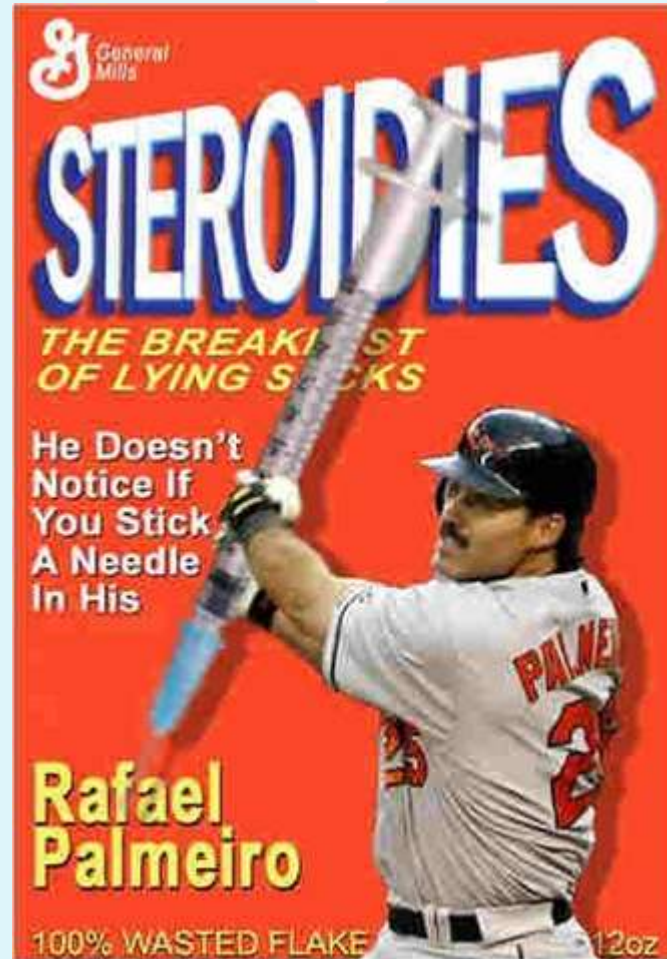


Husain A Alawadhi MD

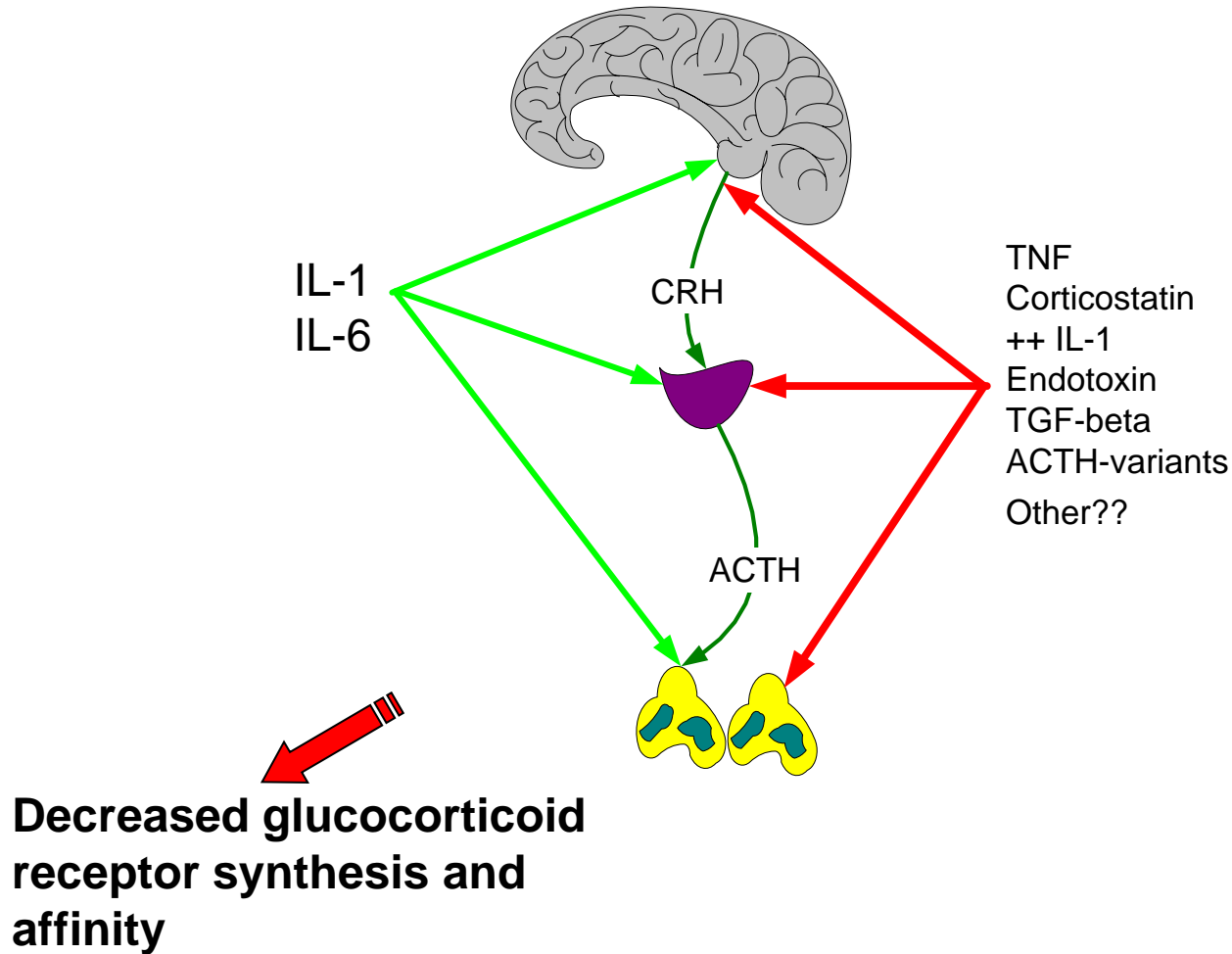


**STEROID IN SEPTIC SHOCK : STILL
CONFUSED**

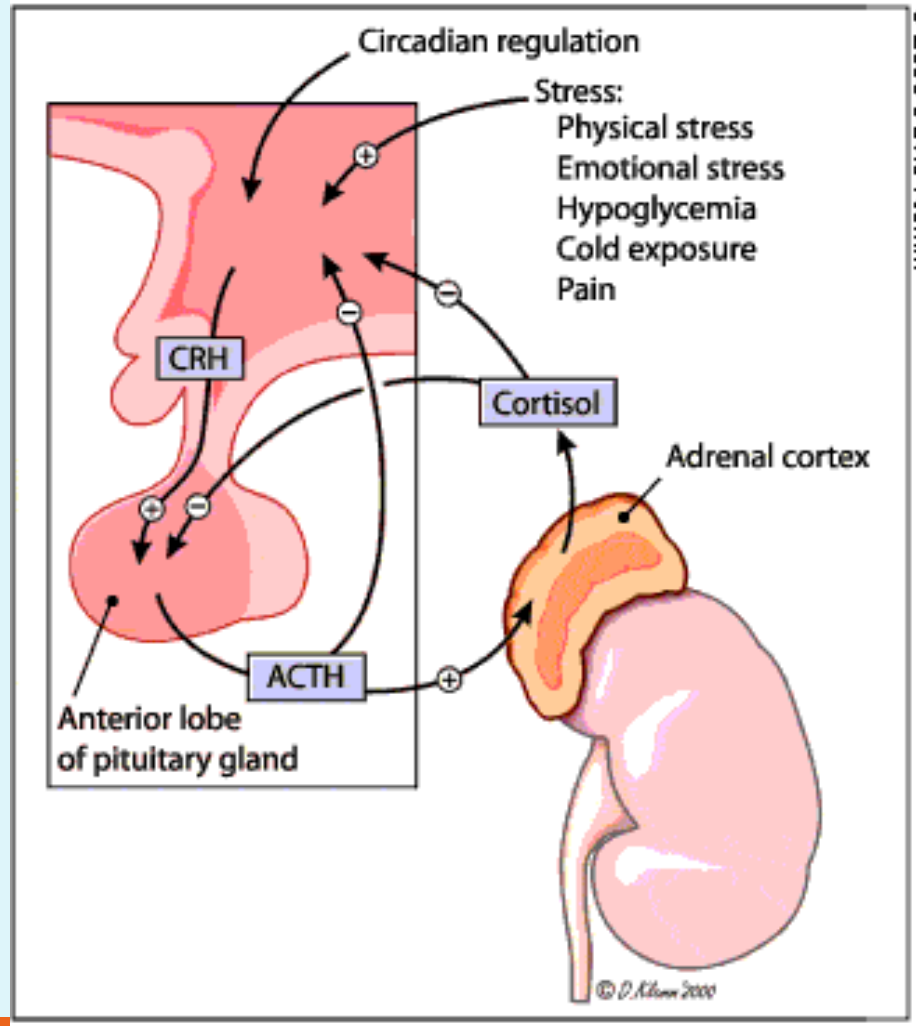
What about steroids?



Sepsis and the HPA Axis



Steroid Physiology





3 Types of Adrenal Insufficiency



- 1 Primary Adrenal Insufficiency (Addison's) >90% destruction of adrenal cortex, Causes: thrombosis, hemorrhage (septic shock with DIC), necrosis from ischemia
- -2 Secondary Adrenal Insufficiency
 - Pituitary or hypothalamic abnormalities
 - Causes: empty sella syndrome, tumors, hypopituitarism, head trauma, postpartum pituitary necrosis
 - 3 Relative or Functional AI

CIRCI: Critical Illness Related Corticosteroid Insufficiency”



- “Critical Illness Related Corticosteroid Insufficiency”
- Inadequate corticosteroid activity for the severity of the illness at hand
- Thought to be comprised of both a relative lack of cortisol, as well as tissue resistance to its effects
 - Possibly due to decreased expression of active form of GC receptor (?effects of TNF alpha and IL-1
- Overall incidence of adrenal insufficiency is estimated to be 20% for all-comers, and as high as 60% for pts with septic shock and burns due to their exaggerated pro-inflammatory response

Diagnosis



- Diagnosis of adrenal insufficiency has traditionally relied upon use of total serum cortisol measurement, usually checking baseline levels and repeating measurements after stim testing with high dose (250mcg) of cosyntropin (synthetic ACTH).
- >90% of circulating cortisol is bound to CBG, and only 10% (free from) is physiologically active
- CBG is noted to be decreased in pts with septic shock, leaving a higher proportion of free cortisol in the serum than in normal conditions



- Lets go back 10 years



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

Djillali Annane, MD, PhD

Véronique Sèbille, PhD

Claire Charpentier, MD

Pierre-Edouard Bollaert, MD, PhD

Bruno François, MD

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Eric Bellissant, MD, PhD

SEVERE SEPSIS REMAINS AN IMPORTANT cause of death, accounting for 9.3% of all deaths in the United States in 1995.¹ If our understanding of the mechanisms of host response to stress has strongly progressed during the last 2 decades,² the various drugs developed for specific targets of the cytokine cascade have failed to improve patient survival.^{3,4}

Corticosteroids were the first anti-inflammatory drugs tested in random-

Context Septic shock may be associated with relative adrenal insufficiency. Thus, a replacement therapy of low doses of corticosteroids has been proposed to treat septic shock.

Objective To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency.

Design and Setting Placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France from October 9, 1995, to February 23, 1999.

Patients Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test.

Intervention Patients were randomly assigned to receive either hydrocortisone (50-mg intravenous bolus every 6 hours) and fludrocortisone (50- μ g tablet once daily) ($n=151$) or matching placebos ($n=149$) for 7 days.

Main Outcome Measure Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test).

Results One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 34; corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; $P=.02$). Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; $P=.001$). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

