Glycemic Control
Adrenal Insufficiency

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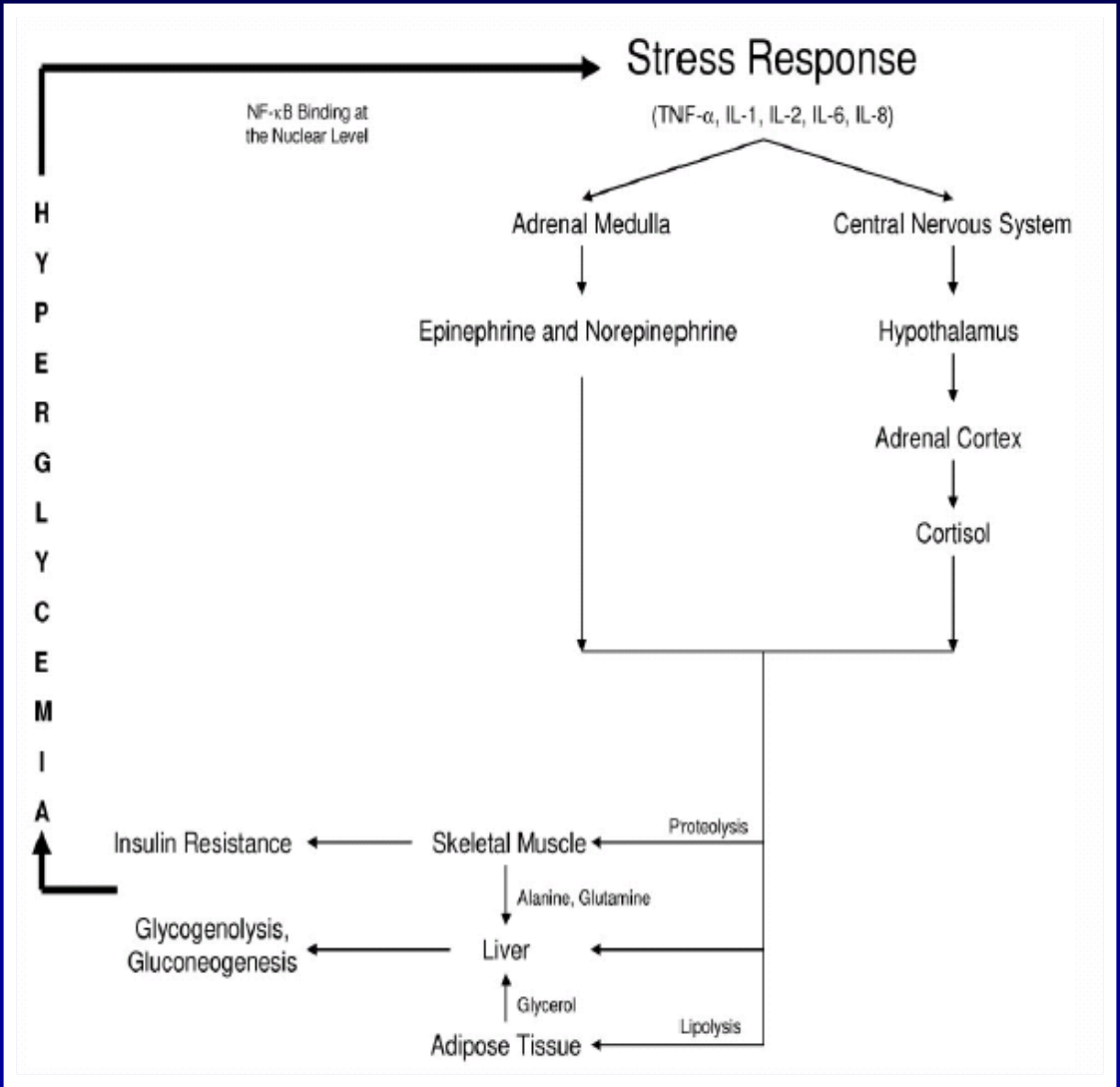
Introduction

- Glycemic Control
  - Issues
  - Hyper
  - Hypo
- Adrenal Insufficiency
  - Anatomy
  - Physiology
  - Issues

Stress Hyperglycemia

- Common following surgery, trauma, burns, and sepsis
- Strongly associated with poor outcomes
- Association appears stronger in non-diabetic patients than in diabetic patients
- Related to a state of insulin resistance (IR) that is promoted by stress related hormones and pro-inflammatory cytokines

Stress Hyperglycemia



- Infl Modulators
- Incr Adrenal response
- Proteolysis/Lipolysis
- Insulin Resistance
- Hyperglycemia

Insulin Resistance

Surgery/Critical Illness

- Biologic response
  - Decreased relative to normal
  - Significant variation
- Increases post-operatively in a dose-dep fashion
  - Based upon magnitude of operative intervention
  - Persists for several weeks
  - 50% increase after open cholecystectomy

Insulin Resistance

Surgery/Trauma/Burn/Sepsis

- Counter-regulatory hormones
  - Epinephrine, glucagon, cortisol, growth hormone
- Pro-inflammatory stimuli
  - $NF_k\beta$, TNF, IL-1, IL-6
- Defects in post-receptor insulin signaling

Hyperglycemia

Effects

- Endothelial dysfunction
- Pro-inflammatory cytokines
- Platelet Activation
- Procoagulation
- Mitochondrial dysfunction
- Acid/base changes
- Immune dysregulation
- Catabolism

Complications

- Renal failure
- Polyneuropathy
- Prolonged Mech Vent
- Transfusion increases
- Sepsis/Wound infection
- Ischemia
- Arrhythmias
- Nephropathy
- Neuropathy

Dungan *Lancet* 2009

Insulin Effects

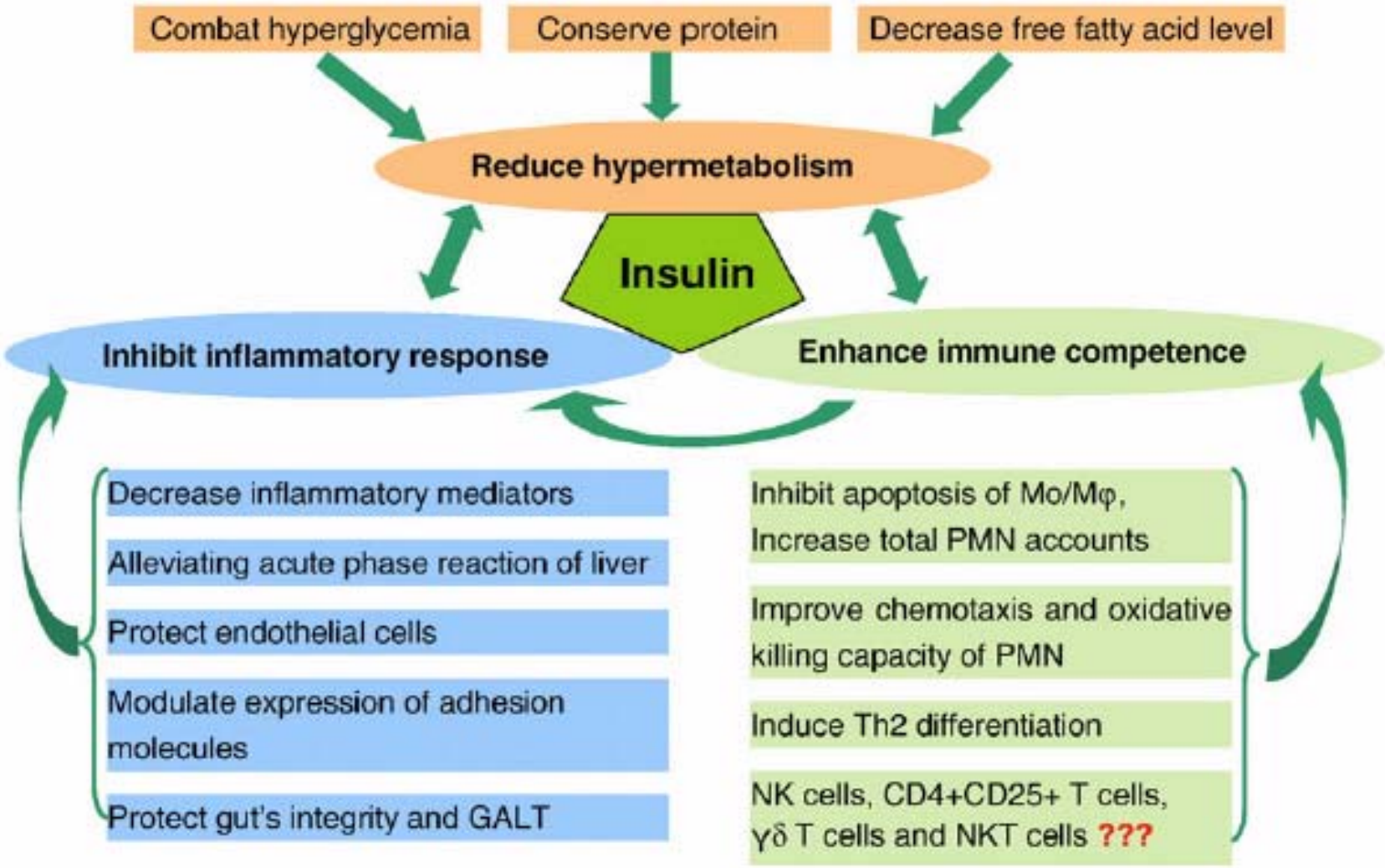
Stress and Critical Illness

- Metabolic
  - Carbohydrate metabolism
  - Lipid metabolism
  - Protein metabolism

Carlson GL. *Ann R Coll Surg Engl* 2004

- Immunologic
  - Reduce pro-inflammatory cytokines
  - Enhance anti-inflammatory cytokines
  - Decrease complement (C3,C4) activation

Deng, H. *Int. Immunopharmacology*


Combat hyperglycemia
Conserve protein
Decrease free fatty acid level
Reduce hypermetabolism
Insulin
Inhibit inflammatory response
Enhance immune competence
Decrease inflammatory mediators
Alleviating acute phase reaction of liver
Protect endothelial cells
Modulate expression of adhesion molecules
Protect gut's integrity and GALT
Inhibit apoptosis of Mo/Mφ, Increase total PMN accounts
Improve chemotaxis and oxidative killing capacity of PMN
Induce Th2 differentiation
NK cells, CD4+CD25+ T cells, γδ T cells and NKT cells ???

