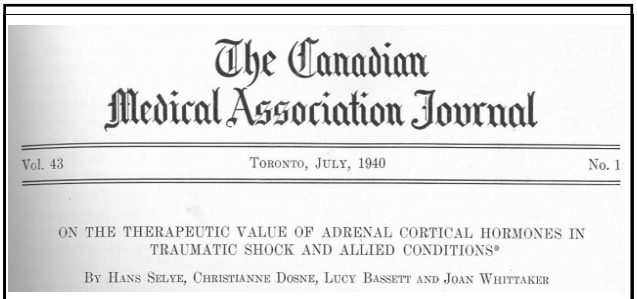
The Adrenal Response to Prolonged Critical Illness



J Clin End Met. 1995;80:1238.

Adrenal Function in Critical Illness

- ↑ Hepatic metabolism of cortisol
  - Rifampin
  - Phenytoin
  - Phenobarbital
- Glucorticoid Resistance



The Canadian Medical Association Journal

Vol. 43 — Toronto, July, 1940 — No. 1

ON THE THERAPEUTIC VALUE OF ADRENAL CORTICAL HORMONES IN TRAUMATIC SHOCK AND ALLIED CONDITIONS*

By Hans Selye, Christianne Dosne, Lucy Bassett and Joan Whittaker

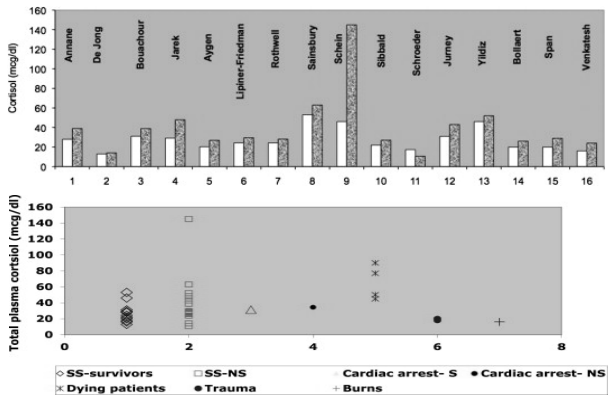
"The fact that cortical hormone therapy exerts beneficial effects in so many conditions makes it rather likely that the hormone is not a specific antidote in any one of these cases but raises shock resistance in general because a condition of relative adrenal insufficiency exists in organisms exposed to non-specific damage."

Cortisol and Septic Shock

%	Basal cortisol	Δ max	mortality

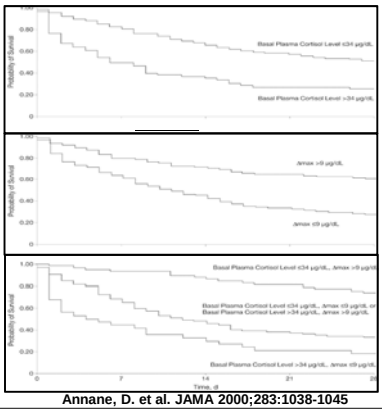
Annane JAMA 2000; 283:1038-1045

Cortisol Levels-Marker of Survival



Venkatesh and Cohen 2011

Prognostic Value of Cortisol Levels and ACTH Response



Annane, D. et al. JAMA 2000;283:1038-1045

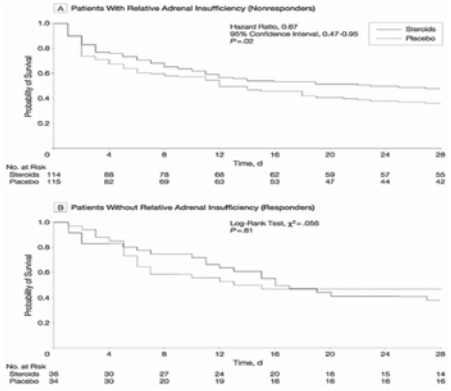
Volume 288(7) 21 August 2002 p 862–871

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

[Caring for the Critically Ill Patient]

Annane, Djillali MD, PhD; Sébille, Véronique PhD; Charpentier, Claire MD; Bollaert, Pierre-Edouard MD, PhD; François, Bruno MD; Korach, Jean-Michel MD; Capellier, Gilles MD, PhD; Cohen, Yves MD, PhD; Azoulay, Elie MD; Troché, Gilles MD; Chaumet-Riffaut, Philippe MD; Bellissant, Eric MD, PhD

Effect of Low Dose Hydrocortisone on Mortality in Patients with Septic Shock



Annane, D. et al. JAMA 2002;288:862-871

Steroids In Septic Shock

Catechlamine dependent septic shock (300)

ACTH Stim Test

76% Non-Responders (229)

24% Responders (70)