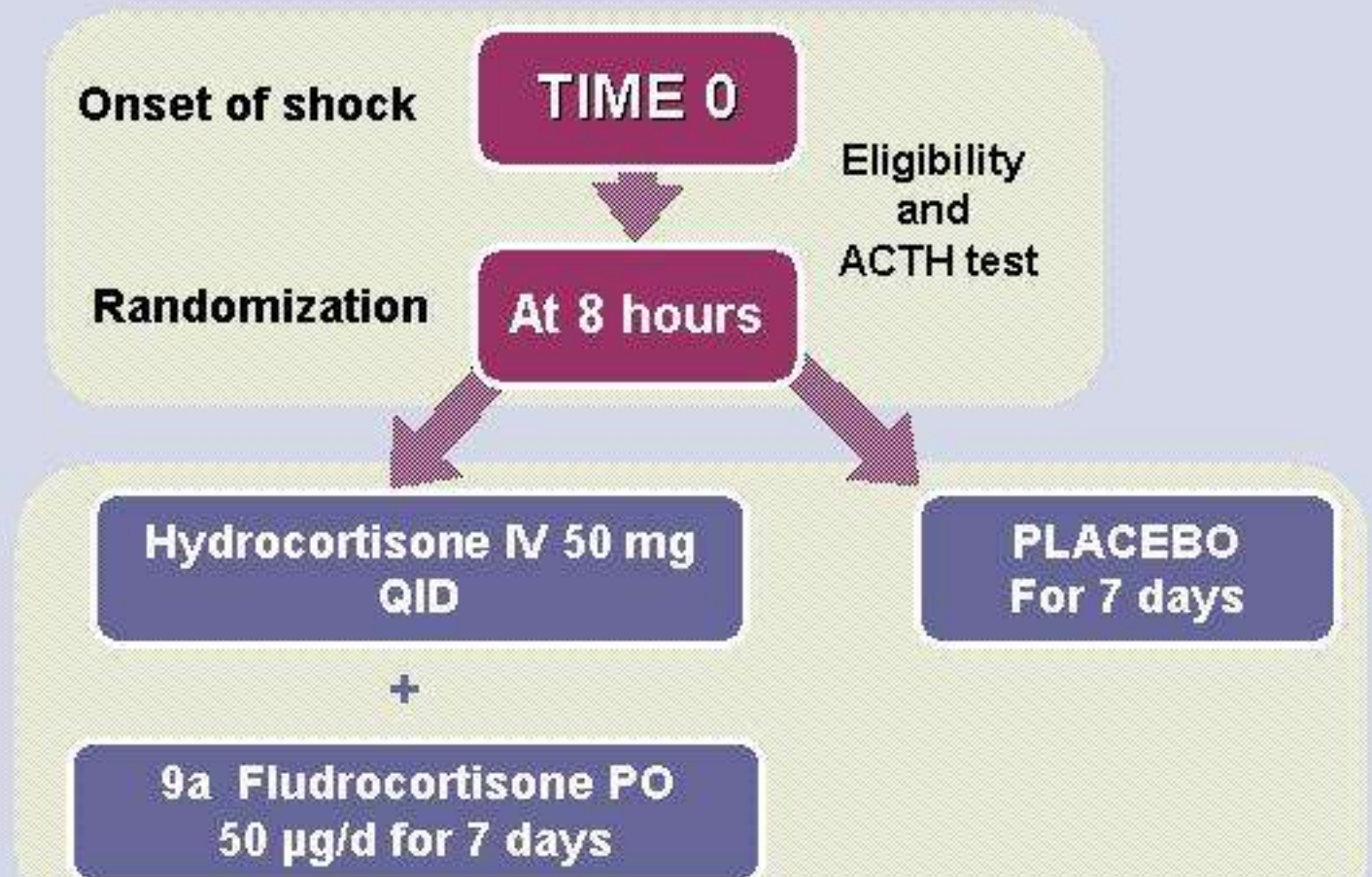
Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