Glucose Control

- Lowers risk of wound infection in diabetics
  - Cardiac patient population

Zerr ***Ann Thorac Surg*** **1997**

- Reduced incidence of sternal infections

Furnary ***Ann Thorac Surg*** **1999**

- Long-term survival benefit after AMI in diabetics (DIGAMI)

Malmberg *BMJ* 1997

Major randomized studies of intensive insulin therapy (IIT) in critically ill patients

1. **Leuven 1: Van den Berghe G. *N Engl J Med*. 2001;345:1359-1367**
2. **Leuven 2: Van den Berghe G. *N Engl J Med*. 2006;354:449-461**
3. **VISEP: Brunkhorst FM. *N Engl J Med*. 2008;358:125-139**
4. **Glucontrol: Preiser JC. *Intensive Care Med*. 2009;35:1738-1748**
5. **NICE-SUGAR: Finfer S. *N Engl J Med*. 2009;360:1283-1297**
6. **Arabi YM. *Crit Care Med*. 2008;36:3190-3197**

Intensive Insulin Therapy Reduces Mortality In Critically Ill Surgical Patients

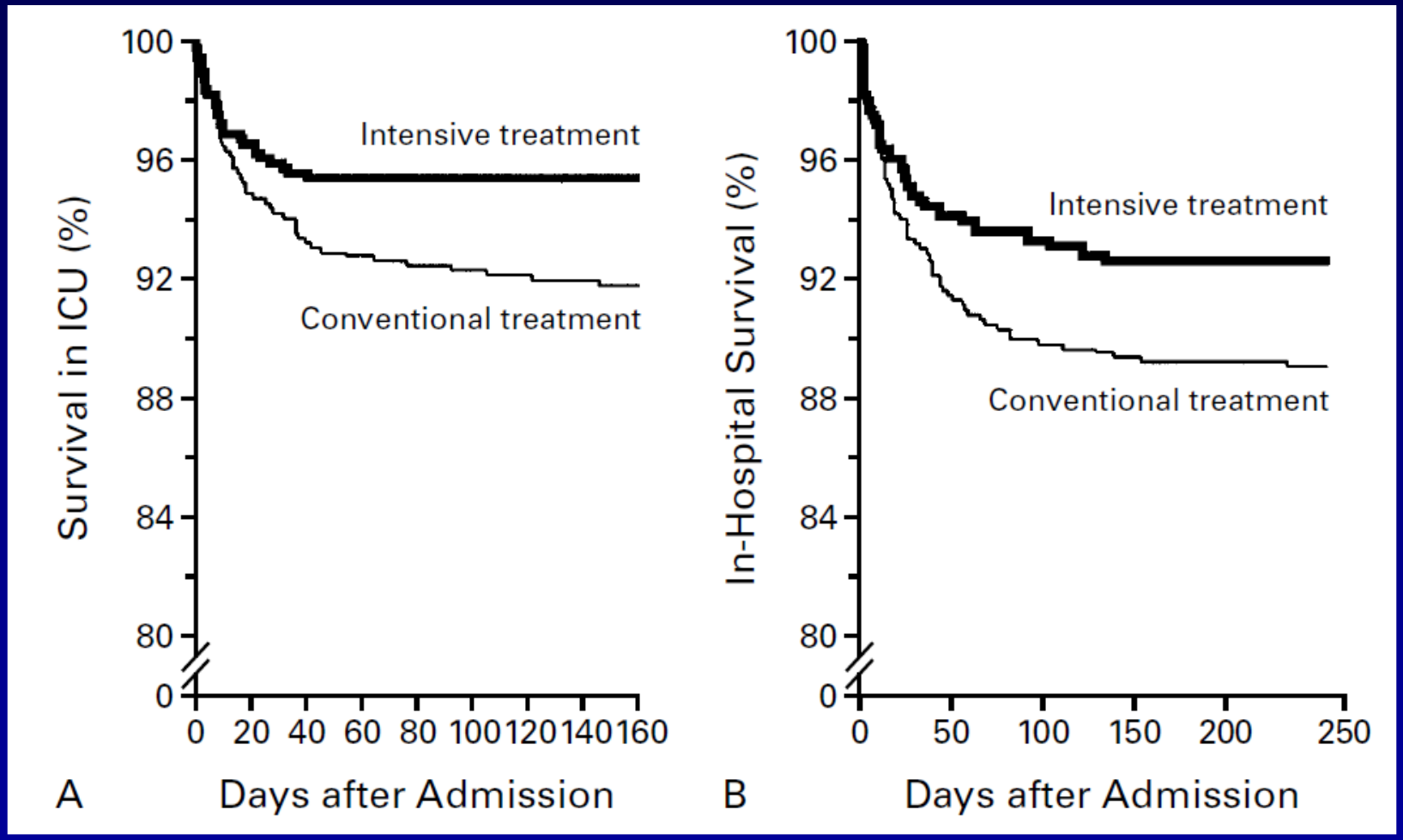
Results

Variable (%)	Control Group	Treatment Group	P value
IV insulin Rx	39	99	< 0.001
hypoglycemia *(< 40 mg/dl)*	<1 (n=6)	5 (n=39)	
In-hosp. Mort			
All patients	10.9	7.2	0.01
ICU > 5d	26.3	16.8	0.01

32% adjusted mortality reduction

Van den Berghe G, et al *NEJM* 2001; 345:1359-67

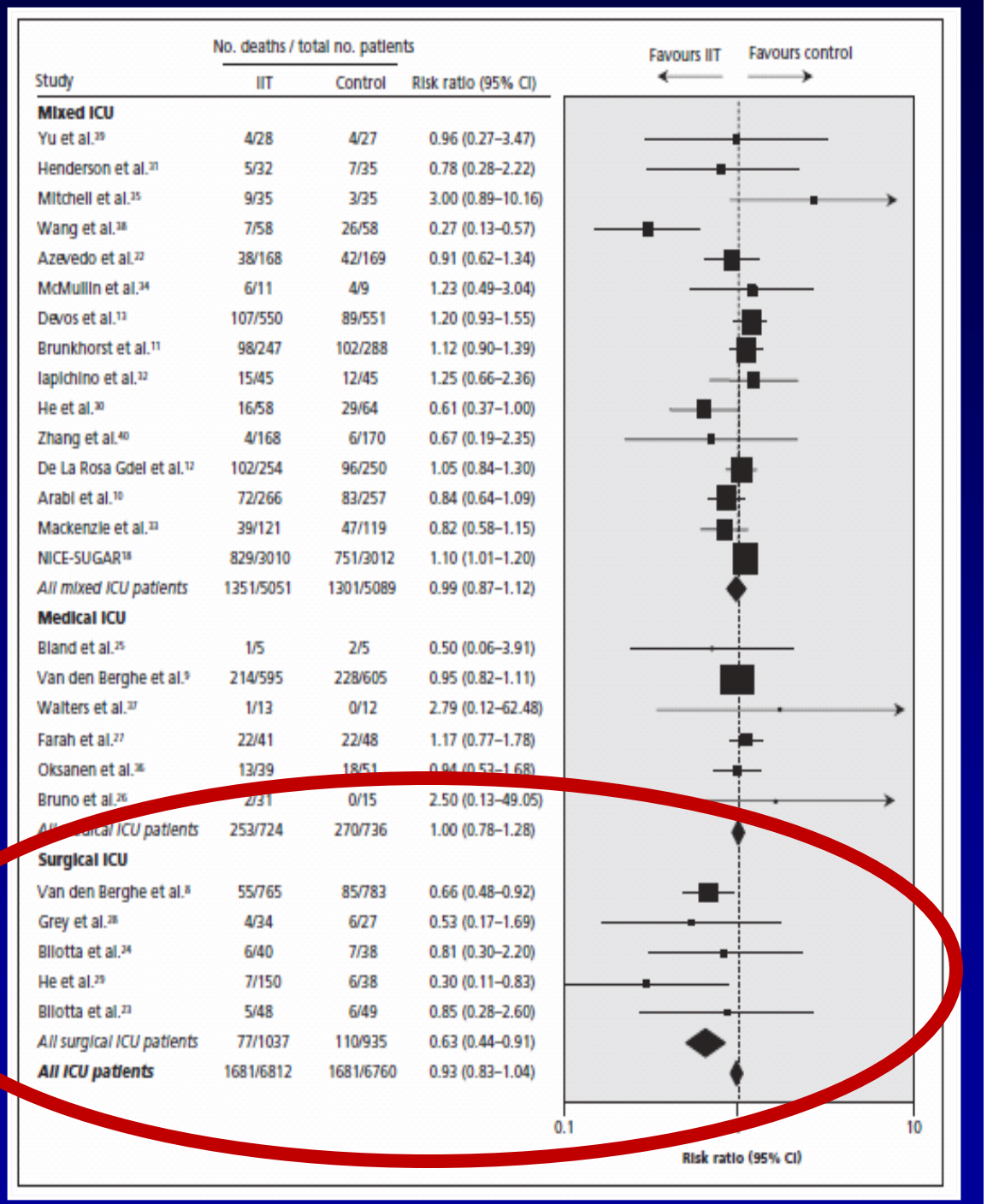
Intensive Insulin Therapy Reduces Mortality In Critically Ill Surgical Patients



Van den Berghe G *NEJM* 2001

Meta-analysis of IIT *critical illness*

- **All studies combined:**
  - **no significant benefit**
- **Surgical ICU studies:**
  - **significant benefit**



