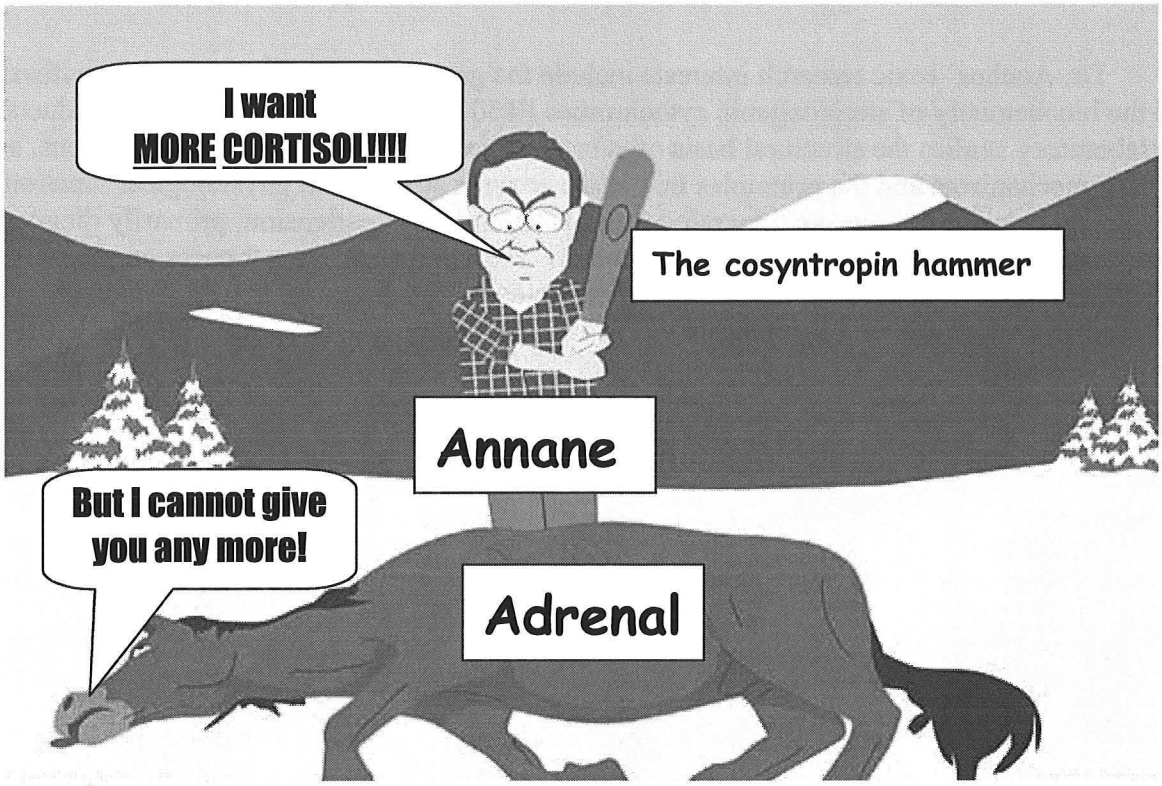
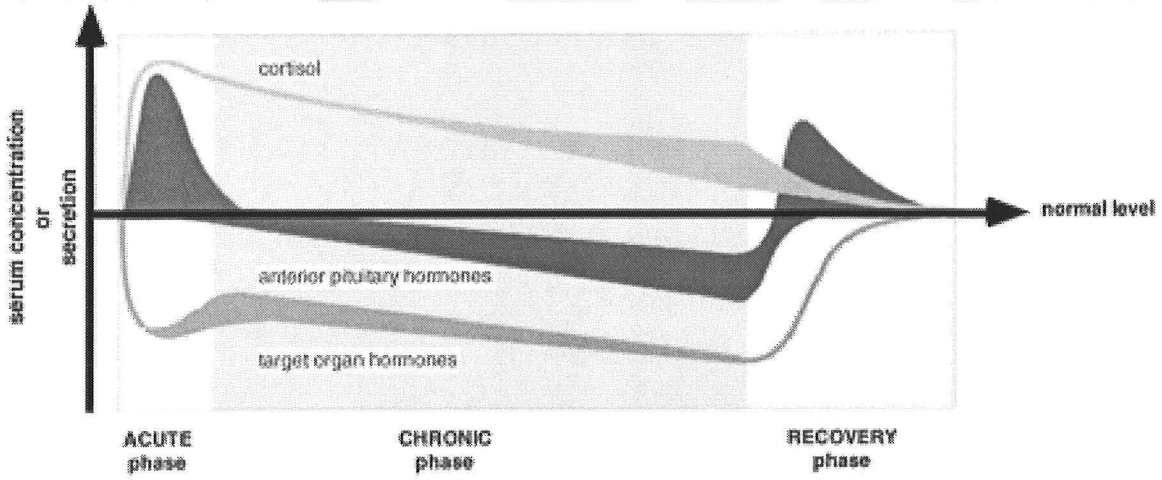
Adrenal Function in Critical Illness





Richard J. Auchus, MD, PhD
Associate Professor of Endocrinology & Metabolism

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This is to acknowledge that Richard J. Auchus, MD, PhD, has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Auchus will not be discussing off-label uses in his presentation.

Dr. Auchus' basic research interests include the genetics of human steroid biosynthesis and the biochemistry of steroidogenic cytochromes P450 and steroid dehydrogenases/reductases. His laboratory studies the structural basis of substrate discrimination, product distributions, and reaction mechanisms and the principles that relate enzyme structure to physiological function. His clinical research focuses on mineralocorticoid-dependent hypertension, primarily diagnostic strategies and genetic mechanisms of hypertension. His clinical practice focuses on pituitary, adrenal, and gonadal disorders, endocrine hypertension, adrenal tumors, and adult patients with genetic disorders of steroid biosynthesis.

Prelude

The purpose of the adrenal glands is primarily to participate in the regulation both of carbohydrate metabolism and blood pressure, the latter through the modulation of salt and water balance as well as vascular tone. Consequently, the adrenal glands are central to the body's response to acute and critical illness. The proper function of the adrenal gland is necessary to maintain blood pressure in the face of cardiac failure, hemorrhage, or sepsis.