JAMA. 2002;288:862-871

www.jama.com

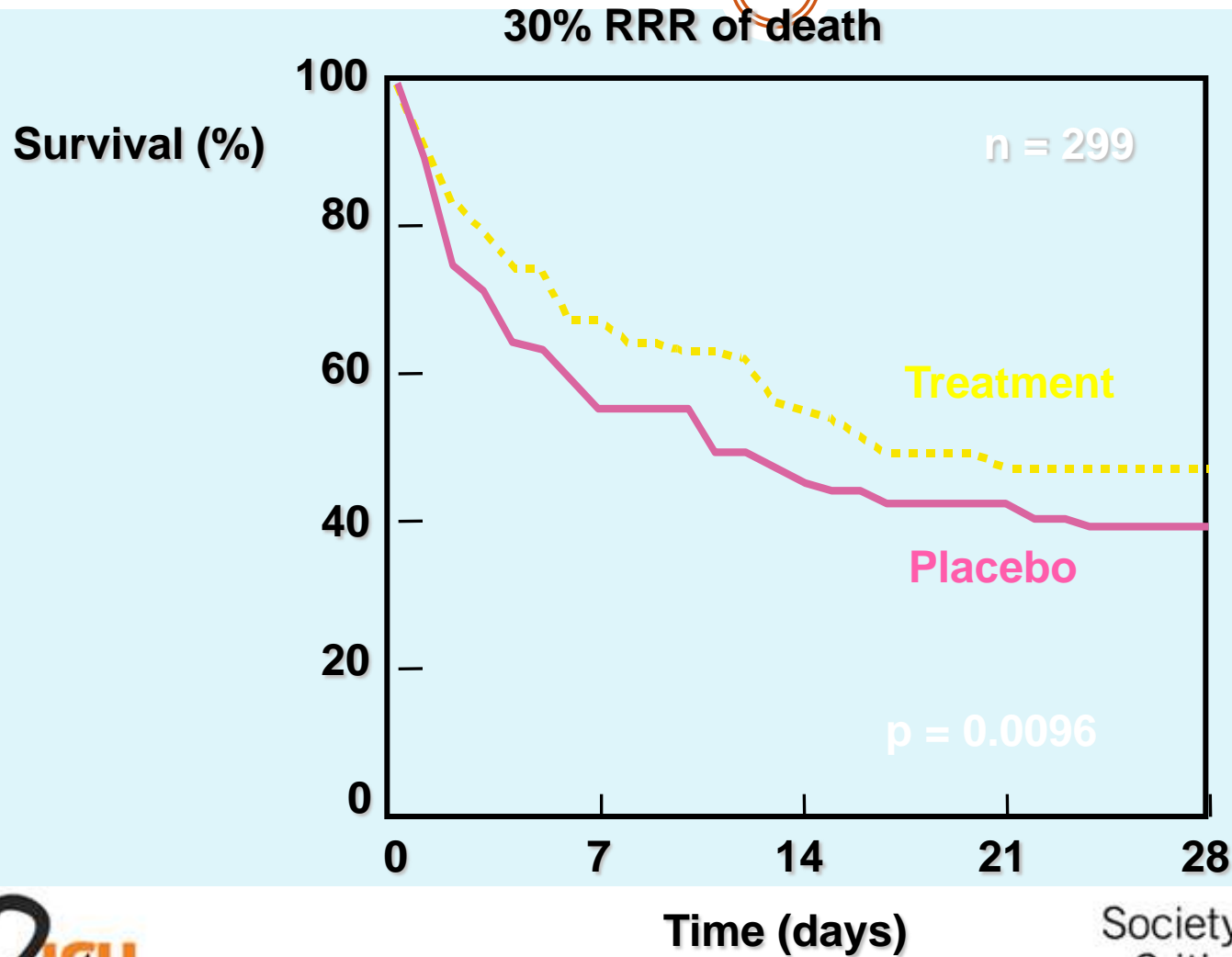
D. Annane, JAMA 2002;288:862-871

Steroids in Septic Shock with Adrenal Insufficiency: Study Design



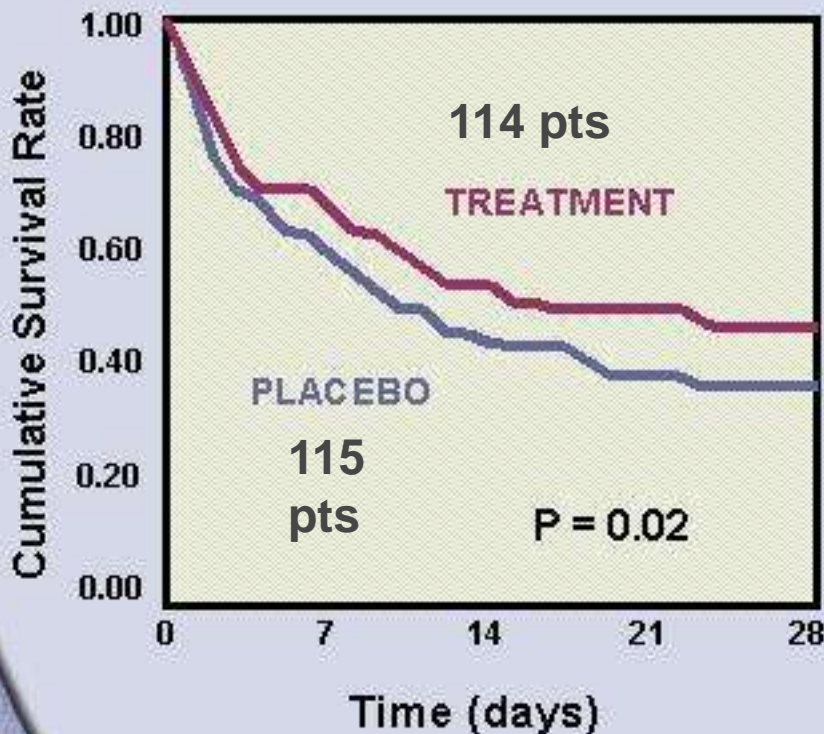
Annane D et al. Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock
JAMA 2002 288: 862-871