Griesdale D *CMAJ* 2009

Meta-analysis of IIT *critical illness*

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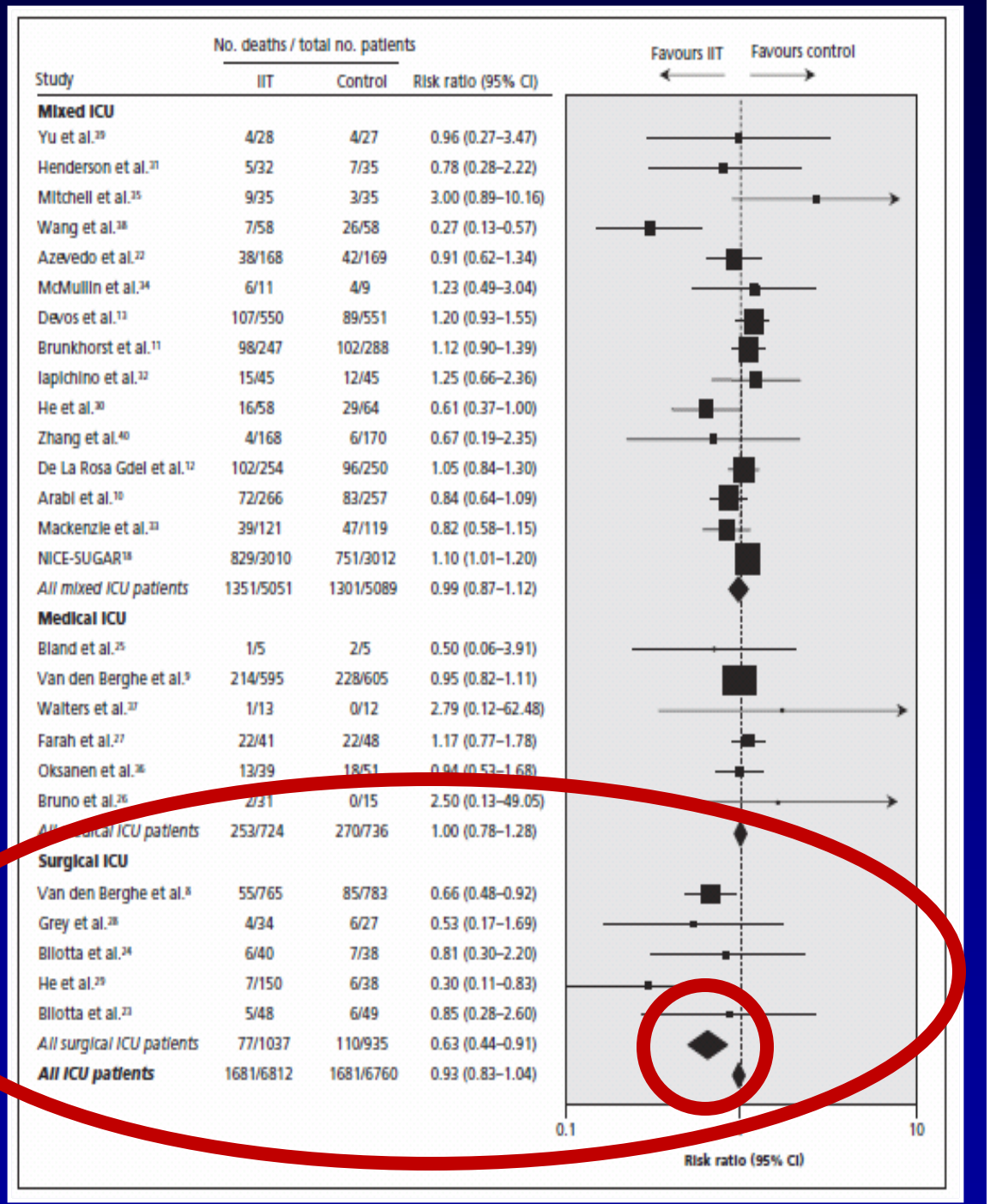
30%Risk Reduction

Griesdale D *CMAJ* 2009



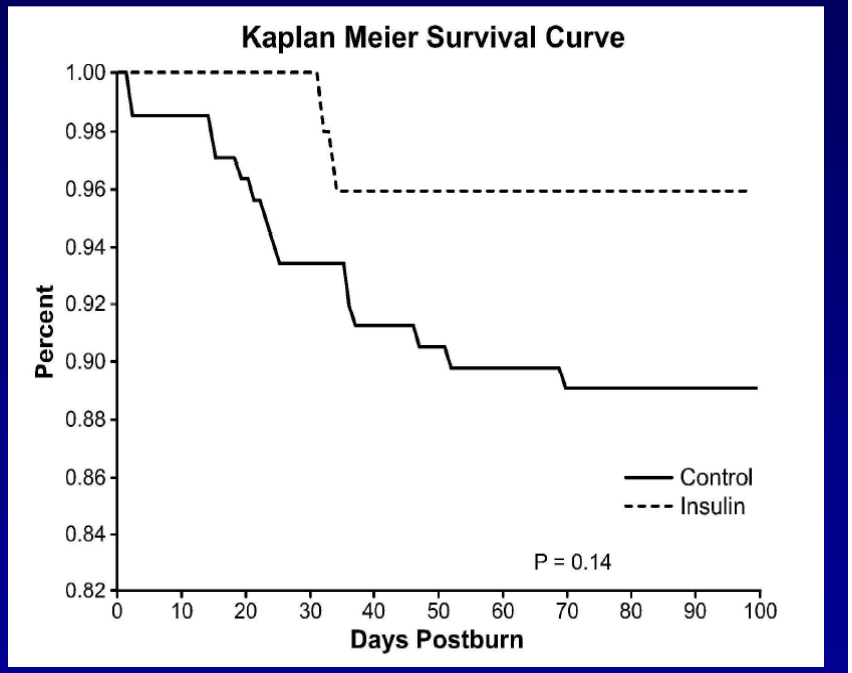
Intensive Insulin Therapy in Severely Burned Pediatric Patients

A Prospective Randomized Trial

Marc G. Jeschke[1,2], Gabriela A. Kulp[1,2,3], Robert Kraft[1,2], Celeste C. Finnerty[1,2], Ron Mlcak[1,2], Jong O. Lee[1,2], and David N. Herndon[1,2]

Summary of results - ITT vs Conventional:

- Older (10.8 vs 7.7 yrs)
- > 3rd degree (52 vs 44)
- ↓ sepsis (8.2% vs 22.6%)
- ↑ organ function (renal, hepatic)
- ↑ lean mass, body mass
- ↓ inflammatory response
- ↑ hypoglycemia (26% vs 9%< 40 mg/dl)
- Mortality 4% vs 11% (p = 0.14)



(power analysis for 50% reduction, 3:1 randomization = 570 pts)

Jeschke *AJRCCM* 2010

IIT in critically ill surgical patients

Conclusions

- Plausible physiologic rationale for its benefit
- Weight of the data supports its benefit
- Many questions remain:
  - Optimum target range
  - Influence of hypoglycemia
  - Influence of timing and type of nutrition
  - Influence of patient factors: IR, variability, diabetes

Glycemic variability and mortality in critically ill

- **Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients.**

  ***Crit Care Med*. 2008;36:3008-3013**

- **Al Dorzi HM - Glycaemic fluctuation predicts mortality in critically ill patients.**

  ***Anaesth Intensive Care*. 2010;38:695-70**

- **Mohr AM - Gender differences in glucose variability after severe trauma.**

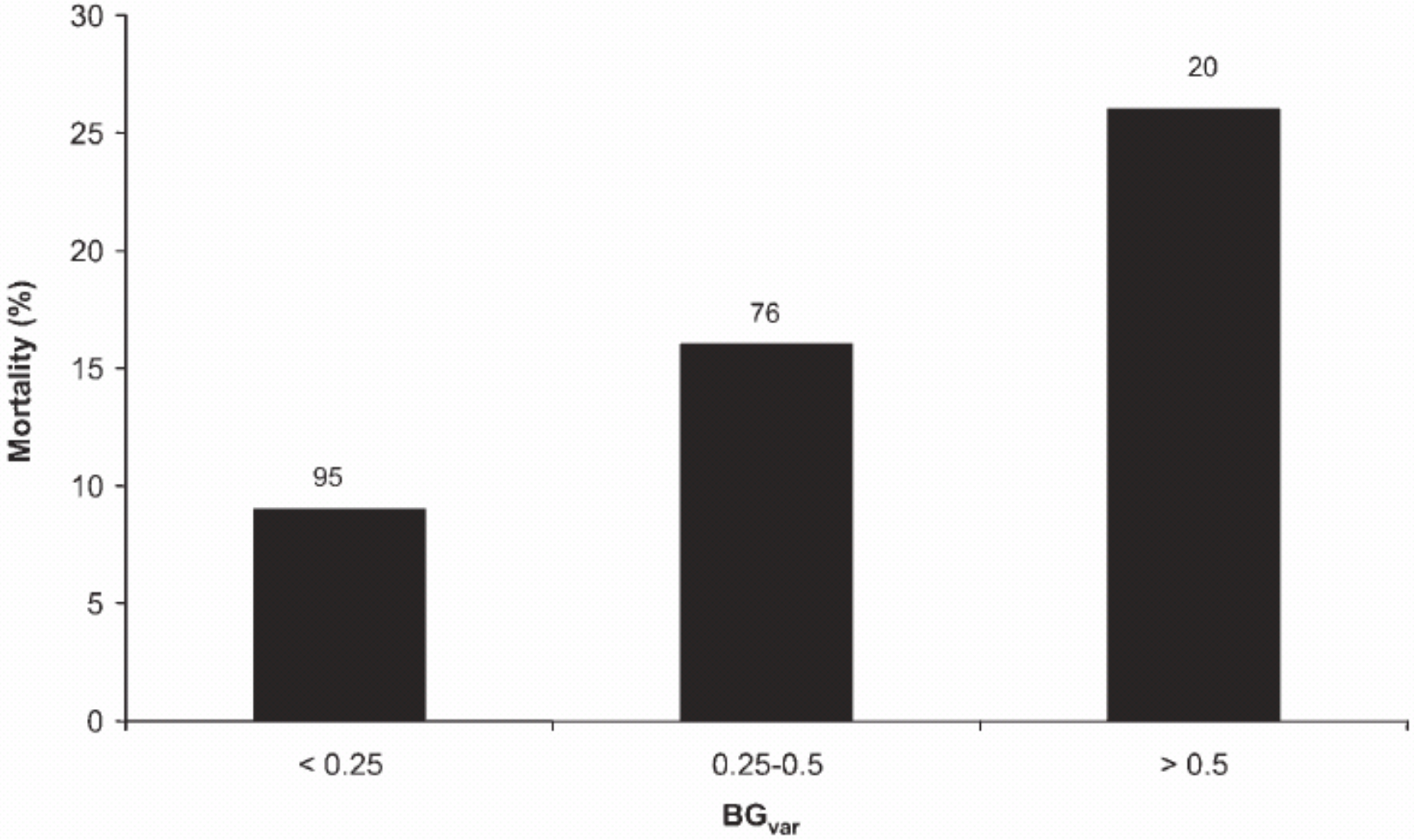
  ***Am Surg*. 2010;76:896-902**

Variables Associated with Mortality

	Odds Ratio	95% CI	*P*
Age	1.04	1.03–1.05	<0.001
Sex	0.72	0.45–1.14	0.163
Penetrating trauma	0.38	0.22–0.64	<0.001
ISS	1.03	1.01–1.05	<0.001
$Shock_{adm}$	0.75	0.51–1.11	0.151
Head AIS	1.40	1.23–1.59	<0.001
GCS_{adm}	0.90	0.86–0.94	<0.001
Pneumonia	2.07	1.37–3.13	<0.001
BG_{adm}	1.00	0.99–1.00	0.741
BG_{mean}	1.00	1.00–1.01	0.05
BG_{var}	5.33	1.83–15.5	<0.001