History

Thomas Addison first associated destruction of the adrenal glands with mortality based on autopsy studies of patients who most likely had tuberculous adrenalitis (1). His suggestion was confirmed a year later by Brown-Sequard, who found adrenalectomy to be uniformly fatal for laboratory animals (2). Trousseau recognized adrenal failure clinically and later named the disease after Addison. The search then began to find the chemical produced by the adrenals, which was necessary for survival during stress. Epinephrine was the first adrenal hormone isolated by Biedel in 1912, but epinephrine did not prevent death in adrenalectomized animals (3). Henry Kendall isolated cortisone (4), and a partial synthesis from deoxycholic acid was devised by Sarett (5). George Thorn and Peter Forsham treated adrenal insufficiency with cortisone in the late 1940s (6) and showed conclusively that the glucocorticoid cortisol was the main hormone produced by the adrenal, which promoted survival during stress.

Adrenal Physiology

The adrenal gland produces a plethora of compounds, but each of its four zones is designed to primarily complete the synthesis of a single hormone (Figure 1). The outer portion, the steroid-producing cortex, is divided into three zones. The outermost zona glomerulosa is a thin layer of cells that produces aldosterone in response to primarily angiotensin II, serving as the final component of the renin-angiotensin-aldosterone system (RAAS). Volume depletion and reduced renal blood flow are the primary stimuli for renin production, and hyperkalemia also directly increases aldosterone synthesis. The middle zone, the zona fasciculata, synthesizes cortisol in response to adrenocorticotropic hormone (corticotropin, ACTH). The third zone, the zona reticularis, produces dehydroepiandrosterone sulfate (DHEAS), also in response to ACTH. The innermost component of the adrenal gland is the medulla, which is really an extension of the sympathetic nervous system that synthesizes epinephrine. Aldosterone production by the zona glomerulosa is also weakly responsive to ACTH.

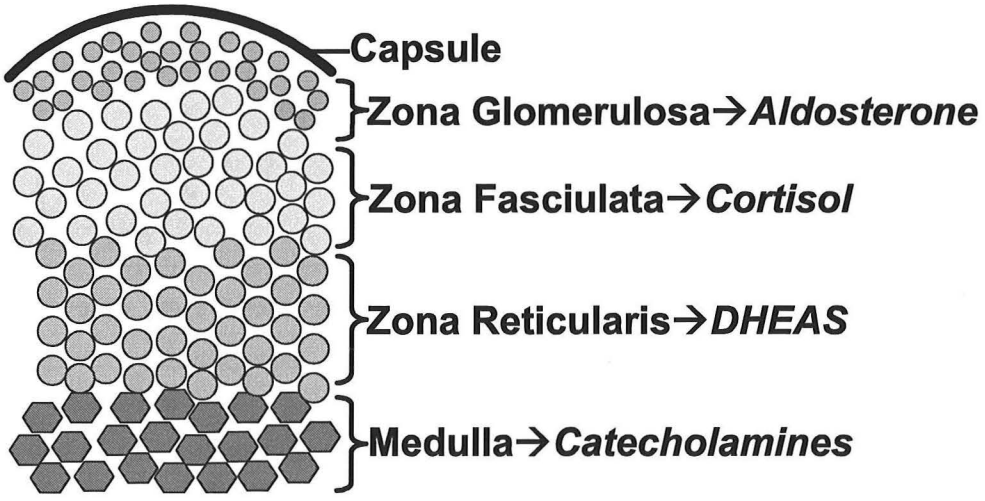


Figure 1. Zones of the adrenal gland and principal products.

As with most hormones, cortisol production is the result of an axis that is subject to negative feedback and external stimuli (Figure 2). The hypothalamic-pituitary-adrenal (HPA) axis receives many inputs from higher brain centers that converge on the paraventricular nucleus (PVN) of the hypothalamus where the corticotropin-releasing hormone (CRH) neurons reside. CRH drives the secretion of proopiomelanocortin (POMC) from the corticotropes. POMC is cleaved to ACTH, and ACTH increases cortisol and DHEAS secretion by the adrenals. The cortisol response to ACTH is twofold: an acute release, mediated by activation of the steroidogenic acute regulatory protein (StAR), which mobilizes mitochondrial cholesterol into the steroidogenic pathways (7), and a chronic effect to maintain the expression of the seven steroidogenic enzymes necessary for cortisol synthesis (Figure 2). Cortisol exerts negative feeback on the hypothalamus and pituitary to dampen cortisol production over minutes to hours. DHEAS does not exert negative feedback, and unlike ACTH and cortisol, its half-life is long (about 1 day), hence serum DHEAS can be used as a reflection of steady-state ACTH production. In addition, cortisol and ACTH (but not DHEAS) show prominent diurnal rhythms, with a peak in the early morning and a nadir in the middle of the night. Nocturnal animals such as rodents have inverted diurnal rhythms with peaks in the night.