Hydrocortisone Increases Survival in Septic Shock

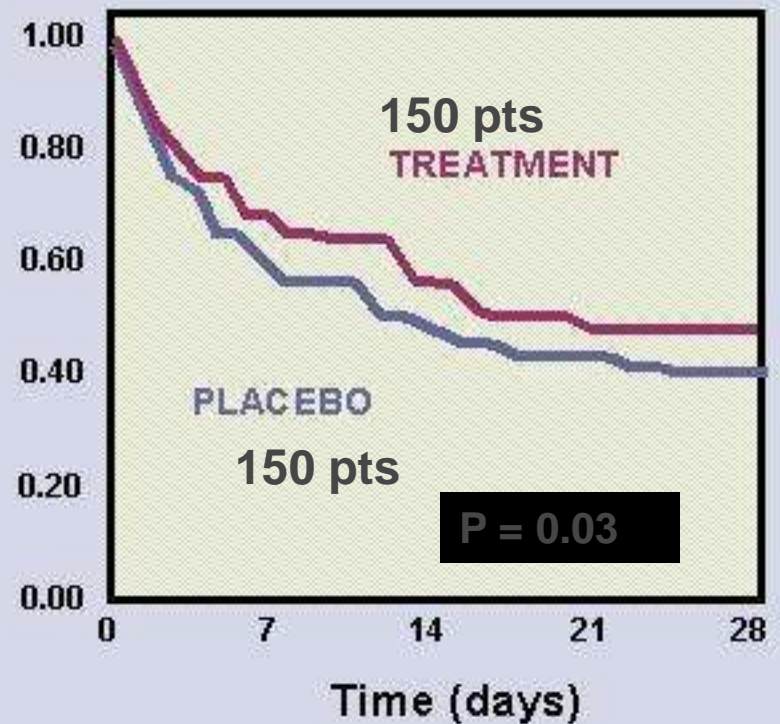


Effect of Steroids in Septic Shock with Adrenal Insufficiency: Results

28-Day Cumulative Survival in Non-Responders

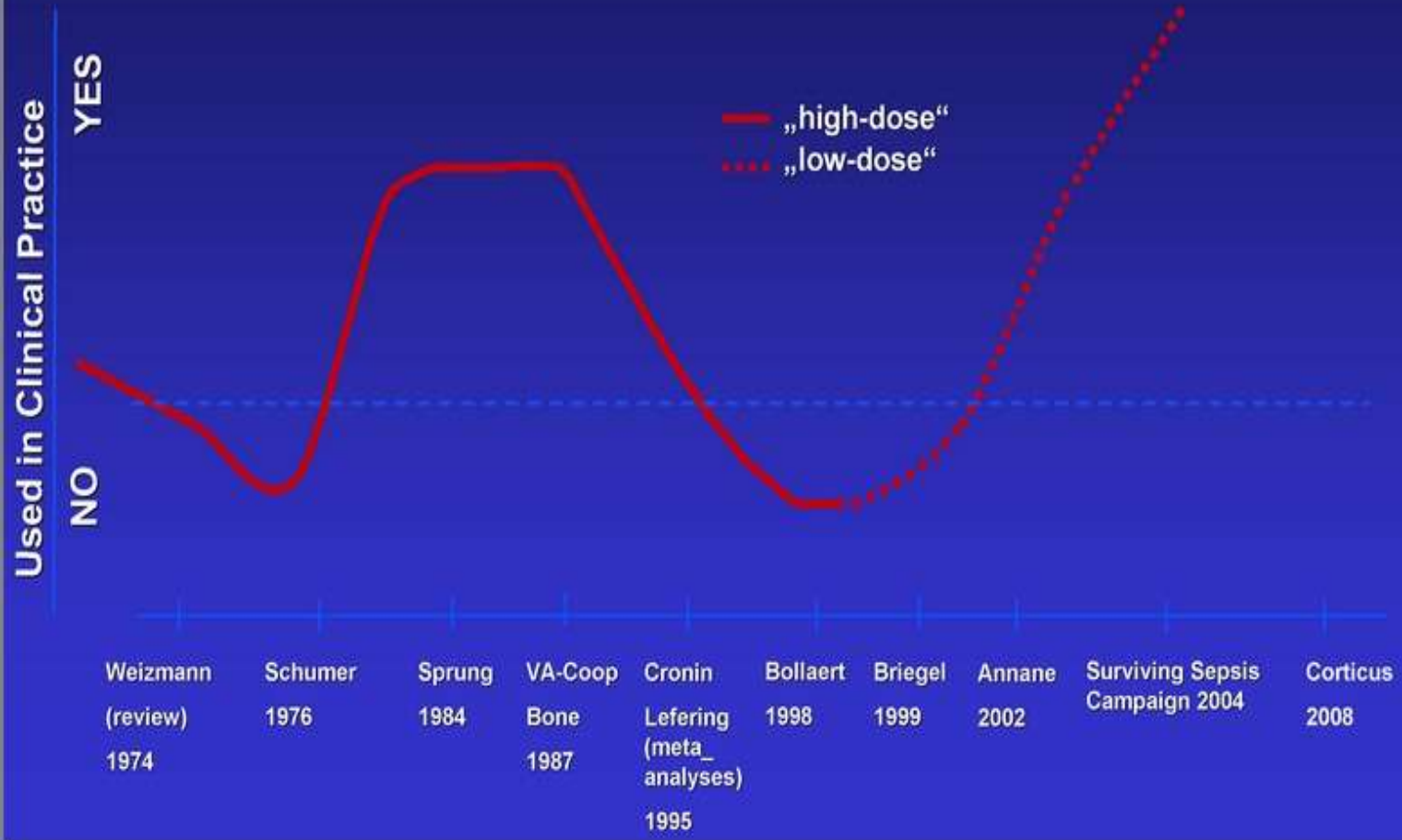


28-Day Cumulative Survival in All Patients



Annane D et al. Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock
JAMA 2002 288: 862-871

Steroids For Treatment of Infections, Sepsis and Septic Shock - *Ups and Downs*





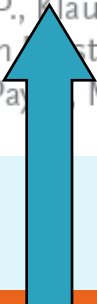
The NEW ENGLAND JOURNAL *of* MEDICINE

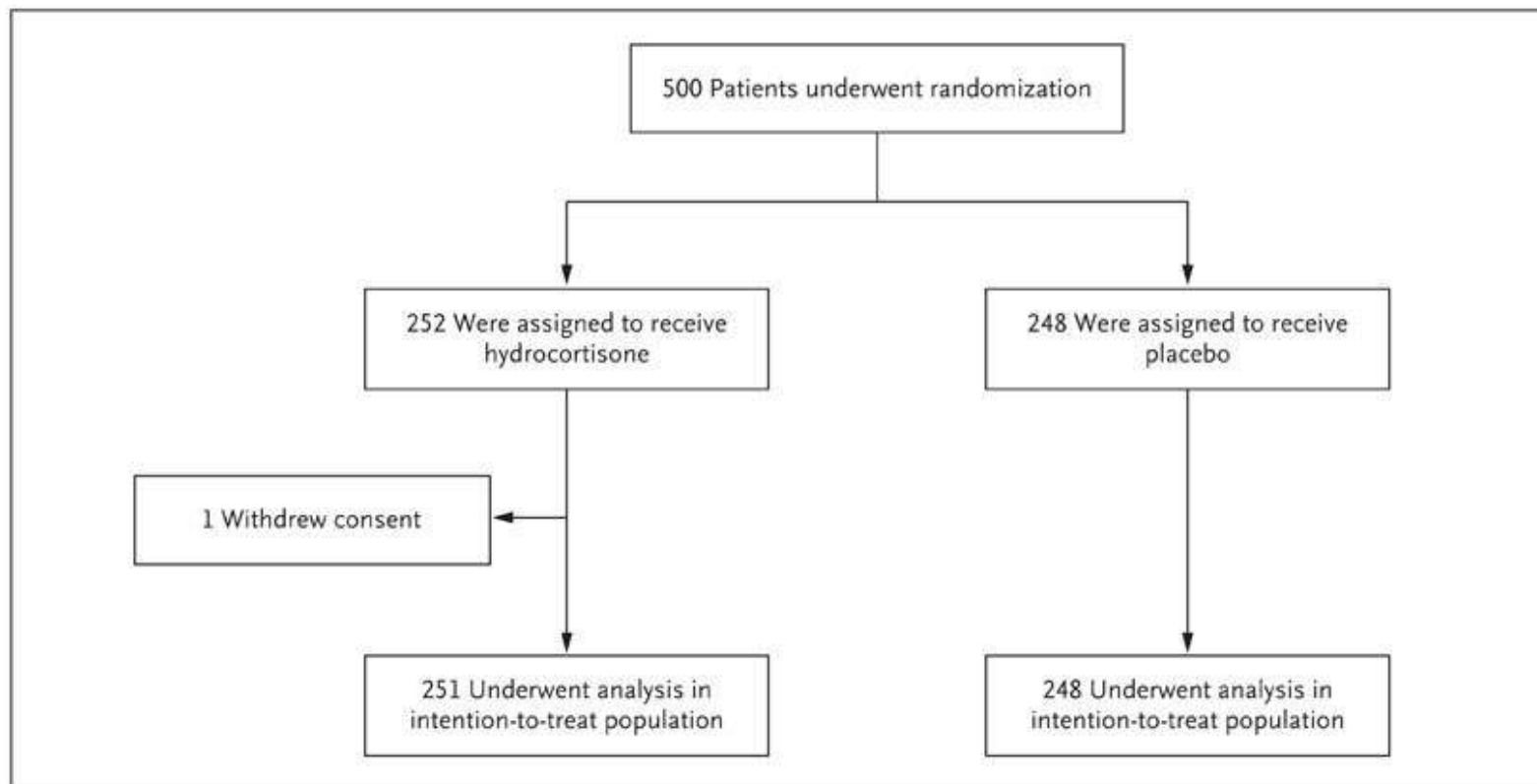
ESTABLISHED IN 1812

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 st, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payan, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*



Short corticotropin test
(499 patients)

No response -
233 patients (46.7%)