<9 ug/dl cortisol

>9 ug/dl cortisol

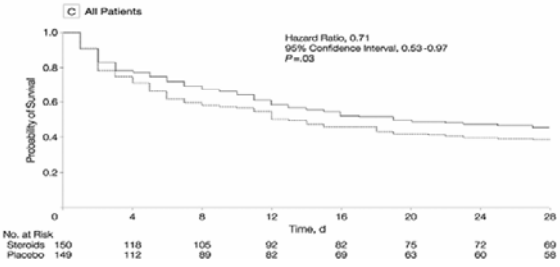
Steroids | Placebo | Steroids | Placebo

50 mg Hydrocortisone q6°
50 ug Fludrocortisone qd

50 mg Hydrocortisone q6°
50 ug Fludrocortisone qd

Annane JAMA 2002; 288:862-871

Effect of Low Dose Hydrocortisone on Mortality in Patients with Septic Shock



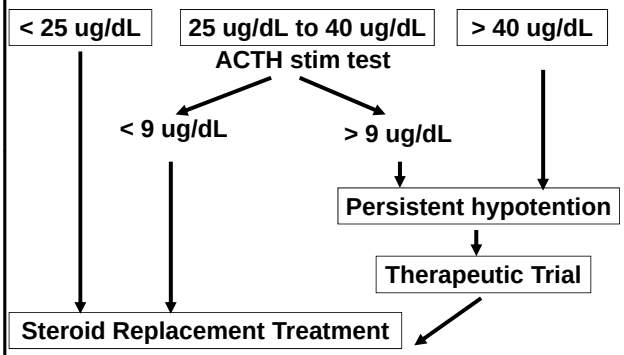
Annane, D. et al. JAMA 2002;288:862-871

Steroids In Septic Shock

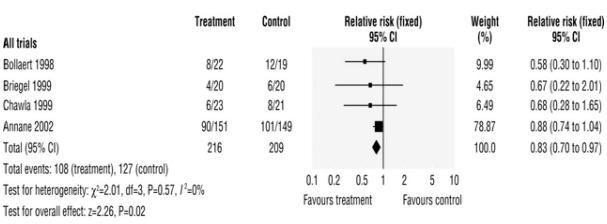
Mortality	Non-Responders		Responders	
	Steroids	Placebo	Steroids	Placebo
28 Day	53%*	63%	61%	53%
ICU	58%*	70%	67%	59%
Hospital	61%*	72%	69%	59%
1 Year	68%*	77%	69%	71%
Vasopressor Withdrawal (28 days)	57%* Median 7	40% Median 10	50% Median 9	53% Median 7

Annane JAMA 2002; 288:862-871

Approach to Suspected Adrenal Insufficiency



Effects of Corticosteroids on Mortality ICU Severe Sepsis and Septic Shock



bmj.com

Annane BMJ 2004;329:480

Concerns

- High mortality in the Control group
- Use of Etomidate
- Design and power
- Severe refractory shock required for enrollment

CORTICUS

The NEW ENGLAND JOURNAL of MEDICINE

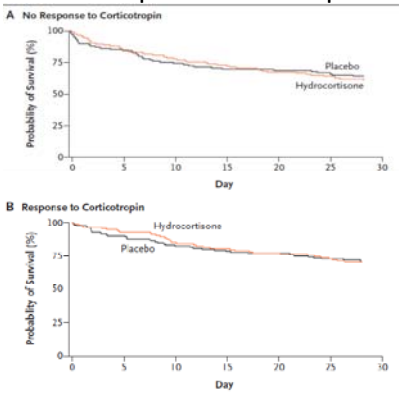
ESTABLISHED IN 1812 JANUARY 10, 2008 VOL. 358 NO. 2

Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

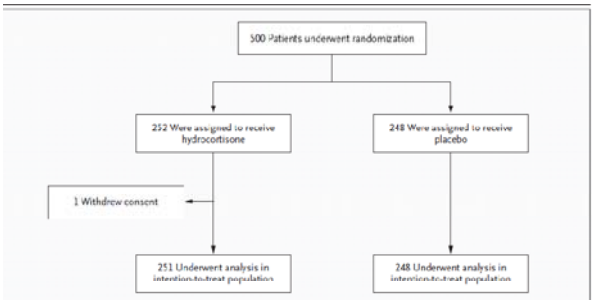
Hydrocortisone Therapy for Patients with Septic Shock

Kaplan–Meier curves for survival at 28 days according to response to corticotropin test