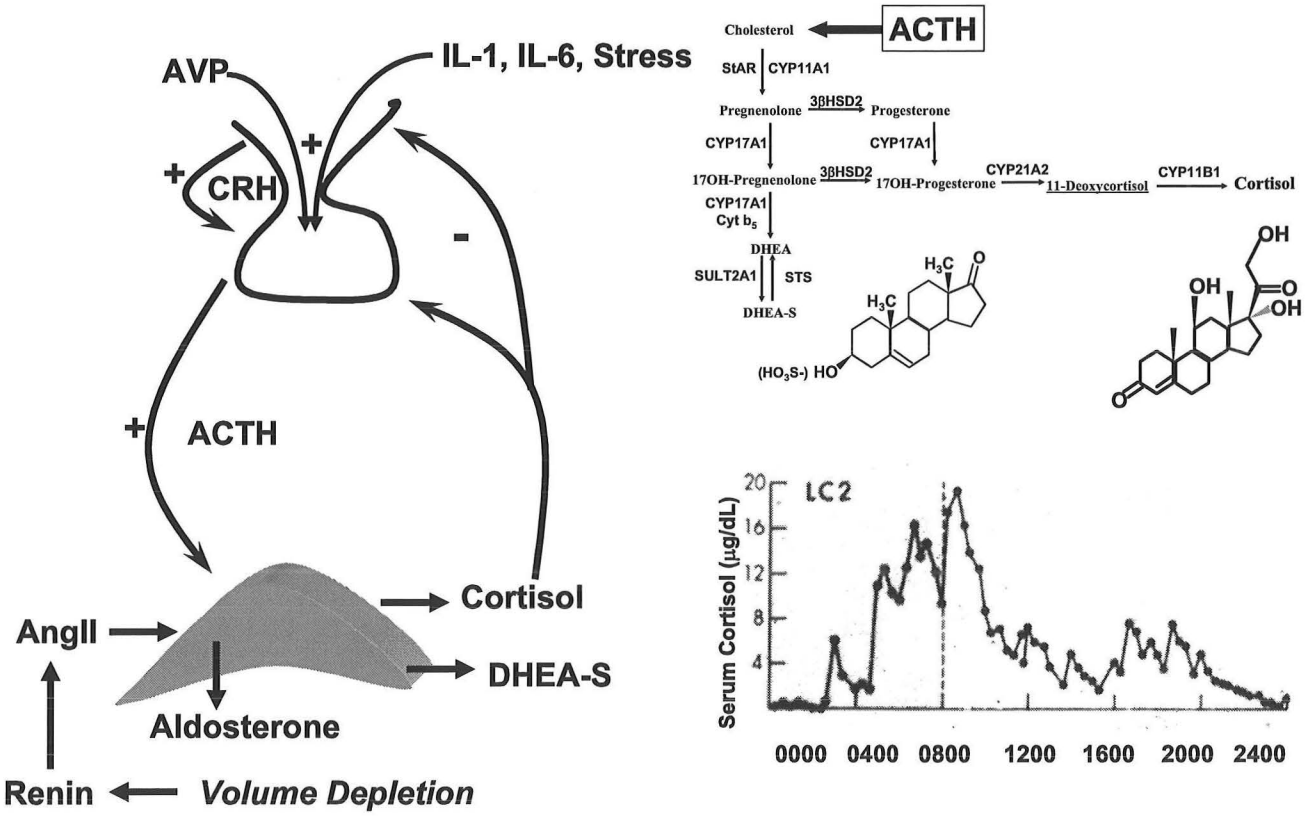


Figure 2. Cortisol production and regulation. Upper left, components of the HPA axis and regulation by external factors. Right, cortisol and DHEA(S) biosynthetic pathways with enzymes and intermediates identified. Lower left, diurnal cortisol rhythm.

The major external regulators of the HPA axis are cytokines. IL-1 and IL-6 are potent activators of the axis (8, 9), as are TNFα and MIF (10, 11). These cytokines not only activate CRH and ACTH release but have direct effects on the adrenals, possibly mediated via their action on intra-adrenal lymphocytes (12). Endothelin, atrial natiuretic peptides (ANP), and substance P likewise stimulate the HPA axis {Vermes, 1995 #646}. Vasopressin (AVP), derived from the parvocellular neurons in the hypothalamic PVN, in the presence of CRH, stimulates corticotropes directly to secrete POMC (14). These neurons are distinct from the neurons that project to the posterior pituitary and secrete AVP in response to hyperosmolality. Exercise is also a potent stimulator of the HPA axis (15), probably via noradrenergic input to the PVN, although the exact mechanisms are not known.

The activation of the HPA axis in critical illness involves several mechanisms (14, 16). The activity of CRH neurons is increased by adrenergic and other input of higher brain centers. Cytokines stimulate all levels of the HPA axis by various mechanisms. In addition, the axis becomes resistant to the negative feedback of cortisol (14, 17), perpetuating the hypercortisolemia. Note that this scenario, in which the CRH neuron is hyperactivated and cortisol excess is driven endogenously and reversibly, is called the "pseudocushing state" or physiologic hypercortisolism.

Diagnosis of Adrenal Insufficiency

The clinical manifestations of adrenal insufficiency are protean, so the history and physical can only suggest the diagnosis, and confirmation of hypocortisolism requires laboratory testing. Given the cortisol diurnal rhythm (Figure 2), random cortisol testing is of limited utility in well outpatients. In contrast, adrenal insufficiency can be excluded with high confidence most of the time obtaining an early morning cortisol, DHEAS, and ACTH, and I recommend this battery as a first step in the evaluation. If hypotension or orthostasis is present, I also obtain a renin and aldosterone. In well outpatients, a morning cortisol of >15 μg/dL obviates need for further testing (18), particularly if the DHEAS is above 85 μg/dL (19) and the ACTH is 20-40 pg/mL (which is typically the case). On the other hand, a cortisol <10 μg/dL is suspicious of adrenal dysfunction, particularly if the DHEAS is <15 μg/dL. When the AM cortisol is low, the ACTH will guide evaluation of primary (ACTH high) or secondary (ACTH low) adrenal insufficiency. The main difficulty encountered in the evaluation of adrenal insufficiency is in patients who have already received glucocorticoid therapy and assessing the influence of this treatment on test results. Sometimes subphysiologic hydrocortisone replacement (10-20 mg QAM only) for a period of time is required before retesting.

Dynamic testing is required when basal testing is equivocal or an immediate answer is needed (20, 21). In accordance with general principles of endocrinology, "if you think it is low, try to stimulate it; if you think it is high, try to suppress it." The classic dynamic test of adrenal function is the cosyntropin stimulation test (CST). The test is performed by giving 250 μg synthetic $ACTH^{1-24}$ (cosyntropin, Cortrosyn or Synachten in Europe) IM or IV and measuring a serum cortisol 60 or 45 min after administration, respectively. I measure basal cortisol only if the test is performed in the early AM to do

basal and dynamic testing concurrently. The criterion for a normal test is a stimulated cortisol value >18-20 µg/dL. Why 18-20? Well for one reason, 18 is 500 nmol/L in SI units, which is a nice round number; 20 is already a nice round number. Based on reviews of patients who have had CSTs and either suffered hypotensive crises with illness or surgery, a value of about 19 µg/dL does seem reasonable (22). The magnitude of the cortisol rise is no longer used as a criterion because the change is inversely proportional to the baseline value. ***NOTE THAT THESE CRITERIA WERE DEVELOPED TO PREDICT SURVIVAL OF THE STRESS OF SURGERY AND THUS ALREADY APPLY TO CRITICAL ILLNESS.***

The only question the CST answers is, "How much cortisol do these adrenals produce under maximal stimulation?" It is a supraphysiologic challenge that has good specificity but poor sensitivity due to false-positives in secondary adrenal insufficiency. Circulating ACTH values (measured by RIA) reach almost 10,000 pg/mL, values that are unobtainable in humans, except perhaps rarely in the ectopic ACTH syndrome. Thus, the CST is a pharmacologic challenge that must be interpreted in this context.