125 in hydrocortisone group
108 in placebo group

49 deaths (39.2%)
39 deaths (36.1%)
P=0.69

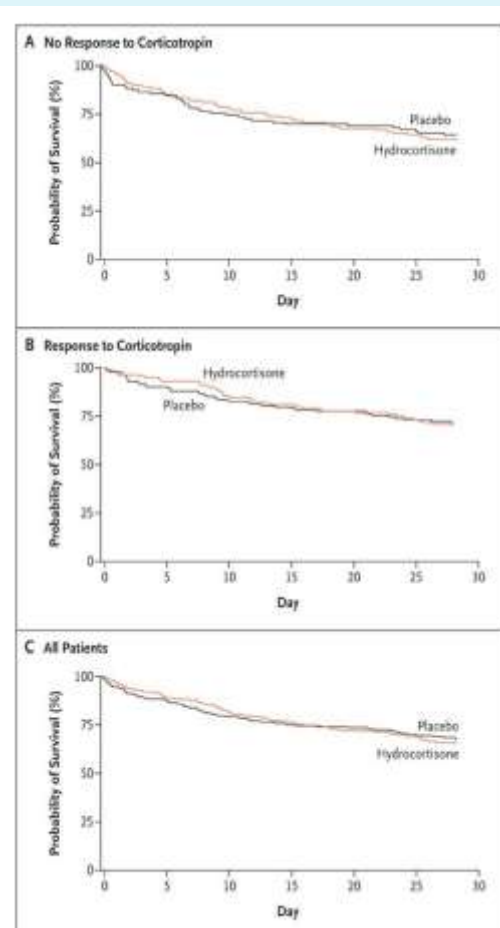
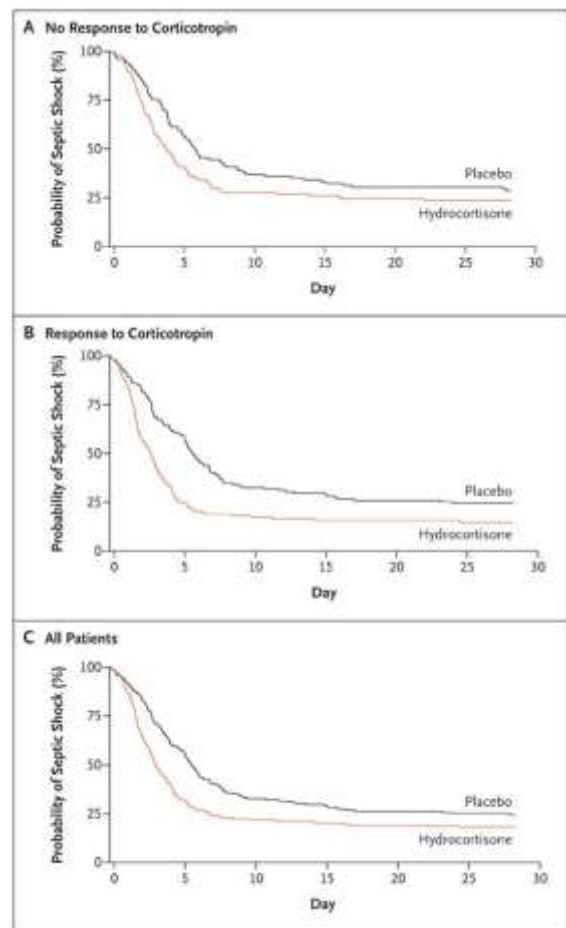
Response -
254 patients (50.9%)

118 in hydrocortisone group
136 in placebo group

34 deaths (28.8%)
39 deaths (28.7%)
P=1.00

Conclusion : Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed

N Engl J Med 358(2):111-124 January 10, 2008





Mortality

- ✦ No significant difference of the rate of death at 28 days among patients who did not have a response to corticotropin.
- ✦ Overall, ($P=0.51$)
 - 86 deaths in the hydrocortisone group (34.3%)
 - 78 deaths in the placebo group (31.5%)



Post hoc analyses

- ✦ Among patients with a SBP persisting < 90 mmHg within 30 hours after study entry,
 - 31 of 69 patients (44.9%) in the hydrocortisone group
 - 32 of 57 patients (56.1%) in the placebo grouphad died.
Absolute difference: -11.2% (95% CI, -18.6 to 6.2; P=0.28)
- ✦ Among patients with a SBP persisting ≥ 90 mmHg within 30 hours after study entry,
 - 55 of 181 patients (30.4%) in the hydrocortisone group
 - 46 of 189 patients (24.3%) in the placebo group***Absolute difference: 6.1%*** (95% CI, -3.0 to 15.1; P=0.20)



Post hoc analyses

- ✦ *The rates of death among the patients who received a study drug within 12 hours after baseline were **similar** in two groups*

- ✦ ***Increased rate** of death at 28 days (**P=0.03**) among patients who received etomidate before randomization in both groups*
 - 23 of 51 patients (45.1%) in the hydrocortisone group
 - 18 of 45 patients (40.0%) in the placebo group

- ✦ *Among patients who did not receive etomidate,*
 - 63 of 200 patients (31.5%) in the hydrocortisone group
 - 60 of 203 patients (29.6%) in the placebo group

Critiques



- Etomidate was the paralytic used in 26% of patients at time of intubation
 - Known to cause ~24hr period of adrenal suppression
 - May have caused false negative CST in some pt's
- The study was ended prematurely, and thus was underpowered (target 800 pt's)
 - Slow recruitment
 - Loss of funding
 - Expiry of study drug

SUMMARY: SEPSIS GUIDELINES 2008

Weak Recommendation (2): Suggested

A



B

APC in high risk and non-surgical

equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis

NIV for ALI/ARDS mild/moderate hypoxemia

C

PRBCs or Dobutamine

APC for high risk and surgical

Low dose steroids for septic shock

ACTH test not to be done

B/S < 150

Prone Position in ARDS

D

Wean Steroids

Corticosteroid (2008)



- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B)
- Hydrocortisone is preferred to dexamethasone (2B)

Corticosteroid (2008)



- Fludrocortisone (50 g orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used (2C)
- Steroid therapy may be weaned once vasopressors are no longer required (2D)
- Hydrocortisone dose should be 300 mg/day (1A)
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D)

OTHER STUDY DIFFERENCES

	<u>Annane</u>	<u>Corticus</u>
Entry window	8 hours	72 hours
SBP < 90 mmHg	> 1 hour	< 1 hour
Treatment	FC	None
Practice/Guidelines	None	Steroids used
SAPS II	59 ± 21	49 ± 17



Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine



[Critical Care Medicine](#) - [Volume 36, Issue 6](#) (June 2008) - Copyright © 2008 Lippincott Williams & Wilkins

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International Task Force Recommendations



- Concerning diagnosis and management of corticosteroid insufficiency in critically ill patients
- Panel of experts from Society of Critical Care Medicine, European Society of Intensive Care Medicine, and Endocrinology experts on adrenal insufficiency from US and abroad.
- Review of the published literature, expert opinions given and consensus derived
- Recommendations were classified as strong (grade 1) or weak (grade 2)
- Quality of evidence for the recommendation also provided
 - A = high quality evidence
 - B = moderate quality
 - C = low quality

Recommendations



- 1. Dysfunction of the HPA axis in critical illness is best described by the term critical illness related corticosteroid insufficiency (CIRCI)
- 2. The terms absolute or relative adrenal insufficiency are best avoided in the context of critical illness
- 3. At this time, adrenal insufficiency in critical illness is best diagnosed by a delta cortisol of $<9\text{mcg/dL}$ (after 250 mcg cosyntropin), or a random cortisol of $<10\text{mcg/dL}$ (2B)
- 4. The use of free cortisol measurements cannot be recommended for routine use at this time. Although the free cortisol assay has advantages...(it) is not readily available. Furthermore, the normal range of free cortisol in critically ill pts is currently unclear (2B)

