corticosteroids in sepsis [created by Paul Young 02/10/07]

corticosteroids in immune modulation

- by interacting with NF-IL6, corticosteroids enhance the synthesis of the acute phase reactants; with AP-1 and NF-kB, they inhibit the synthesis of various proinflammatory factors.
- corticosteroids prevent the migration of inflammatory cells from circulation to tissues by blocking the synthesis of various chemokines
- prevent the synthesis of almost all proinflammatory cytokines including several interleukins (IL-1, IL-2, IL-3, IL-6), interferon-g (IFN-g), granulocyte macrophage colony stimulating factor, and tumor necrosis factor-a (TNF-a).
- They also enhance the production of the macrophage migration inhibitory factor (MIF)
- by stimulating the synthesis of lipocortin-1, corticosteroids inhibit the synthesis of soluble phospholipase A2 (PLA2) and the subsequent arachidonic acid cascade, reducing the production of leukotrienes
- inhibit the synthesis of inducible cyclooxygenase-2 (COX2) and of inducible but not constitutive nitric oxide synthase

corticosteroids in cardiovascular modulation

- chronic corticosteroid excess induces hypertension, whereas adrenal insufficiency induces hypotension
- Animal studies have demonstrated that both glucocorticoids and mineralocorticoids enhance the vasoconstrictor response to epinephrine
- underlying mechanisms remained unclear, and may involve multiple pathways like iNOS and COX-2 inhibitions or the stimulation of the phosphoinositide system
- In septic shock, adrenal insufficiency was associated with a marked hyporesponsiveness to norepinephrine, which was fully reversed 1 h after 50 mg of intravenous hydrocortisone

diagnosis of steroid insufficiency in sepsis

- Annane et al (2006) have demonstrated that both free and total cortisol response can be used to determine whether adrenal insufficiency is present in septic shock by comparing with a metyrapone stimulation test as a gold standard:

Diagnostic Tests	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Positive Likelihood Ratio (95% CI)
Basal total cortisol concentration < 10 μg/dl or Δ ⩽ 9 μg/dl	0.45 (0.26–0.63)	0.96 (0.87–1)	0.94 (0.86–1)	0.96 (0.89–1)	10.29 (1.47–72.27)
Basal total cortisol concentration < 10 μg/dl or cosyntropin-stimulated cortisol < 20 μg/dl	0.24 (0.08–0.39)	0.96 (0.87–1)	0.90 (0.78–0.99)	0.86 (0.88–1)	5.45 (0.74–40.25)
Basal free cortisol concentration < 0.8 μg/dl or Δ < 2 μg/dl	0.57 (0.39–0.76)	0.84 (0.68–1)	0.87 (0.80–0.96)	0.90 (0.82–0.97)	3.62 (1.22–10.73)
Basal free cortisol concentration < 0.8 μg/dl or cosyntropin-stimulated cortisol < 3.1 μg/dl	0.46 (0.28–0.65)	0.90 (0.76–1)	0.84 (0.76–0.95)	0.84 (0.77–0.96)	4.41 (1.12–17.36)

cellular mechanisms of action (genomic)

- Cells from most tissues are responsive to corticosteroids, which freely cross cell membranes.
- The glucocorticoids receptor forms an inactive intracytosolic complex with chaperone proteins like heat shock protein (HSP) 40, HSP56, HSP70, and HSP90, immunophillins, P23, and other unknown proteins
- Binding of corticosteroids to the glucocorticoids receptor induces the release of chaperone proteins and the dimerization of the complex, which then, enters into the nucleus and interacts with specific binding sequences, the glucocorticoid responsive element
- Subsequent transcription of genes (e.g.most cytokines, adhesion molecules, lipoxygenase, etc.) initiated by various transcriptional factors such as AP1, NF-AT and NF-kB are prevented.
- Glucocorticoids receptor dimers induce the inhibitor of NFkB (IkB).
- In contrast, other GRE sites upregulate the transcription of numerous other genes (e.g. lipocortin-1, thymosin-b4 sulfoxide)

cellular mechanisms of action (non-genomic)

- there are membrane binding sites for different corticosteroids in many tissues, including liver plasma membranes and neuronal synaptic membranes
- physicochemical interactions occur in-between the cell's membrane and corticosteroids inducing very rapid (within seconds), nonspecific, nongenomic effects
- neural modulation by corticosteroids may explain the rapid restoration of sympathetic modulation on heart and vessels, and may account for the hydrocortisone induced rapid pressure sensitization to exogenous catecholamine in septic shock