When evaluating secondary adrenal insufficiency, tests of the entire HPA axis are necessary. Tests that interrogate all or most of the axis include CRH stimulation testing, insulin tolerance testing (ITT), metyrapone testing, and exercise. CRH tests the pituitary and adrenal glands but omits the hypothalamus and higher centers. The test is performed by injecting 100 µg ovine CRH (oCRH, ACTHREL) and measuring cortisol (sometimes also ACTH) every 15 min for 90 min. ITT is the true gold standard but is labor intensive and carries risk of seizure and myocardial infarction. A bolus if regular insulin (0.05-0.2 U/kg) is given IV, and glucose and cortisol are measured every 15 min for 90 min. ACTH measurements during ITT do not improve the diagnostic utility beyond measurement of cortisol alone (23). Criteria for normal responses in the CRH test and ITT are the same as for the CST (18-20 µg/dL). Exercise is a reproducible stimulus of the axis (15, 24), although uniform protocols and criteria have not been defined. Metyrapone (Metopirone) is an inhibitor of 11β-hydroxylase (CYP11B1), which blocks cortisol synthesis and allows ACTH to rise and the cortisol precursor 11-deoxycortisol to accumulate (Figure 3). An oral dose of 30 mg/kg metyrapone is administered with a snack at bedtime, and an AM cortisol and 11-deoxycortisol are measured. If the cortisol has fallen to <5 µg/dL (indicating adequate blockade), a rise in 11-deoxycortisol to >7 µg/dL is considered normal. The test can be done in outpatients, although metyrapone causes nausea and can precipitate adrenal crisis. The drug is not sold commercially but may be obtained free from Novartis (1-888-669-6682).

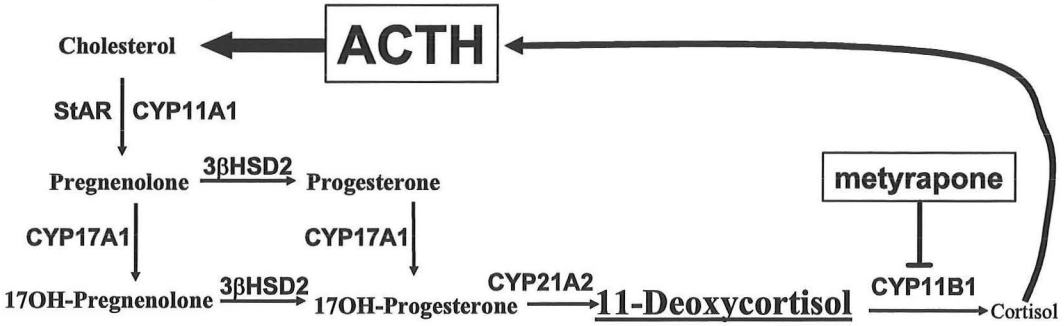


Figure 3. The physiologic and biochemical basis for the metyrapone test.

In the evaluation of sick patients, however, the diurnal rhythm is lost (25), the adrenal is already vigorously stimulated, and random cortisol values are very useful. In addition, the adrenal axis undergoes several temporal phases during prolonged illness, and test results must be interpreted in this context (26). In the first phase, which lasts about 3-5 days, all levels of the axis are activated, and circulating concentrations of ACTH, cortisol, and DHEA(S) are all high. After 5 days, plasma ACTH falls, but cortisol production remains elevated for weeks, maintained by other mechanisms including endothelin and ANP {Vermes, 1995 #646}, intra-adrenal lymphocytes, and direct actions of cytokines (12). In protracted critical illness that lasts a month or longer, cortisol values may fall eventually for unknown reasons, and this is a very poor prognostic sign (26). One would think that DHEAS measurements would complement cortisol measurements, but DHEAS is low in critical illness even when cortisol is elevated (27), in part because of a shift from DHEAS to DHEA (28). All of the endocrine axes undergo physiologic alterations in critical illness, and these phases are schematized in Figure 4. The "sick euthyroid syndrome," now simply referred to as changes from "non-thyroidal illness," is the classic manifestation of these alterations. During recovery from critical illness, many hormones (like thyrotropin [TSH]) show a compensatory transient rise, whereas cortisol production moderates to baseline values, and the diurnal rhythm resumes.

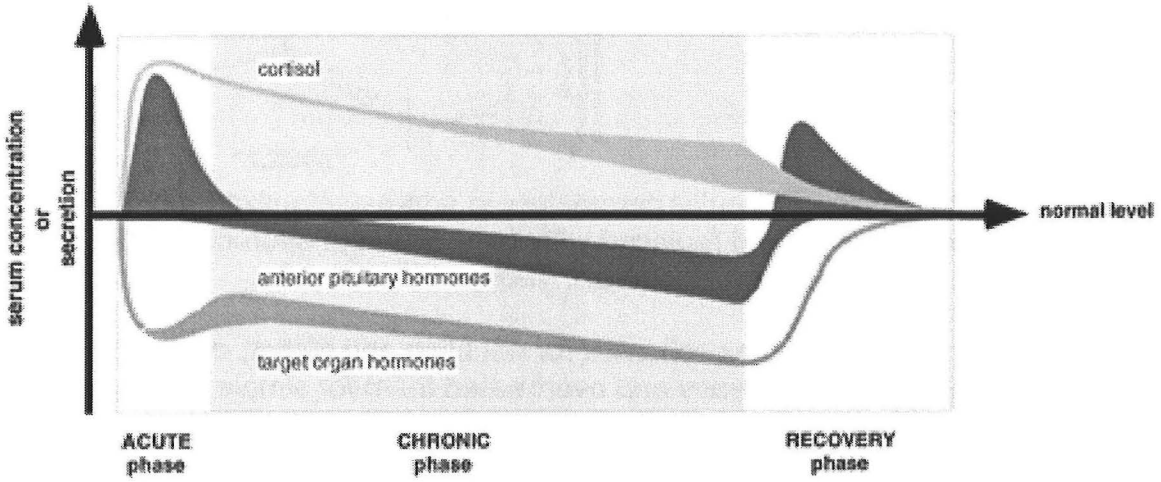


Figure 4. Cartoon of endocrine axis changes during different phases of critical illness (from Van den Berghe 1998).