Mohr AM. Amer Surg. 2010; 8:896-902

Percent mortality by glycemic variability



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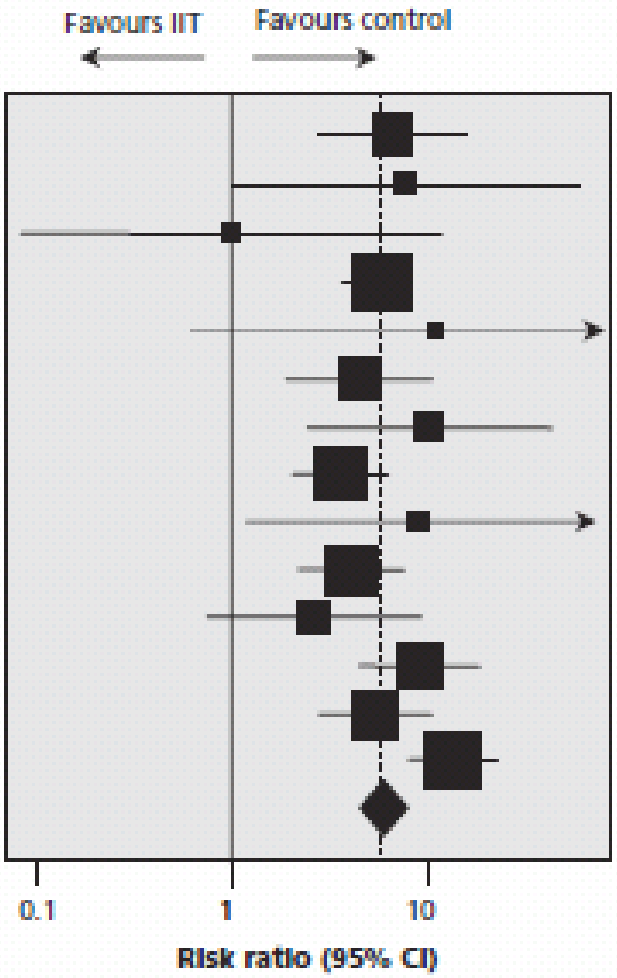
What about hypoglycemia?

Study	No. events / total no. patients: IIT	Control	Risk ratio (95% CI)
Van den Berghe et al.[8]	39/765	6/783	6.65 (2.83–15.62)
Henderson et al.[35]	7/32	1/35	7.66 (1.00–58.86)
Bland et al.[25]	1/5	1/5	1.00 (0.08–11.93)
Van den Berghe et al[9]	111/595	19/605	5.94 (3.70–9.54)
Mitchell et al.[35]	5/35	0/35	11.00 (0.63–191.69)
Azevedo et al.[23]	27/168	6/169	4.53 (1.92–10.68)
De La Rosa Gdel et al.[12]	21/254	2/250	10.33 (2.45–43.61)
Devos et al.[13]	54/550	15/551	3.61 (2.06–6.31)
Oksanen et al.[36]	7/39	1/51	9.15 (1.17–71.35)
Brunkhorst et al.[11]	42/247	12/290	4.11 (2.21–7.63)
Iapichino et al.[32]	8/45	3/45	2.67 (0.76–9.41)
Arabi et al.[10]	76/266	8/257	9.18 (4.52–18.63)
Mackenzie et al.[33]	50/121	9/119	5.46 (2.82–10.60)
NICE-SUGAR[18]	206/3016	15/3014	13.72 (8.15–23.12)
Overall	654/6138	98/6209	5.99 (4.47–8.03)



Griesdale D. *CMAJ 2009;180(8):821-827*

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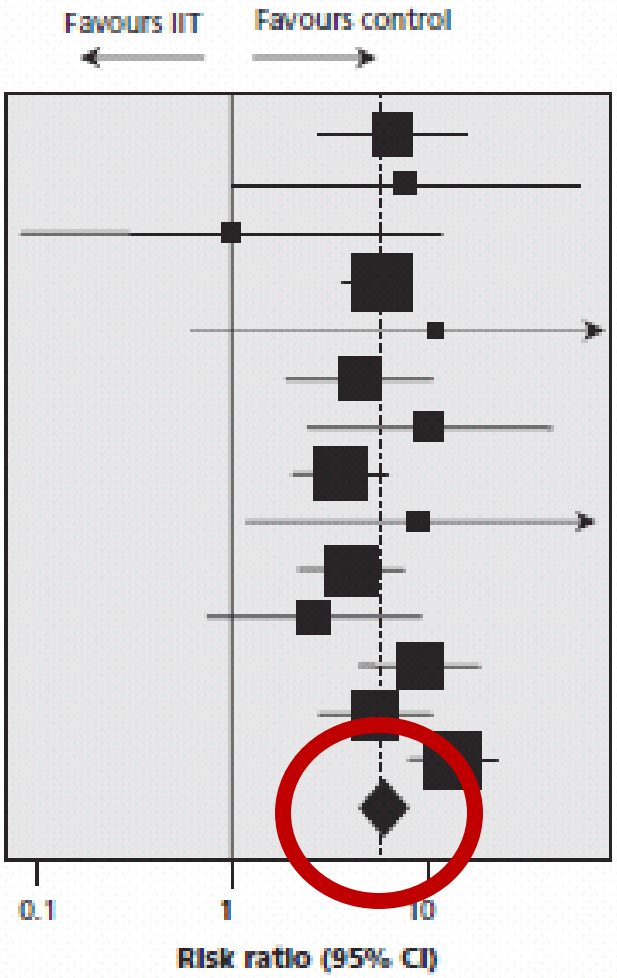


Griesdale D. *CMAJ 2009;180(8):821-827*

Hypoglycemia

Cause of mortality or Result of Illness severity

Several studies demonstrate association of hypoglycemia with death:

- **Krinsley JS - Severe hypoglycemia in critically ill patients: risk factors and outcomes**

  ***Crit Care Med*. 2007;35:2262-2267**

Some studies demonstrate hypoglycemia associated with severity of illness and not an independent predictor of death:

- **Arabi YM - Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality**

  ***Crit Care Med*. 2009;37:2536-2544**

- **Mowery NT - Severe hypoglycemia while on intensive insulin therapy is not an independent predictor of death after trauma**

  ***J Trauma*. 2010;68:342-347**

Effect of balanced nutrition on hypoglycemia

Insulin protocol:

- **Mandates D10W @ 30 ml/hr if no nutritional source**
- **Examined risk of subsequent hypoglycemia (<50 mg/dl) for 2 hour blocks increments by glucose source**

Rate of hypoglycemia:

- **Pts with TPN / enteral: 2.2/1000**
- **Pts without TPN / enteral: 5.7/1000**

Regression analysis -

- **Significant predictors of hypoglycemia:**
  - **No TPN / enteral: OR 3.6**
  - **Age > 65: OR 1.5**
- **Not significant: APACHE II, diabetes, time on protocol**

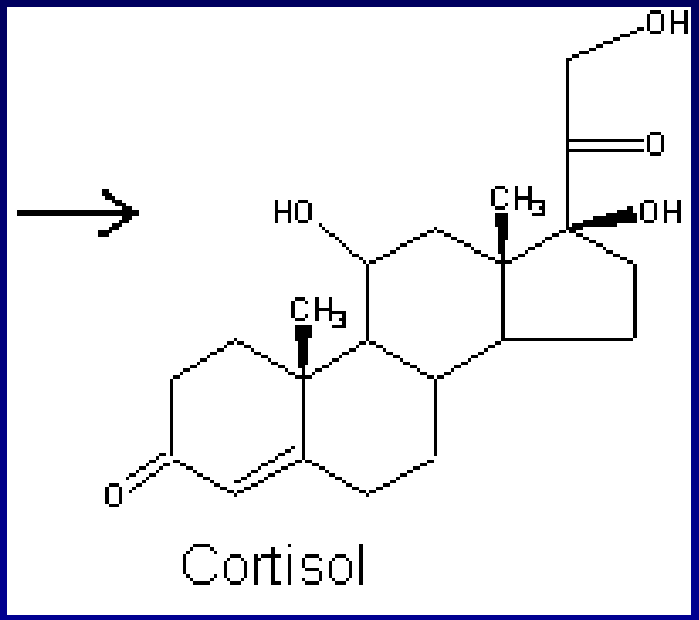
Predictors of Hypoglycemia:
regression analysis

- **Predictive**
  - **Increased BG variability**
  - **Time since last BG measurement**
  - **Weight**
  - **Age**
  - **Previous low BG (<60 mg/dL)**
  - **Provision of balanced nutrition (tube feeds, TPN)**
- **Not Predictive**
  - **APACHE II**
  - **History of diabetes**
  - **Time on protocol**
  - **Hematocrit**
  - **WBC count**
  - **Heart rate**
  - **Time off unit**
  - **Pressor use**

Only beginning to find the "truth" about glycemic control in critically ill surgical patients

- **Stress hyperglycemia is a complex topic**
- **IIT in critically ill surgical patients provides outcome benefit**
  - **Optimum target unknown**
- **Outcomes and degree of IR are related**
- **Glucose variability, hypoglycemia, and outcome are related**
- **Influence of timing and type of nutrition inadequately understood**
- **Influence of patient factors remain unclear:**
  - **IR, variability, diabetes**