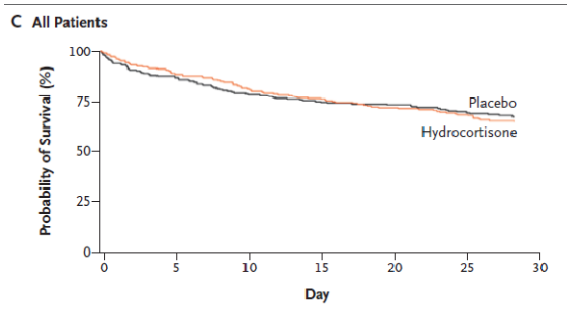
Sprung et al NEJM 2008

Hydrocortisone Therapy for Patients with Septic Shock Sprung et al NEJM 2008



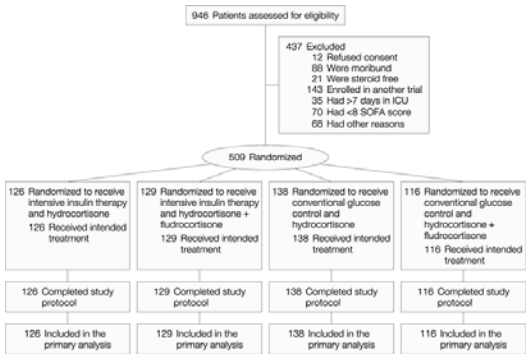
Enrolment and Outcome

Hydrocortisone Therapy for Patients with Septic Shock
Kaplan–Meier Curves for Survival at 28 Days



Sprung et al NEJM 2008

Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults



JAMA 2010;303:341-348

Corticosteroids for ARDS NEJM 2006 "ARDSNET"

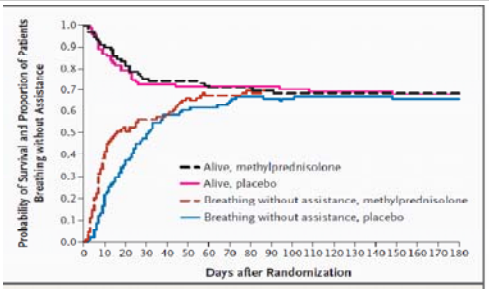


Figure 2. Probability of Survival and the Proportion of Patients with Persistent ARDS Who Became Able to Breathe without Assistance during the First 180 Days after Randomization.

At 180 days, 29 patients in the placebo group had died, 58 had been discharged home, and 4 had not been discharged home; the respective values in the methylprednisolone group were 28, 57, and 4. The status was known for all 180 patients at 180 days.

Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults___

Variables	Intensive Insulin Therapy (n = 255)	Conventional Glucose Control (n = 254)	*P* Value Unadjusted	*P* Value Adjusted[a]	Hydrocortisone + Fludrocortisone (n = 245)	Hydrocortisone Alone (n = 264)	*P* Value Unadjusted	*P* Value Adjusted[a]
In-hospital death, No./total (%)	117/255 (45.9)	108/254 (42.9)	.50	.37	105 (42.9)	121 (45.8)	.50	.91
Overall survival								
Deaths, No. (%)	122 (47.9)	118 (46.5)			112 (45.7)	128 (48.5)		
Kaplan-Meier estimate of survival rates, HR (95% CI), d	1.04 (0.80-1.34)	1 [Reference]	.78	.39	0.94 (0.73-1.21)	1 [Reference]	.61	.67
28	62.2 (56.4-68.5)	61.1 (55.3-67.5)			62.5 (56.6-68.9)	60.9 (55.2-67.1)		
90	51.8 (45.9-58.4)	54.8 (48.9-61.4)			54.2 (48.2-61.0)	52.4 (46.6-58.9)		
180	50.9 (45.0-57.6)	52.1 (46.2-58.8)			52.9 (46.9-59.7)	50.2 (44.4-56.6)		
No. of patients who died	103	82			105	121		
Causes of death, No. (%)								
Multiple organ failure	92 (78.6)	66 (60.6)	.004[b]	.005[b]	75 (71.4)	83 (68.6)	.67[b]	.74[b]
Cardiovascular	9 (8.7)	7 (6.5)			7 (6.7)	9 (7.4)		
Stroke	1 (1.0)	2 (2.4)			3 (2.9)	0		
Brain hemorrhage	0	2 (2.4)			0	2 (1.7)		
Refractory hypoxia	1 (1.0)	2 (2.4)			2 (1.9)	1 (0.8)		
Unknown	0	3 (3.7)			3 (2.9)	0		
No. of days, median (IQR)								
Vasopressor-free within the first 7 days	4 (1-6)	4 (2-5)	.58	.60	4 (2-5)	4 (1-5)	.62	.61
Mechanical ventilation-free within 28 days	10 (2-22)	13 (2-23)	.51	.29	12 (2-23)	12 (2-22.5)	.50	.81
Cumulative incidence of SOFA <8 at day 7 (95% CI)	64.3 (58.6-70.1)	60.6 (54.7-66.6)	.38	.75	63.3 (57.3-69.2)	61.7 (56.0-67.5)	.75	.78
Length of stay, median (IQR), d								
ICU								
All patients	9 (4-19)	9 (4-15)	.70	.39	9 (4-16)	9 (4-17.5)	.86	.35
Survivors	10 (6-19)	9 (5-15)	.68	.46	10 (6-16)	9 (5-17)	.52	.10
Hospital								
All patients	16 (6-34)	15 (7-30)	.87	.94	14 (6-25)	18 (7-34)	.15	.07
Survivors	24 (12-43)	22 (11-39)	.87	.57	19 (5-40)	25.5 (14-42)	.09	.13