Stress Dosing Hydrocortisone for Adrenal Insufficiency

We are all familiar with the custom of "stress dosing" of hydrocortisone in patients with known adrenal insufficiency when they are sick. This practice derives from the experimental studies in animals and from old reports of sudden and unexplained postoperative deaths which were attributed to adrenal crisis (29), often without laboratory substantiation. Even so, the number of patients who have truly suffered Addisonian crisis with surgery or illness is exceedingly small, and a detailed review of the topic could only find three confirmed cases in the world's literature (30). Where does the customary dose of 100 mg IV Q8h come from? Nobody really knows, and for

certain this dose is not based on any real data. This dose is about 15-times physiologic, but is that much necessary under any circumstances? In monkeys undergoing cholecystectomy, physiologic replacement dosing was equivalent to 10-times physiologic in preventing deaths (31), but 0.1x was insufficient (Figure 5). The "100 Q8" regimen is some mythical number like the 10 mg x 3 dose of vitamin K developed with no good rationale. About 50 mg Q12 h is the most hydrocortisone ever needed solely to replace normal adrenal function in any illness.

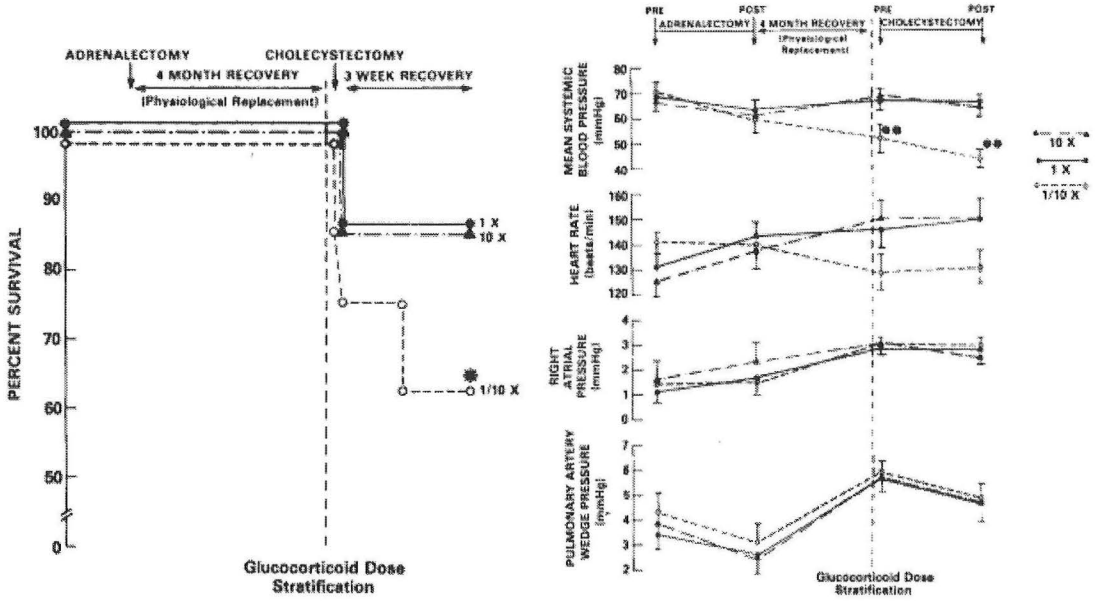


Figure 5. Survival and cardiovascular parameters in adrenalectomized monkeys undergoing cholecystectomy and replaced with three doses of hydrocortisone, 1x (physiologic), 10x, and 0.1x (from Udelsman, 1986).

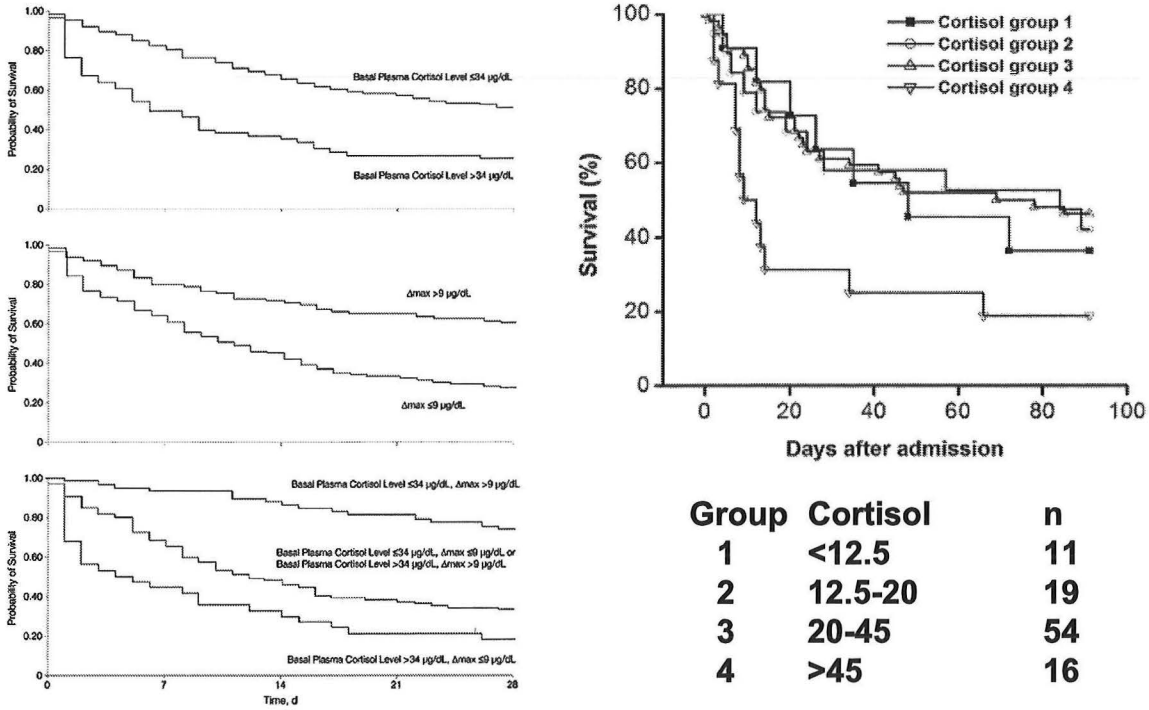
For years, we had complex schemes for doubling and tripling doses in outpatients with adrenal insufficiency and overtreated them for simple viral syndromes. Now I tell my patients with adrenal insufficiency to double their dose of hydrocortisone when they cannot defend their volume status ("When you cannot put back what is coming out"): vomiting, diarrhea, or high fever with anorexia such that they cannot replace their fluids and electrolytes. I have them maintain the double dose until they are well for one day. For more serious illnesses, they should give themselves an IM dose of 1 mL (4 mg) dexamethasone sodium phosphate and come to the hospital if they have not started improving within 24 hours. I have even had one patient spiral into a sort of adrenal crisis playing a long weekend golf tournament in the 100-degree Texas heat. Now I tell patients who are exerting themselves for long periods in extreme conditions (i.e. Prairie Man Half-Ironman) to double both their hydrocortisone and fludrocortisone starting the morning of the competition.