Adrenal Insufficiency

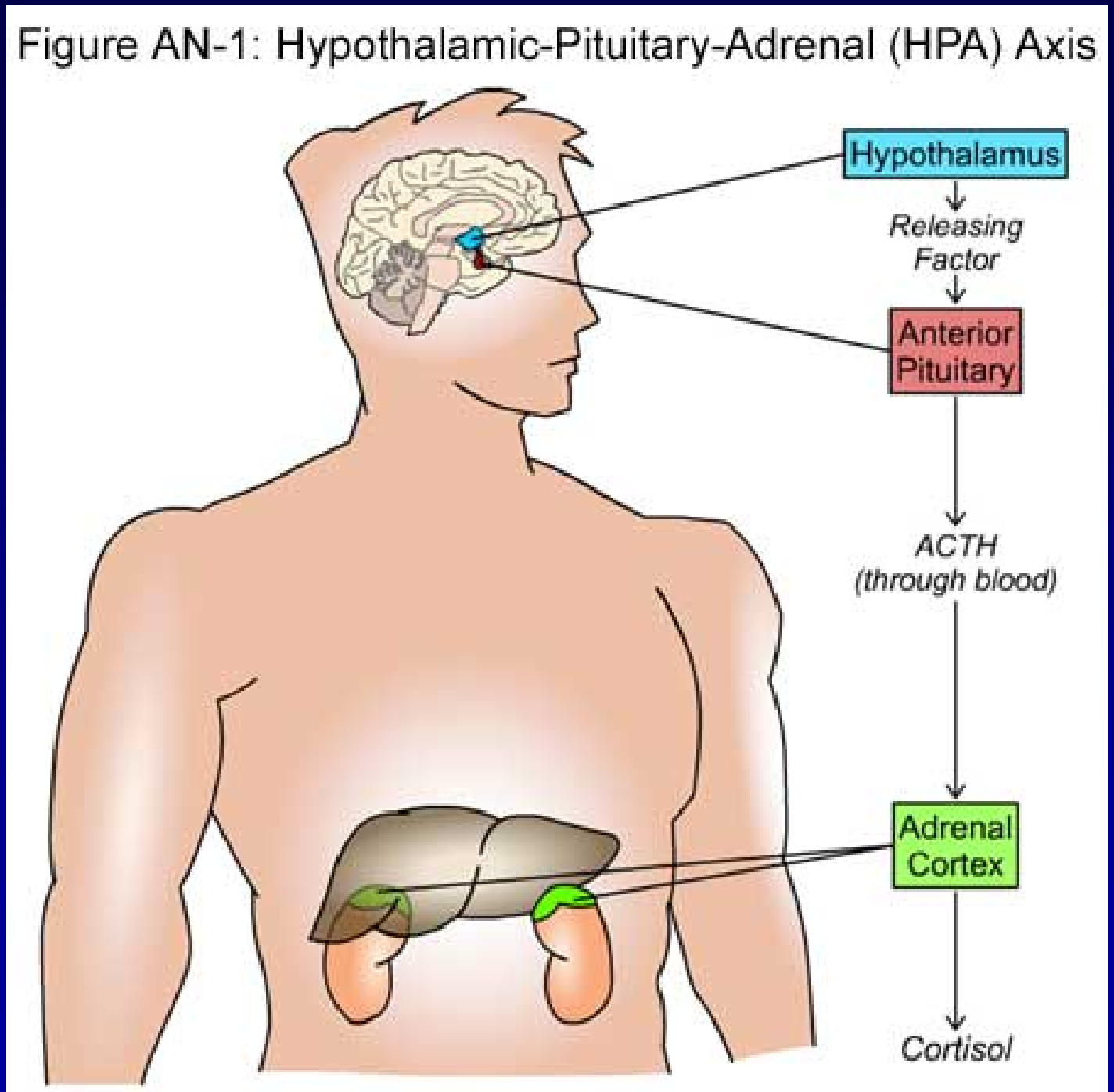


Cortisol

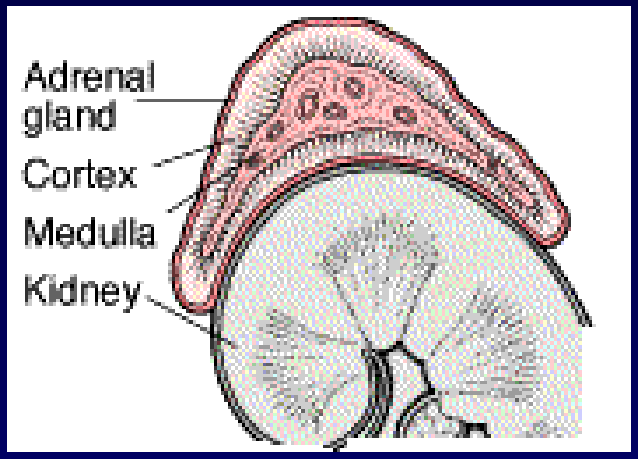
Clinical Scenario

- 32 y male, MVC, unrestrained driver
  - Positive LOC, required intubation for agitation
    - Etomidate/succinylcholine RSI at scene
  - CT: SAH, bilateral rib fractures, no solid organ
- ICU management
  - Arrive to the bedside
    - 30 mic/min levophed…

Figure AN-1: Hypothalamic-Pituitary-Adrenal (HPA) Axis



Anatomy-Output



- ADRENAL CORTEX
  - Zona glomerulosa - Aldosterone
  - Zona fasciculata
  - Zona reticularis

  Cortisol
  Androgens
  Estrogens
- ADRENAL MEDULLA- Catecholamines

Physiologic Actions

Metabolic

- ⇑ hepatic gluconeogenesis
- ⇓ adipose tissue glucose uptake
- Stimulate free FA release via lipoloysis
- Stimulate amino-acid release from protein
- Stimulate insulin release due to increased glucose production

Barseghian, *Endocrinology* 1982

Physiologic Actions

Cardiovascular

- ⇑ transcription and expression of catecholamines and catecholamine receptors
- Inhibit production of nitric oxide
- Inhibit release of histamine from mast cells

Barseghian, *Endocrinology* 1982

Physiologic Actions

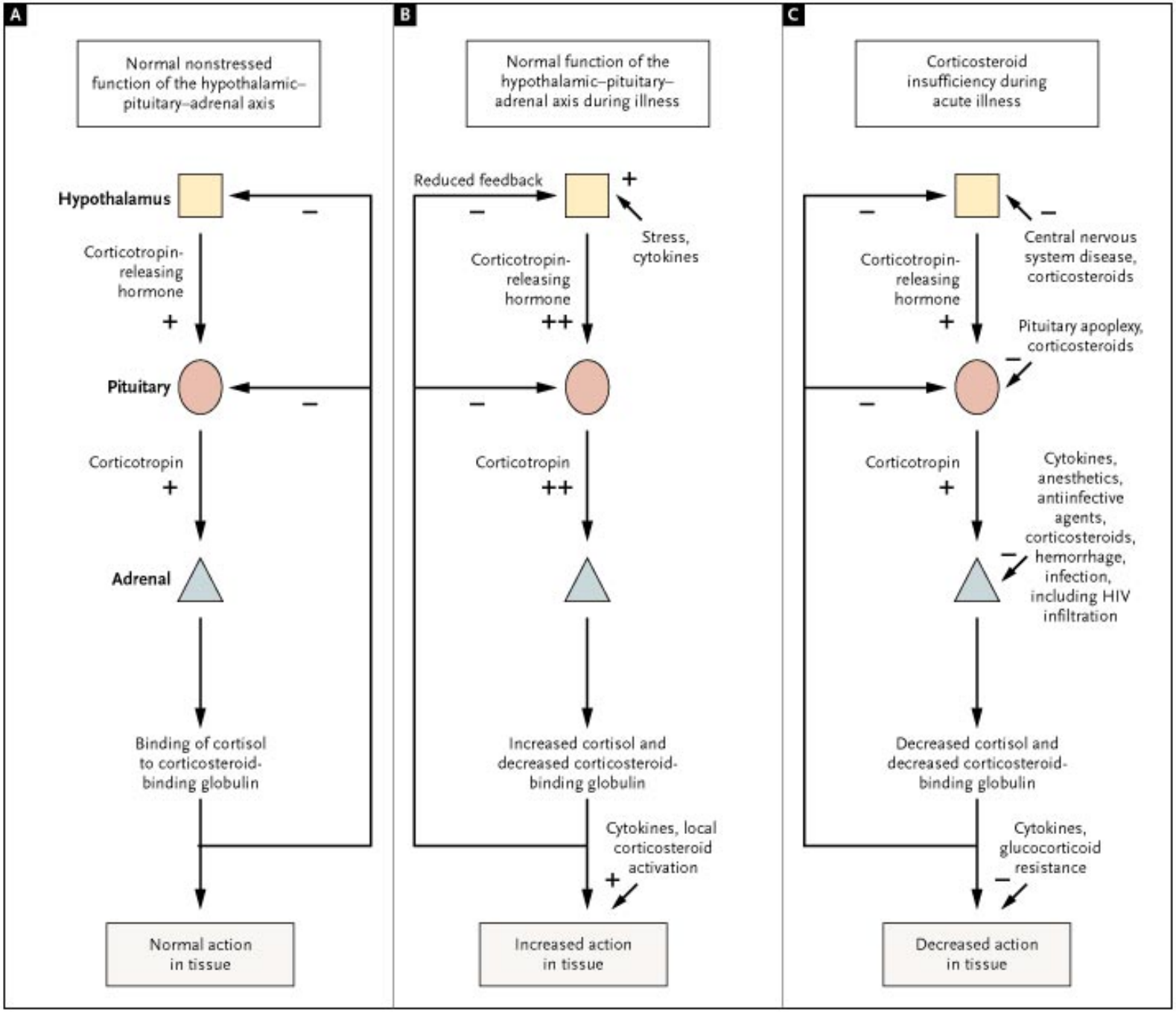
Immunologic

- Suppress cytokine production by inhibiting transcription factors
  - IL- 1, 2, 3, 6, interferon-γ, TNF-α
- Enhance release of anti-inflammatory factors
  - IL-1 receptor antagonist, soluble TNF receptor, IL-10
- Increase release of neutrophils from bone marrow, inhibits migration from blood vessels

Barseghian, *Endocrinology* 1982

Adverse Reactions

- Fluid/electrolyte disturbances
  - Na+ retention, K+ loss
  - Fluid retention
- Osteoporosis
- Protein catabolism
  - Negative Nitrogen Balance
- Gastrointestinal
  - Peptic ulcer perforation
  - Pancreatitis
- Endocrine
  - Secondary HPA-axis inhibition
  - Diabetes
- Central Nervous System
  - Delirium???
- Infection
  - Estimated risk
    - 1.5 times control


A
Normal nonstressed function of the hypothalamic–pituitary–adrenal axis
Hypothalamus
Corticotropin-releasing hormone
+
Pituitary
Corticotropin
+
Adrenal
Binding of cortisol to corticosteroid-binding globulin
Normal action in tissue
B
Normal function of the hypothalamic–pituitary–adrenal axis during illness
Reduced feedback
Stress, cytokines
Corticotropin-releasing hormone
++
Corticotropin
++
Increased cortisol and decreased corticosteroid-binding globulin
Cytokines, local corticosteroid activation
+
Increased action in tissue
C
Corticosteroid insufficiency during acute illness
Central nervous system disease, corticosteroids
Corticotropin-releasing hormone
+
Pituitary apoplexy, corticosteroids
Corticotropin
+
Cytokines, anesthetics, antiinfective agents, corticosteroids, hemorrhage, infection, including HIV infiltration
Decreased cortisol and decreased corticosteroid-binding globulin
Cytokines, glucocorticoid resistance
Decreased action in tissue

SYNDROMES

Acute Insufficiency

- Severe/Acute illness
  - Intrinsic adrenal disease
  - Inadequate adrenal reserve
  - HIV, TB, primary autoimmune adrenalitis, chronic steroid administration
  - HIV
    - # 1 primary adrenal insufficiency
    - Opportunistic infection/HIV virus

SYNDROMES

Acute Insufficiency

- A-Severe/Acute illness
  - Steroid administration
    - #1 secondary adrenal insufficiency
    - Recovery may take 9-12 months
    - 10 days
    - 5mg prednisone
    - Inhaled glucocorticoids
      - Azmacort
      - Beclovent
      - Flovent
      - Vanceril
- B-Adrenal hemorrhage
  - Rogoff's sign
  - Blunt trauma
  - Coagulopathy
  - Pregnancy

SYNDROMES

Sub-acute Insufficiency

- Normal baseline function
- Common in septic ICU patients ?*
- Think adrenal insufficiency:
  - Volume-unresponsive/pressor-dependent
  - Unable to wean off low-dose pressors
  - Ventilator unresponsive

”High incidence of adrenocortical insufficiency in patients with the Multiorgan Dysfunction Syndrome”.
Polderman. University Hospital Vrije Universiteit.