JAMA 2010;303:341-348

Role of Steroids in Specific Conditions

Good

- **Meningitis**
- **Typhoid fever**
- **Spinal cord injury**
- **Pneumocystis Carinii Pneumonia**
- **No evidence**
  - **Fibroproliferative ARDS?**
  - **Sepsis?**

Bad

Industrial strength pharmacologic does

Surviving Sepsis 2008

- **We suggest that intravenous hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).**
- **We suggest that the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).**
- **We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available (grade 2B).**

Adrenal Insufficiency: Current Practice 2012

Lawrence S. Kirschner, MD, PhD
Professor of Medicine
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The Ohio State University's Wexner Medical Center

Surviving Sepsis 2008

- **daily addition of oral fludrocortisone (50 µg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (grade 2C).**
- **that clinicians wean the patient from steroid therapy when vasopressors are no longer required (grade 2D).**
- **We recommend that doses of corticosteroids comparable to >300 mg hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (grade 1A).**
- **that corticosteroids not be administered for the treatment of sepsis in the absence of shock. (grade 1D).**

Treatment of Adrenal Insufficiency

Treatment of Adrenal Insufficiency: Glucocorticoid Replacement

- Hydrocortisone
  - Metabolized to cortisol
  - Approx 10-12 mg/m2 is replacement dose of HC
  - In most people, this is about 20-25 mg/day
    - 5'9", 155 lb patient. BSA = 1.85. Dose = 18-22 mg
    - 6', 300 lb patient. BSA = 2.63. Dose = 26-31 mg
  - Mimic the diurnal variation (2/3 steroid A.M.; 1/3 evening)
    - Evening dose given mid afternoon (e.g., 3pm) unless patient is night owl
  - Can also be given as single AM dose if patient tolerates

Treatment of Adrenal Insufficiency: Mineralocorticoids

- Replacement of mineralocorticoid needed if primary adrenal failure
- Florinef is synthetic mineralocorticoid (fludrocortisone)
  - Comes in only 1 size (100 mcg)
  - Most patients need 1 tab/day, but may need to titrate to symptoms or electrolytes
  - In patients on high dose HC (>50 mg/day), enough MC activity so that florinef not usually needed

Glucocorticoid equivalents

- Hydrocortisone: 20 mg
- Cortisone acetate: 25 mg
- Prednisone 4-5 mg
- Prednisolone 5 mg
- Dexamethasone 0.75-1 mg
  - Synthetic steroids have longer half life, and may have increased incidence of side effects (e.g., osteoporosis, weight gain, immune suppression)

Treatment of Adrenal Insufficiency: Androgens

- Anecdotal evidence suggests that replacing DHEA(S) may help improve patient well-being, but randomized studies have all been NEGATIVE
- Patients may benefit from a trial of DHEA 50 mg.
  - Patient feels better → great!
  - No better → stop.

Treatment of Adrenal Insufficiency: Efficacy

- There is no single lab test that will judge adequacy of replacement, so patient symptomatology important
- ACTH goals:
  - Generally, aim for AM ACTH 50-150 pg/ml [normal 10-50]
  - Lower ACTH values generally indicate overtreatment
- Renin goals:
  - Normalized
  - Note that it may be very difficult to control ACTH levels if patient has significant mineralocorticoid deficient

Recovery from critical illness

- Patients that are suspected of having adrenal insufficiency should have their steroids weaned once critical illness has resolved
- Typically, patients can be weaned to replacement level treatment at the time of discharge
- Further evaluation and tapering can then be done in the outpatient setting

Recovery from Addison's?

- Patients who fail an ACTH stim should be retested to verify
- Patients with Cushing Syndrome that are cured by surgery will be insufficient until their axis recovers
  - Requirement for steroids post-op is a *good* sign
  - Patients with Cushing syndrome can take 1-2 years to recover
- Patients on chronic steroids for many years may take many years to recover their axis

Facilitating HPA recovery

- Use Hydrocortisone
  - Shorter biological half-life means axis can recover while patient on therapy
  - If patient tolerates, put on once daily replacement of HC and wait
    - Go for lowest dose that patient will tolerate
  - Retest by ACTH stim q3-4 months until recovery
- Can also use prednisone (low dose or qod dosing) but usually doesn't work as well