Confusion in Critical Illness

Given the central role of cortisol in response to stress, it is not surprising that the contribution of adrenal insufficiency to critical illness has been studied for many years.

Serum cortisol values in critical illness are often 50-100 µg/dL, up to 10-times higher than normal (14, 25). Free cortisol values are even more elevated (32, 33), since many of these patients are hypoalbuminemic and malnourished. These observations have made many physicians question whether cortisol concentrations near 100 µg/dL are ***required*** to survive serious illness and if typically "high" values of 20 µg/dL are inadequate. The corollary to this consideration is that supraphysiologic doses of corticosteroids might benefit the critically ill by supplementing this "deficiency." This concept of "relative adrenal insufficiency" has become popularized in the critical care literature (16, 34) but, as explained above, has no basis in endocrinology (14).

What is true beyond any doubt is that serum cortisol is a good prognostic factor in the critically ill. The higher the cortisol, the sicker the patient, and the less likely is survival. Cortisol values >34 µg/dL are particularly associated with poor prognosis (35-37). This paradigm can be tested further by administering cosyntropin to the critically ill, which I would never do otherwise if the cortisol was >20 µg/dL. The sickest patients have the highest cortisol production, so cortisol will not rise further with cosyntropin administration. A cortisol rise of <9 µg/dL during a CST is associated with a poor prognosis, and the worst prognosis is a combination of high basal cortisol and a small rise with cosyntropin (35)—these people are ***VERY SICK*** (Figure 6). The blunted response to cosyntropin is a normal response to stress that can be demonstrated in human subjects undergoing coronary bypass surgery. Of patients who passed a CST preoperatively, 38% had a cortisol rise <9 µg/dL the day after CABG, due to the stress of surgery already stimulating cortisol production to near maximal rates (38).



Group	Cortisol	n
1	<12.5	11
2	12.5-20	19
3	20-45	54
4	>45	16

Figure 6. Cortisol and CST as prognostic factors. Left, survival is poor with serum cortisol >34 µg/dL or a rise <9 µg/dL (from Annane, 2000). Right, similar data analyzed by quartiles of serum cortisol (from Sam, 2004).

Corticosteroids in Septic Shock and "Relative Adrenal Insufficiency"

Corticosteroid treatment in critical illness has been in and out of favor for decades. Studies are difficult to compare because the patient populations and treatments are not uniform, but the best studies involve septic shock. In the mid-1980s, 3 large studies using high doses of methylprednisolone or dexamethasone found no benefit and suggested harm in some subpopulations (39-41), and similar results were seen in one study of ARDS (42). Some investigators felt that the treatment doses were excessive and restudied the problem in ARDS and sepsis using more modest but still supraphysiologic doses (43). In particular, a study from Memphis using hydrocortisone at 100 mg Q8h in septic shock showed improved reversal of shock and lower mortality (44). Importantly, CST results did not predict treatment benefit in their study. Furthermore, no untoward effects were observed to a greater degree in the treatment group, demonstrating that this regimen is safe and probably also effective. The authors concluded that this dose of hydrocortisone might be broadly beneficial to all patients with septic shock.

These prior reports led to the widely-quoted study by Annane and colleagues published in JAMA in 2002 (34). These authors randomized 299 patients with septic shock to hydrocortisone 50 mg Q6h + fludrocortisone acetate 0.05 mg QD versus placebo with the primary endpoint as survival and secondary endpoint as time to withdrawal of pressor therapy. Before randomization, all participants received a CST. "Non-responders" or "relative adrenal insufficiency" was defined as a rise in cortisol <9 µg/dL; 229 or 77% of the patients met this definition, leaving only 70 "responders." In the "non-responders," those randomized to treatment showed a small and unimpressive but marginally statistically significant improvement in survival and time to withdrawal of pressors. The authors concluded that hydrocortisone treatment improves survival but only in those with "relative adrenal insufficiency" and suggested that the treatment was beneficial BECAUSE the therapy compensated for the inability of the adrenal to respond to cosyntropin. While I will not quibble with the possibility that hydrocortisone therapy may be beneficial in septic shock (as was shown in other studies), any benefit in patients with normal cortisol production (random cortisol >18 µg/dL) is not because of any adrenal dysfunction.

Why This Paper Should Be Retracted

The results of the Annane study are entirely not surprising for several reasons. First, as we have seen over and over again, the patients with the blunted cortisol rise are the sickest and most likely to benefit from intervention. Second, this group also contains some patients with bona fide adrenal insufficiency. Third, the "responder" group was so small that it was woefully underpowered to show a benefit.

The study was horrifically flawed and the conclusions entirely unjustified for several reasons. First, the study was in fact underpowered to conclude a prespecified clinically significant (20% survival) benefit in even the larger "non-responder" group. Secondly, 72 randomized subjects received etomidate within 8 hours of randomization.