Recommendations



- 5. The ACTH stimulation test should not be used to identify those patients with septic shock or ARDS who receive glucocorticoids (2B)
- 6. Hydrocortisone should be considered in the management strategy of patients with septic shock, particularly those who have responded poorly to fluid resuscitation and vasopressor agents (2B)
- 7. Moderate dose glucocorticoids should be considered in patients with early severe ARDS ($\text{PaO}_2 / \text{FiO}_2 < 200$) and before day 14 in patients with unresolving ARDS (2B)
- 8. In patients with septic shock, intravenous hydrocortisone should be given in a dose of 200mg/day in four divided doses or as a continuous infusion at 10mg/hr (240mg/day). The optimal initial dosing regimen in patients with early severe ARDS is 1mg/kg/day of methylprednisolone as a continuous infusion. (1B)

Recommendations



- 9. The optimal duration of glucocorticoid treatment...is unclear. However, based on published studies and pathophysiological data, patients with septic shock should be treated for 7 or more days before tapering...patients with early ARDS for 14 or more days before tapering. (2B)
- 10. Glucocorticoid treatment should be tapered slowly and not stopped abruptly (2B)
- 11. Treatment with oral fludrocortisone is considered optional (2B)
- 12. Dexamethasone is not recommended for the treatment of septic shock or ARDS (1B)

2009



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Vol. 301 No. 22, June 10, 2009

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Caring for **the** Critically Ill Patient

CLINICIAN'S CORNER

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

A Systematic Review

Djillali Annane, MD; Eric Bellissant, MD; Pierre-Edouard Bollaert, MD; Josef Briegel, MD; Marco Confalonieri, MD; Raffaele De Gaudio, MD; Didier Keh, MD; Yizhak Kupfer, MD; Michael Oppert, MD; G. Umberto Meduri, MD

JAMA. 2009;301(22):2362-2375.



Online article and related content
current as of May 3, 2010.

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults: A Systematic Review

Djillali Annane; Eric Bellissant; Pierre-Edouard Bollaert; et al.

JAMA. 2009;301(22):2362-2375 (doi:10.1001/jama.2009.815)

<http://jama.ama-assn.org/cgi/content/full/301/22/2362>

- Overall, this review showed no significant effect of corticosteroid treatment on 28-day mortality, intensive care unit mortality, or hospital mortality in severe sepsis or septic shock .



Online article and related content
current as of May 3, 2010.

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults: A Systematic Review

Djillali Annane; Eric Bellissant; Pierre-Edouard Bollaert; et al.

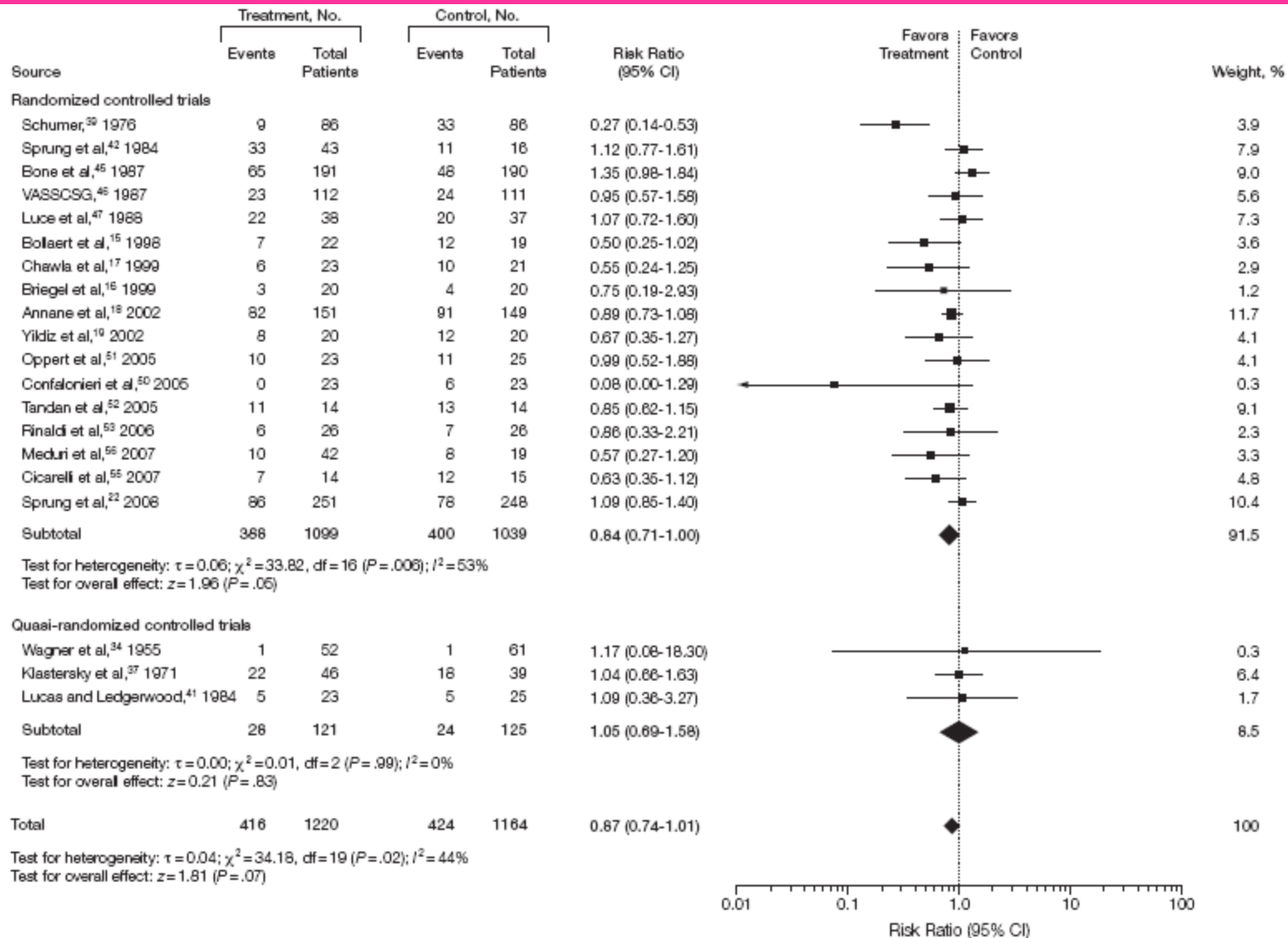
JAMA. 2009;301(22):2362-2375 (doi:10.1001/jama.2009.815)

<http://jama.ama-assn.org/cgi/content/full/301/22/2362>

Conclusions Corticosteroid therapy has been used in varied doses for sepsis and related syndromes for more than 50 years, with no clear benefit on mortality. Since 1998, studies have consistently used prolonged low-dose corticosteroid therapy, and analysis of this subgroup suggests a beneficial drug effect on short-term mortality.