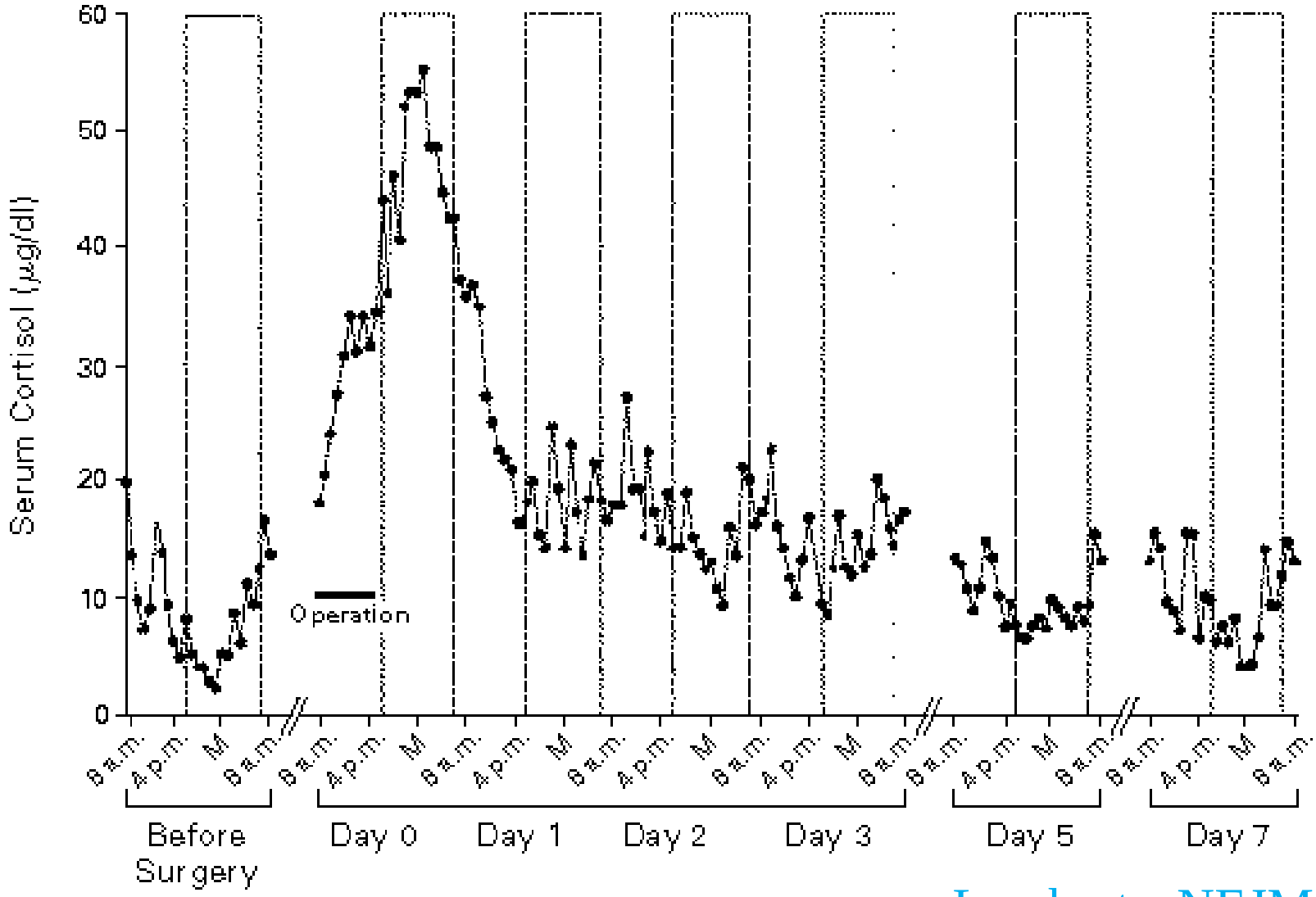
Adrenergic Pathology

	Plasma Cortisol	Plasma ACTH
Primary Hypercortisolism	↑	↓
Secondary Hypercortisolism (pituitary, Cushing's disease)	↑	↓
Primary Hypocortisolism (Addison's disease)	↓	↑
Secondary Hypocortisolism (pituitary)	↓	↑

SIGNS/SYMPTOMS

- Shock
  - Hypovolemic
  - Hyperdynamic
- ⇓ Na
- ⇑ K
- Metabolic acidosis
- Hypoglycemia
- Eosinophilia

Cortisol with Stress



Lamberts, NEJM 1997

All-Cause Mortality at 28 Days

Short Course, High Dose	
	Intervention
Klastersky 1971	B-meth 1mg/kg/day x 2doses for 3d; Placebo
Schumer 1976	Dex 3mg/kg; M-pred 30mg/kg; Placebo – repeat x1 in 4hrs
Lucas 1984	Dex 2mg/kg, 2mg/kg/24h x 2d
Sprung 1984	Dex 6mg/kg; M-pred 30mg/kg; Placebo – repeat x1 in 4hrs
Bone 1987	M-pred 30mg/kg; Placebo
VASSCSG 1987	M-pred 30mg/kg, 5mg/kg/hr x 9hrs
Luce 1988	M-pred 30mg/kg q6h x 24hrs; Placebo
Slusher 1996	Dex 0.2 mg/kg q8h x 2d; Placebo

Annane, D. et al. BMJ 2004;329:480

All-Cause Mortality at 28 Days

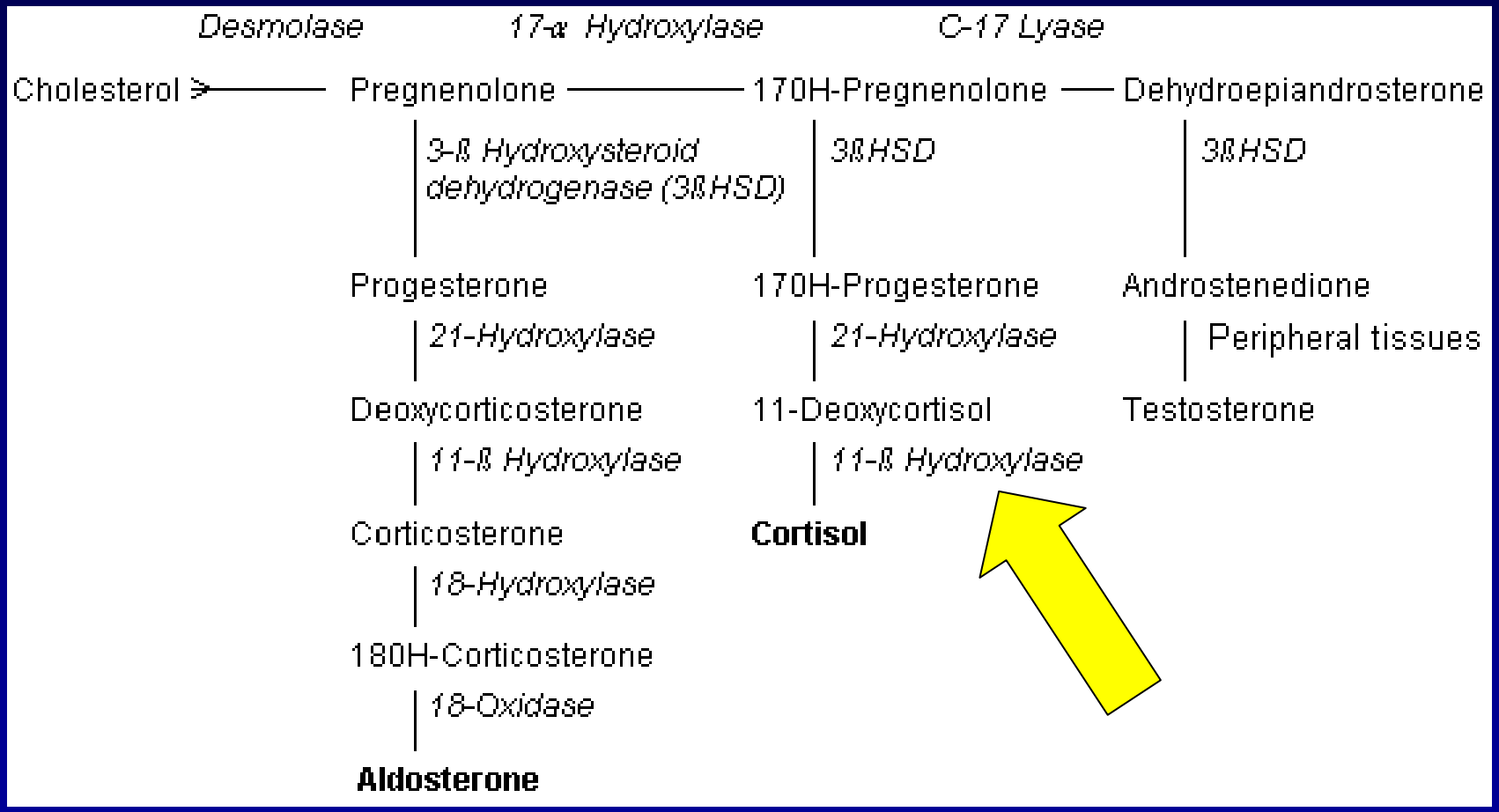
Short Course, High Dose				
	Treatment	Control	Weight	RR (Fixed) 95% CI
Klastersky 1971	22/46	18/39	11.47%	1.04 (0.66 to 1.63)
Schumer 1976	9/86	33/86	19.43%	0.27 (0.27 to 0.53)
Lucas 1984	5/23	5/25	2.82%	1.09 (0.36 to 3.27)
Sprung 1984	33/43	11/16	9.44%	1.12 (0.77 to 1.61)
Bone 1987	65/191	48/190	28.34%	1.35 (0.98 to 1.84)
VASSCSG 1987	23/112	24/111	14.20%	0.95 (0.57 to 1.58)
Luce 1988	22/38	20/37	11.94%	1.07 (0.72 to 1.60)
Slusher 1996	6/36	4/36	2.36%	1.50 (0.46 to 4.87)
Total	**575**	**540**	**100%**	**0.99 (0.83 to 1.17)**