Etomidate is an azole drug that inhibits several adrenal cytochromes P450, particularly 11β-hydroxylase (CYP11B1) and 17α-hydroxylase/17,20-lyase (CYP17A1), which causes partial adrenal insufficiency. Of these 72 subjects, 68 (94%) were "non-responders," comprising 30% of the "non-responder" group. Third, the authors did not consider free or biologically active cortisol in their assignment of adrenal status. Arafah and colleagues have shown elegantly that free cortisol is even more elevated in critically ill than total cortisol (32), and these results were reproduced in a British study (33). Fourth, the authors cannot prove that the benefit was from the hydrocortisone rather than the fludrocortisone acetate. Fifth, the claim that the treatment was "low dose" is misleading. If the reason these patients benefited from hydrocortisone therapy was because the adrenals could not increase cortisol production by 9 µg/dL, then raising the serum cortisol by 9 µg/dL should be sufficient. Administration of 50 mg Q6h elevates serum cortisol concentrations to over 100 µg/dL (14)!! The hydrocortisone dose needed to raise cortisol by 9 µg/dL is only 5-20 mg/day, and I seriously doubt that this dose would do anything. The reason 200-300 mg of hydrocortisone per day may be beneficial in septic shock is because this is a supraphysiologic dose that cannot be achieved in human physiology, and this high dose exerts pharmacologic anti-inflammatory effects—regardless of adrenal function.

More recently, the French group has endeavored to use the metyrapone test to diagnose adrenal insufficiency in the critically ill, despite the fact that this test has never been rigorously evaluated in this population. Using 2 cohorts that totaled 101 patients, the authors found that 60% of patients with sepsis met conventional criteria for adrenal insufficiency (45). Although the endocrinologic testing was performed well and conventional criteria were applied, the utility of this study is unclear. Compared to healthy volunteers, the subjects with sepsis had much higher total and free cortisol, but their plasma ACTH values were significantly lower at baseline. Since metyrapone testing relies on an ACTH rise to increase 11-deoxycortisol production, it is not surprising that many of these patients failed this test. In fact, the sum of 11-deoxycortisol + cortisol after metyrapone should be higher than at baseline in everyone. This rise was seen in the controls, but this sum was only about 30% of baseline in patients with sepsis and 50% of baseline in the critically ill group without sepsis. The results of this study are intriguing in that they suggest that, in sepsis, cortisol production is maintained by ACTH-independent mechanisms and that the adrenal is insensitive to ACTH—which further explains why so many patients with sepsis show a poor cortisol rise with cosyntropin. These data may provide some insight to the different mechanisms that maintain cortisol production in sepsis versus other illnesses, but I see no practical utility of metyrapone testing in this population.

What Then Should We Do??

From an endocrine standpoint, we consider patients to have adrenal insufficiency or not, and we do not use the term "relative adrenal insufficiency." I recognize that there is a grey zone, for example an asthmatic recently given a pulse of prednisone who then becomes septic and has cortisol values of 8 and 13 µg/dL in a CST might need hydrocortisone treatment at least for a few days. It is important to distinguish those who

truly have adrenal insufficiency due to hemorrhage, infection, autoimmune diseases, and undiagnosed Addison's disease from patients who temporarily benefit from supraphysiologic hydrocortisone therapy. Relegating someone to lifelong adrenal replacement therapy is no trivial matter. This disease requires medical alert identification, stress dosing instructions, and careful titration and monitoring. In addition, a diagnosis of adrenal insufficiency makes it difficult for patients to get life insurance and some forms of employment, precludes military service, and places them at risk for overtreatment with its consequences: osteoporosis, metabolic syndrome, etc.

My analysis of the literature indicates that hydrocortisone 200-300 mg/d probably is beneficial to patients with septic shock, and there is no major downside to using this therapy in hypotensive ICU patients for 2-5 days, particularly in the case of septic shock. Until there are definitive data, I cannot recommend hydrocortisone for all patients on pressors, but I would not discourage this practice either since the existing data are encouraging. There is no evidence that the CST is of any use other than as a prognostic factor in the ICU. A random cortisol is sufficient to determine if a critically ill patient has true adrenal insufficiency, and I would recommend this practice, particularly in ICU patients with the highest risk of adrenal insufficiency: sepsis (especially meningiococcemia), recent treatment with drugs that cause adrenal insufficiency (corticosteroids, etomidate, ketoconazole, megestrol acetate), or anyone for whom you plan to give hydrocortisone empirically. If the random cortisol is >18 µg/dL and hydrocortisone is administered, adrenal function will recover promptly. If the random cortisol is <10 µg/dL, these patients may need lifelong therapy, certainly if <5 µg/dL. If you are not sure, you can always retest with basal cortisol, ACTH, and DHEAS with/without a CST, metyrapone, or ITT when they are well and off hydrocortisone for 24 hours.

The Future

The Corticus project intends to study 800 patients randomized to hydrocortisone or placebo to settle the issues of whether supraphysiologic doses of hydrocortisone are beneficial in septic shock and if the CST is a useful diagnostic test in the ICU. Further investigation into the mechanisms regulating ACTH and cortisol production in critical illness is clearly warranted. Is it possible that the cytokines produced in sepsis not only activate the HPA axis but also cause a temporary cortisol resistance syndrome? If so, what are the molecular mechanisms responsible and tissues affected by this process? We also need to know whether the HPA alterations and adaptations are different in sepsis versus other forms of critical illness, but the sepsis problem should be resolved first. Unraveling the molecular mechanisms of ACTH-independent cortisol production in the critically ill may provide insights to the treatment of Cushing syndrome, congenital adrenal hyperplasia, and maybe even garden-variety hypertension and metabolic syndrome. The optimal management of the endocrine adaptations to critical illness is a complex and challenging problem. Adrenal testing during critical illness, in contrast, is really quite straightforward, despite the confusion that has been unnecessarily created.