JAMA. 2009;301(22):2362-2375

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SUBGROUP ANALYSIS



- analyses of the trials investigating prolonged course (5 days) of low-dose corticosteroid treatment (300 mg of hydrocortisone or equivalent) demonstrated a significant reduction in 28-day all-cause mortality ($P=.02$) and hospital mortality ($P=.05$).



EDITORIAL

Steroid use in critically ill septic patients: acknowledging the uncertainty*

Roman Jaeschke^{1,2,3}, Gordon Guyatt^{1,3}

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2 Polish Institute of Evidence Based Medicine, Kraków, Poland

3 Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

2010



- **THE STEROID WILL CAUSE HYPERGLYCEMIA >> INCREASE SIDE EFFECTS >> REMOVE THE BENEFITS OF STEROID**
- **FLUDROCORTISINE WAS NOT STUDIED IN PREVIOUS RCT**

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Online article and related content
current as of January 31, 2010.

**Corticosteroid Treatment and Intensive Insulin Therapy
for Septic Shock in Adults: A Randomized Controlled
Trial**

The COITSS Study Investigators

JAMA. 2010;303(4):341-348 (doi:10.1001/jama.2010.2)

<http://jama.ama-assn.org/cgi/content/full/303/4/341>

946 Patients assessed for eligibility

Flowchart of the Trial

437 Excluded
12 Refused consent
88 Were moribund
21 Were steroid free
143 Enrolled in another trial
35 Had >7 days in ICU
70 Had <8 SOFA score
68 Had other reasons

509 Randomized

126 Randomized to receive intensive insulin therapy and hydrocortisone
126 Received intended treatment

129 Randomized to receive intensive insulin therapy and hydrocortisone + fludrocortisone
129 Received intended treatment

138 Randomized to receive conventional glucose control and hydrocortisone
138 Received intended treatment

116 Randomized to receive conventional glucose control and hydrocortisone + fludrocortisone
116 Received intended treatment

126 Completed study protocol

129 Completed study protocol

138 Completed study protocol

116 Completed study protocol

126 Included in the primary analysis

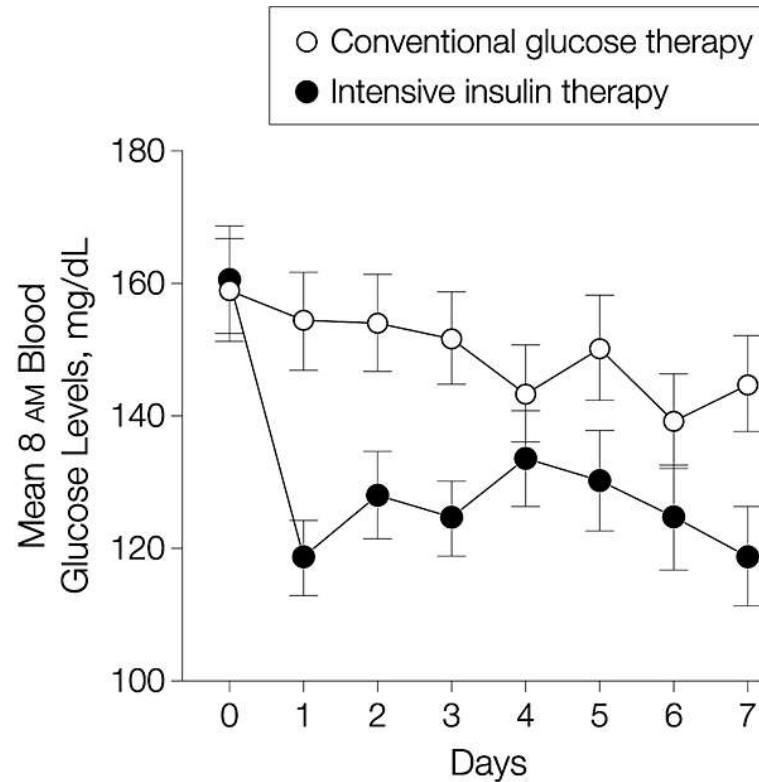
129 Included in the primary analysis

138 Included in the primary analysis

116 Included in the primary analysis

The COITSS Study Investigators, JAMA 2010;303:341-348.

Comparison of Mean 8 AM Blood Glucose According to Intensive Insulin Therapy and to Conventional Glucose Control



No. of patients

Conventional glucose therapy	252	246	234	219	203	186	174	162
Intensive insulin therapy	252	238	220	205	195	181	166	153

The COITSS Study Investigators, *JAMA* 2010;303:341-348.

Primary and Secondary Outcomes

Table 2. Primary and Secondary Outcomes

Variables	Intensive Insulin Therapy (n = 255)	Conventional Glucose Control (n = 254)	P Value		Hydrocortisone + Fludrocortisone (n = 245)	Hydrocortisone Alone (n = 264)	P Value	
			Unadjusted	Adjusted ^a			Unadjusted	Adjusted ^a
In-hospital death, No./total (%)	117/255 (45.9)	109/254 (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]	.76	.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 (44.4-56.8)		
No. of patients who died	103	82			105	121		
Causes of death, No. (%)								
Multiple organ failure	52 (78.6)	66 (80.6)			75 (71.4)	83 (68.6)		
Cardiovascular	9 (8.7)	7 (8.5)			7 (6.7)	9 (7.4)		
Stroke	1 (1.0)	2 (2.4)	.004 ^b	.005 ^b	3 (2.9)	0	.67 ^b	.74 ^b
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	.61
Cumulative incidence of SOFA <3 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 (5-19)	9 (5-15)	.68	.46	10 (5-16)	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

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment

^aAdjusted on baseline prognostic variables, namely age, time in hospital prior to ICU admission, time in ICU prior to randomization, Simplified Acute Physiology Score II, SOFA score, lactate level and mechanical ventilation, and a random center effect.

^bComparison of multiple organ failure vs other causes.

The COLITSS Study Investigators, JAMA 2010;303:341-348.

Conclusions



- Compared with conventional insulin therapy, intensive insulin therapy did **NOT IMPROVE** in-hospital mortality among patients who were treated with hydrocortisone for septic shock. The addition of oral fludrocortisone **DID NOT** improvement in in-hospital mortality.

COMMENT



- The current study showed NO evidence to support a strategy of intensive insulin therapy aimed at maintaining blood glucose levels in the range of 80 to 110 mg/dL for treating septic shock with corticosteroids. Furthermore, NO evidence supports the routine use of oral fludrocortisone.

SO WHAT SHALL I DO NOW ?



STEROID >> NO SIGNIFICANT BENEFIT •
IT SUGGEST A BENEFITS. •