Annane, D. et al. BMJ 2004;329:480

Adrenal Insufficiency in Septic Shock

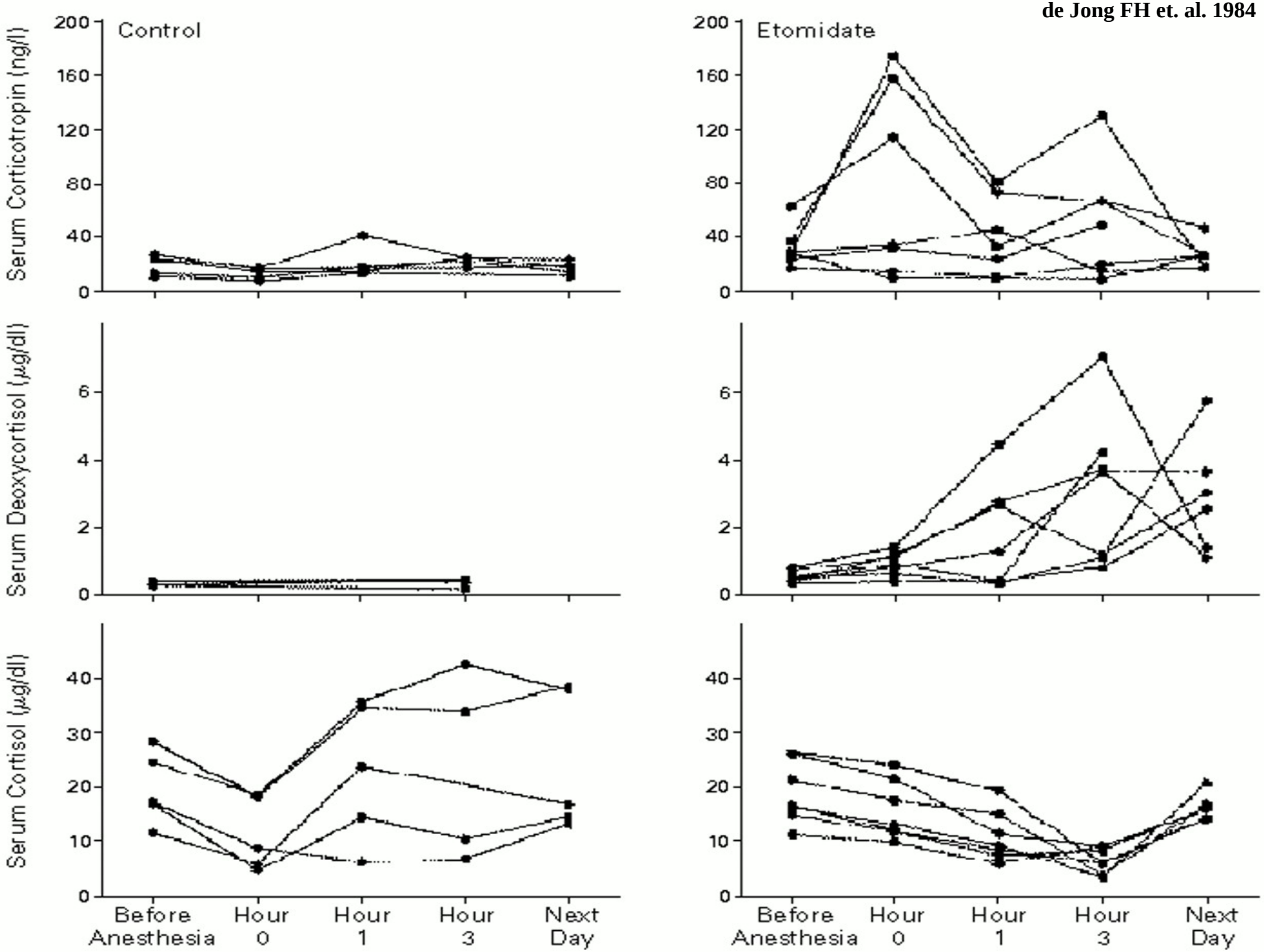
- Turney 1987
  - Pts w/cortisol levels (> 60 µg/dl) had ⇑ mortality, compared to pts who stimulated > 18 µg/dl after ACTH injection had improved outcomes
- Rothwell 1991
  - 32 pts with septic shock
    - 13 exhibited cortisol response (≤9 µg/dl,) all of whom died
- Moran 1995
  - Regression analysis predicted ⇑ mortality by ⇑ cortisol and onset of shock
- Soni 1995
  - Mortality in pts w/Al was 80% at 4 weeks as compared to 43.8% in pts with normal adrenal response.

Etomidate is the Devil



de Jong FH et. al. 1984

de Jong FH et. al. 1984



Cortisol Response to Corticotropin in Septic Shock

- 189 consecutive patients with septic shock
- Intervention:
  - 0.25mg tetracosactrin
  - Cortisol samples taken at T_0, T_{30}, and T_{60}
- Outcome Measures:
  - 28-day mortality as a function of variables collected at onset of septic shock

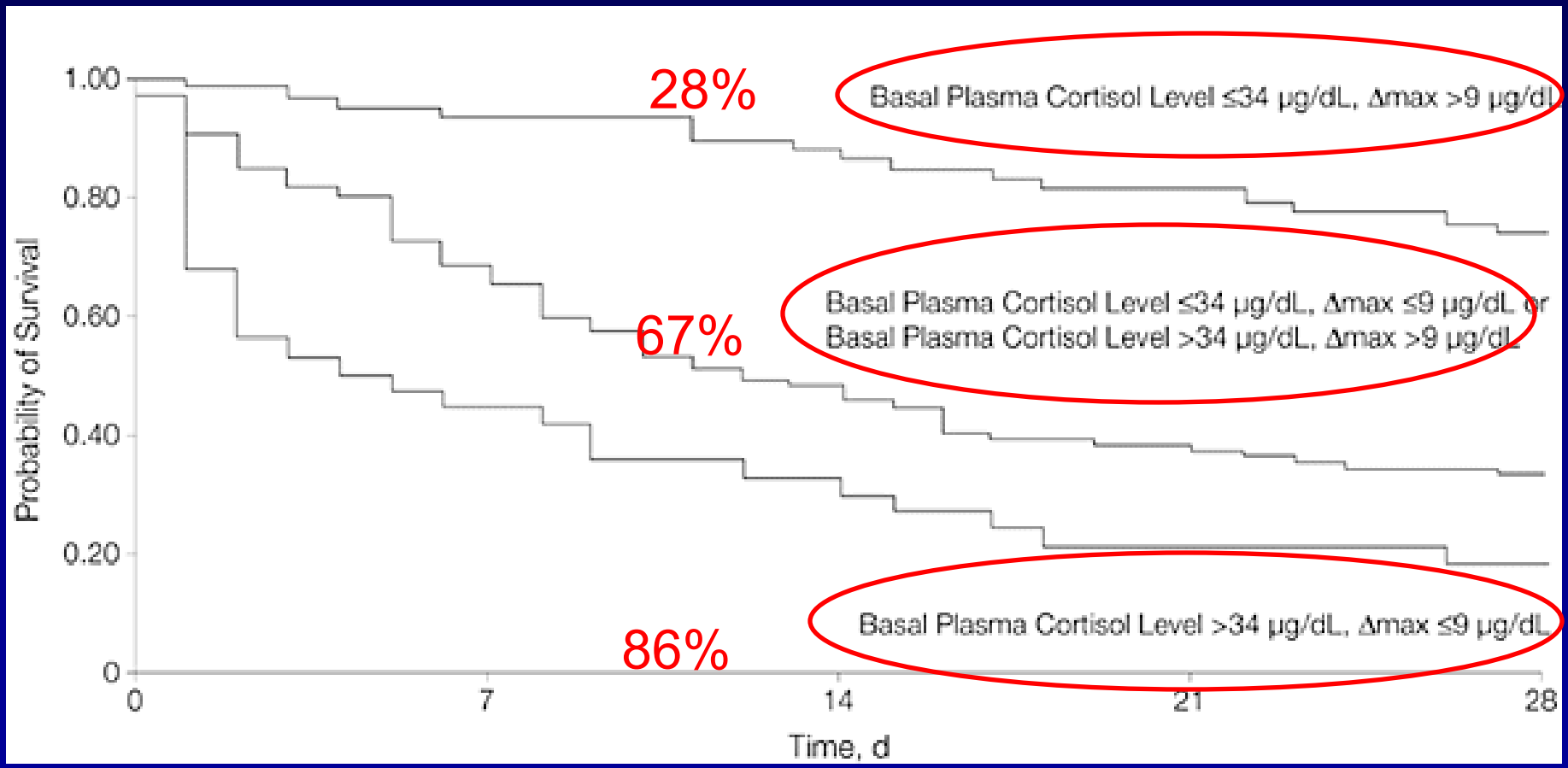
Annane *JAMA* 2000.

Cortisol Response to Corticotropin in Septic Shock

- Mortality Outcomes
  - 109 (58%) died within 28 days
  - Median time to death was 17 days
- Median Cortisol at T_0
  - All patients – 34 μg/dl
  - Survivors – 28 μg/dl
  - Non-survivors – 39 μg/dl

Annane *JAMA* 2000.