References

1. **Addison T** 1855 On the constitutional and local effects of disease of the suprarenal capsules. London, Highly
2. **Brown-Sequard CE** 1856 Recherches experimentales sur la physiologie et la pathologie des capsules surrenales. Acad Sci Paris 43:422-425
3. **Biedl A** 1912 The internal secretory organs: their physiology and pathology. In: Foster L, ed. London: Bale and Danielson
4. **Kendall EC** 1937 A chemical and physiological investigation of the suprarenal cortex. Symp Quant Biol 5:299
5. **Sarett L** 1946 The synthesis of hydrocortisone from desoxycholic acid. J Biol Chem 162:601
6. **Thorn GW, Forsham PH** 1949 The treatment of adrenal insufficiency. Rec Prog Horm Res 4:229
7. **Stocco DM, Clark BJ** 1997 The role of the steroidogenic acute regulatory protein in steroidogenesis. Steroids 62:29-36
8. **Mastorakos G, Chrousos GP, Weber JS** 1993 Recombinant interleukin-6 activates the hypothalamic pituitary adrenal axis in humans. J Clin Endocrinol Metab 77:1690-1694
9. **Chrousos GP** 1995 The hypothalamic-pituitary-adrenal axis and the immune-mediated inflammation. N Engl J Med 332:1351-1362
10. **Naito Y, Tamai S, Shingu K** 1993 Responses of plasma ACTH, cortisol, and cytokines during and after upper abdominal surgery. Anaesthesiology 77:426-431
11. **Beishuizen A, Thijs LG, Haanen C, Vermes I** 2001 Macrophage migration inhibitory factor and hypothalamic pituitary adrenal function during critical illness. J Clin Endocrinol Metab 86:2811-2816
12. **Bornstein SR, Chrousos GP** 1999 Adrenocorticotropin (ACTH) and non-ACTH mediated regulation of the adrenal cortex and immune input. J Clin Endocrinol Metab 84:1729-1736
13. **Vermes I, Beishuizen A, Hampsink RM, Haanen C** 1995 Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab 80:1238-1242
14. **Arafah BM** 2006 Hypothalamic pituitary adrenal function during critical illness: Limitations of current assessment methods. J Clin Endocrinol Metab 91:3725-3745
15. **Petrides JS, Mueller GP, Kalogeras KT, Chrousos GP, Gold PW, Deuster PA** 1994 Exercise-induced activation of the hypothalamic-pituitary-adrenal axis: marked differences in the sensitivity to glucocorticoid suppression. J Clin Endocrinol Metab 79:377-383
16. **Cooper MS, Stewart PM** 2003 Corticosteroid insufficiency in acutely ill patients. N Engl J Med 348:727-734
17. **Reincke M, Allolio B, Wurth G, Winkelmann W** 1993 The hypothalamic-pituitary-adrenal axis in critical illness: response to dexamethasone and corticotropin-releasing hormone. J Clin Endocrinol Metab 77:151-156
18. **Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL** 1988 A rational approach for assessing the hypothalamo-pituitary-adrenal axis. Lancet 1(8596):1208-1210

19. **Nasrallah MP, Arafah BM** 2003 The value of dehydroepiandrosterone sulfate measurements in the assessment of adrenal function. J Clin Endocrinol Metab 88:5293-5298
20. **Oeklers W** 1996 Adrenal insufficiency. N Engl J Med 335:1206-1212
21. **Grinspoon SK, Biller BM** 1994 Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 79:923-931
22. **May ME, Carey RM** 1985 Rapid adrenocorticotropic hormone test in practice. Retrospective review. Am J Med 79:679-684
23. **Auchus RJ, Shewbridge RK, Shepherd MD** 1997 Which patients benefit from provocative adrenal testing after transsphenoidal pituitary surgery? Clin Endocrinol (Oxf) 46:21-27
24. **Singh A, Petrides JS, Gold PW, Chrousos GP, Deuster PA** 1999 Differential hypothalamic-pituitary-adrenal axis reactivity to psychological and physical stress. J Clin Endocrinol Metab 84:1944-1948
25. **Lamberts SW, Bruining HA, de Jong FH** 1997 Corticosteroid therapy in severe illness. N Engl J Med 337:1285-1292
26. **Van den Berghe G, de Zegher F, Bouillon R** 1998 Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 83:1827-1834
27. **Parker LN, Levin ER, Lifrak ET** 1985 Evidence for adrenocortical adaptation to severe illness. J Clin Endocrinol Metab 60:947-952
28. **Arlt W, Hammer F, Sanning P, Butcher SK, Lord JM, Allolio B, Annane D, Stewart PM** 2006 Dissociation of serum dehydroepiandrosterone sulphate in septic shock. J Clin Endocrinol Metab 91:2548-2554
29. **Fraser CG, Preuss FS, Bigford WD** 1952 Adrenal atrophy and irreversible shock associated with cortisone therapy. JAMA 149:1542-1543
30. **Salem M, Tainsh Jr RE, Bromberg J, Loriaux DL, Chernow B** 1994 Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 219:416-425
31. **Udelsman R, Ramp J, Gallucci WT, Gordon A, Lipford E, Norton JA, Loriaux DL, Chrousos GP** 1986 Adaptation during surgical stress. A reevaluation of the role of glucocorticoids. 77:1377-1381
32. **Hamrahian AH, Oseni TS, Arafah BM** 2004 Measurements of serum free cortisol in critically ill patients. N Engl J Med 350:1629-1638
33. **Ho JT, Al-Musalhi H, Chapman MJ, Quach T, Thomas PD, Bagley CJ, Lewis JG, Torpy DJ** 2006 Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab 91:105-114
34. **Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E** 2002 Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862-871
35. **Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E** 2000 A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283:1038-1045
36. **Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME** 2004 Cortisol levels and mortality in severe sepsis. Clin Endocrinol (Oxf) 60:29-35

37. **Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, Briegel J, Keh D, Singer M, Moreno R, Bellissant E, Annane D, Group CS** 2007 Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 35:1012-1018
38. **Widmer IE, Puder JJ, König C, Pargger H, Zerkowski HR, Girard J, Müller B** 2005 Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab 90:4579-4586
39. **Bone RC, Fisher Jr CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA** 1987 A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653-658
40. **Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M** 1984 The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. N Engl J Med 311:1137-1143
41. Veterans Administration Systemic Sepsis Cooperative Study Group 1987 Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659-665
42. **Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, Kariman K, Higgins S, Bradley R, Metz CA, the NHLBI ARDSnet** 1987 High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317:1565-1570
43. **Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA** 1998 Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 280:159-165
44. **Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A** 1998 Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26:645-650
45. **Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P** 2006 Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Resp Crit Care Med 174:1319-1326