Cortisol Response to Corticotropin in Septic Shock



Annane, *JAMA* 2000

Cortisol Response to Corticotropin in Septic Shock

- Median Time to Death
  - Baseline Cortisol >34 μg/dl
    - 6 days (95% CI 4-12 days)
  - Cortisol ΔMax ≤9 μg/dl
    - 11 days (95% CI 8-15 days)
  - Baseline Cortisol >34 AND ΔMax ≤9
    - 5 days (95% CI 2-12 days)

Annane *JAMA* 2000

All-Cause Mortality at 28 Days

Long Course, Low Dose	
	Intervention
Bollaert 1998	HC 100mg q8h x5d, taper over 6d
Briegel 1999	HC 100mg, 0.18mg/kg/hr, ⇓ 0.08mg/kg/hr x6d at shock resolution. Tapered by 24mg/day by infection resolution or when sodium >155mmol/L
Chawla 1999	HC 100mg q8h x72h, taper over 4d
Yildiz 2002	Pred 5mg at 0600, 2.5mg at 1800 x10d
Annane 2002	HC 50mg q6h + fludrocortisone 50µg tab qd x 7d

Annane *BMJ* 2004

All-Cause Mortality at 28 Days

Long Course, Low Dose				
	Treatment	Control	Weight	RR (Fixed) 95% CI
Bollaert 1998	7/22 (32%)	12/19 (63%)	9.84%	0.50 (0.25 to 1.02)
Briegel 1999	3/20 (15%)	4/20 (20%)	3.05%	0.75 (0.19 to 2.93)
Chawla 1999	6/23 (26%)	10/21 (48%)	7.98%	0.55 (0.24 to 1.25)
Yildiz 2002	8/20 (40%)	12/20 (60%)	9.16%	0.67 (0.35 to 1.27)
Annane 2002	82/151 (54%)	91/149 (61%)	69.96%	0.89 (0.73 to 1.08)
Total	**236**	**229**	**100%**	**0.80 (0.67 to 0.95)**

Annane *BMJ* 2004

Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

- 300 pts with septic shock
- Intervention:
  - All pts underwent cort-stim
  - Randomized to HC 50mg q6h + fludrocortisone 50µg tab qd x 7d or placebo
- Primary Endpoint:
  - 28-day survival distribution in pts w/relative adrenal insufficiency (non-responders) compared to responders

Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

- Outcomes:
  - 229 non-responders
  - 70 responders

28-day Mortality			
	Placebo	Corticosteroid	
Responders	53%	61%	P = .96
Non-responders	63%	53%	P = .04
All	61%	55%	P = .09

Low Dose Hydrocortisone and Fludrocortisone & Mortality in Septic Shock

- Outcomes:
  - 229 non-responders
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28-day Mortality			
	Placebo	Corticosteroid	
Responders	53%	61%	P = .96
Non-responders	**63%**	**53%**	**P = .04**
All	61%	55%	P = .09

Serum Free Cortisol

- Corticosteroid Levels in Serious Illness
  - Low Albumin — Grp 1: 36
  - Normal Albumin — Grp 2: 30
  - Healthy Volunteers — Grp 3: 33
- Apache III scores > 15
- Stim Test 2p – 6p
  - Serum Total Cortisol
  - Aldosterone
  - Free Cortisol Levels

Hamrahian, JAMA 2004

Serum Free Cortisol

Table 1. Characteristics of Critically Ill Patients and Healthy Volunteers.*

Characteristic	Group 1 (N=36)	Group 2 (N=30)	Healthy Volunteers (N=33)
Age (yr)	65.2±14.2†	66.9±10.9†	54.6±16.6
Plasma corticotropin (ng/liter)‡	38.7±12.9§	37.8±18.8§	24.9±9.8
Corticosteroid-binding globulin (mg/liter)	17.7±5.9§¶	21.4±6.8§	26.0±3.8
Serum albumin (g/dl)	1.9±0.3§‖	3.1±0.4§	3.9±0.3
Total serum protein (g/dl)	4.7±0.8§**	6.0±1.0§	6.8±0.3
Duration of hospitalization before testing (days)	21.2±16.2**	6.4±5.6	NA
Severity-of-illness score	41.6±15.8	40.6±21.4	NA
No. died/no. survived	12/24	7/23	NA
Mean blood pressure (mm Hg)	78±9	81±11	82±5

Serum Free Cortisol

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

cosyntropin-stimulated serum total cortisol and free cortisol concentrations are higher in critically ill patients than in healthy volunteers

Serum Free Cortisol

- Conclusions:
  - base-line serum free cortisol 2.0 µg/dL
    - Low end level in healthy volunteers
    - *threshold* patients at risk for AI during critical illness
  - Free cortisol not correlated with mortality, yet
  - Glucocorticoid-resistance may be present
    - Therefore higher values still shows signs of AI

JAMA 2004

Adrenal Function

- Annane
  - 477 pts
  - ACTH stim test on day diagnoses septic
  - Non-survivors higher baseline cortisol
    - 29.5 33.5 vs. 24.3 16.5 g/dL p=0.03
  - Similar peak levels
    - 37.6± 40.2 vs. 35.2 ± 22.9 g/dL, p=0.42

CCM 2007

Adrenal Function

- Baseline cortisol <15 g/dL or a max <9 g/dL
  - likelihood ratio of dying of 1.26
    - (95% confidence interval, 1.11–1.44)
  - longer duration of shock
  - a shorter survival time
- Max <9 g/dL with *any* baseline cortisol value
  - likelihood ratio of dying of 1.38
    - (95% confidence interval, 1.18 –1.61).

CCM 2007

Odds of Poor Outcome, Controlling for Confounders

Logistic Regression

Table 4. Odds of Poor Outcome, Controlling for Confounders, by Logistic Regression

	OR (95% CI)				
Variable	**Pneumonia**	**BSI**	**UTI**	**Other Infection**	**Mortality**
Steroid use	2.64 (1.21-5.76)*	3.25 (1.26-8.38)*	2.32 (0.95-5.68)	2.58 (0.87-7.67)†	1.89 (0.82-4.40)
APACHE II score	1.07 (1.00-1.13)*	1.04 (0.97-1.11)	1.04 (0.97-1.11)	1.03 (0.95-1.11)	1.16 (1.08-1.25)*
Age	1.00 (0.98-1.03)	1.00 (0.98-1.04)	0.99 (0.97-1.02)	0.98 (0.95-1.00)	1.04 (1.01-1.07)*
Pulmonary disease	4.16 (1.00-17.26)*	2.64 (0.56-12.41)	0.76 (0.09-6.62)	1.34 (0.15-12.32)	0.24 (0.02-2.93)
Diabetes	2.02 (0.55-7.47)	1.10 (0.25-4.82)	0	0	0.20 (0.02-1.90)
Hypertension	0.71 (0.23-2.16)	0.75 (0.22-2.55)	1.51 (0.43-5.22)	0	0.83 (0.25-2.74)
Other medical conditions	1.13 (0.41-3.08)	2.40 (0.82-7.08)	0.81 (0.23-7.81)	0	0.33 (0.10-1.11)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BSI, bloodstream infection; CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

*$P<.05$.

†$P<.10$.

Britt, *Arch Surg* 2006

Chance of Longer LOS, Controlling for Confounders

Slope of Regression Line

Table 5. Chance of Longer LOS, Controlling for Confounders, Expressed as Slope of Regression Line

Variable	ICU LOS	Ventilator LOS
Steroid use	7.35*	5.05*
APACHE II score	0.29†	0.32‡
Age	0.04	0.06
Pulmonary disease	2.06	−0.49
Diabetes	−6.49	−4.98†*
Hypertension	3.64	−0.92
Other Infection	3.41	−1.41

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; LOS, length of stay.

*$P<.05$.

†$P<.10$.

‡$P<.01$.

Britt, *Arch Surg* 2006

Chance of Longer LOS, Controlling for Confounders

Slope of Regression Line

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Age	0.04	0.06
Pulmonary disease	2.06	−0.49
Diabetes		−4.98†*
Hypertension		−0.92
Other Infection		−1.41

Steroid Use
ICU LOS: 7.35
Vent LOS: 5.05

Abbreviations: A ronic Health Evaluation II; ICU, intensive care unit; LOS, length of stay.
*$P<.05$.
†$P<.10$.
‡$P<.01$.

Britt, *Arch Surg* 2006

Current Opinion

Corticus

- 'Hydrocortisone Therapy for Patients with Septic Shock'
  - Multicenter, randomized, double-blind, placebo-controlled
  - 499 pts
  - 251: 50mg Hydrocortisone every 6 hrs for 5 days
  - 248: placebo
- Primary Outcome:
  - Death *in those that had no response to corticotropin test*

NEJM 2008

Current Opinion

- Results:
  - 233 Pts without response
    - 125 Hydrocortisone group
    - 81 placebo
  - 28 day mortality- no difference
  - Overall mortality-NO DIFFERENCE
    - 86/251 (34.3%) Hydrocortisone group
    - 78/248 (31.5%) Placebo group

NEJM 2008

Current Opinion

- Interesting Findings:
  - 12% dopamine use
  - 10% epinephrine use
  - 8% activated protein c
- Responders: decrease time to reversal of shock
- SOFA score 10.6 ± 3.2
  - Mortality rate of 10%
- Increased risk of ‘super infections’
  - OR 1.37 (95% CI, 1.05-1.97)
- Increased Hyperglycemia
  - OR 1.18 (95% CI, 1.07-1.31)

NEJM 2008

Current Opinion

- Limitations
  - Underpowered (needed 800)
  - 52 European Centers
  - Etomidate in 26% of patients-with unresponsiveness
- Clinical Significance
  - Super infection 33 v 26 pts
  - Hyperglycemia >150 at any point in first seven days
    - 85 v 72 pts

NEJM 2008

Critical Illness-related Corticosteroid Insufficiency

"CIRCI"

- Inadequate corticosteroid activity for the level of severity of illness
  - 20-60% adrenal insufficiency in critical illness
  - Due to corticosteroid tissue resistance AND low levels of free cortisol

Marik, *CHEST*, 2009

CIRCI

Clinical Manifestations

- Predicated on exaggerated pro-inflammatory immune response
  - Hypotension refractory to fluids
  - Requirement of pressors
  - Hyperdynamic profile (*Sepsis-like*)

or

- Progressive ARDS with supportive care

Marik, *CHEST*, 2009

CIRCI

Treatment

- Steroid replacement therapy
  - NO ACTH stimulation test necessary
  - 50 mg every 6 hrs at least 7 days
    - May be up to 14 days
  - Taper when OFF pressors/ventilator
- Surveillance
  - Infection
  - Hyperglycemia

Marik, *CHEST*, 2009

What does it all mean?

- Adrenal insufficiency not present
  - Steroids are not beneficial
- Adrenal Insufficiency present
  - Chose the correct group to study/treat:
    - Low cortisol value
    - Low stim value
    - Pressors/Ventilator dependant
  - If steroids work, beneficial
  - If steroids don’t work, not beneficial

Glycemic Control
Adrenal Insufficiency

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