

## Adrenal Insufficiency in the ICU Patient

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Dynamics 2008  
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## Objectives

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- ❑ Where are the adrenal glands?
  - ❑ What do they do?
  - ❑ What happens when they don't work?
  - ❑ How do we know they aren't working?
  - ❑ What are the treatment options?
  - ❑ Questions?
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## Pathophysiology

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- ❑ There are two adrenal glands
  - ❑ Lie at the superior poles of both kidneys
  - ❑ Consist of adrenal medulla and the adrenal cortex
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## Pathophysiology

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- ❑ The adrenal medulla works with the central nervous system to secrete hormones (epinephrine and norepinephrine) in response to sympathetic stimulation
  - ❑ The adrenal cortex has three zones with the outer zone secreting the mineralocorticoid aldosterone and the inner zone secreting glucocorticoids like cortisol as well as androgens
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## Pathophysiology

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- ❑ Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to synthesize and secrete cortisol and aldosterone
  - ❑ Cortisol regulates carbohydrate, protein and lipid metabolism
  - ❑ Aldosterone regulates fluid and electrolyte balance through sodium and potassium homeostasis
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## Pathophysiology

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- ❑ Cortisol levels respond within minutes to stressful stimuli
  - ❑ This helps to protect the body from the stress
  - ❑ This protective mechanism is not completely understood but without it the body could not withstand mental or physical stress
  - ❑ Even minor illness could result in death
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## HPA Axis

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- The hypothalamus, anterior pituitary and adrenal cortex are collectively known as the hypothalamic-pituitary-adrenal (HPA) axis
  - This works to maintain appropriate levels of glucocorticoids
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## Cortisol

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- HPA axis is regulated by three distinct modes: diurnal rhythm in basal cortisol secretion, marked increases in steroidogenesis in response to stress, and the negative feedback regulation by adrenal cortisol
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## Cortisol

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- Is released in bursts in a diurnal pattern
  - ACTH secretion rises during the late hours and peaks in early morning, around 8 am
  - The negative feedback regulation then kicks in and keeps the glucocorticoid levels in the appropriate range
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## Cortisol

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- Stressful circumstances as well as chronic disease may alter the normal mechanisms resulting in marked increases in plasma levels
  - This may be increased as much as 20 times
  - Examples of stressful stimuli include trauma, major surgery, severe infection, pain, hypoglycemia, hypovolemia, hypotension, hypoxemia, bleeding, fear and intense heat or cold
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## Cortisol

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- Primary glucocorticoid in humans
  - Regulates carbohydrate, protein and fat metabolism and indirectly leads to insulin secretion to counterbalance glucocorticoid induced hyperglycemia
  - Also has antiinflammatory and immunosuppressive effects
  - Maintains cardiovascular integrity
  - Produced at a rate of 10mg/day (equivalent to 20-30mg/day of hydrocortisone)
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## Aldosterone

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- Acts on the distal tubules and collecting ducts of the kidney to promote the reabsorption of sodium and to increase the urinary excretion of potassium and hydrogen ions
  - Therefore, its deficiency in patients who are adrenally insufficient can lead to sodium loss, volume depletion, hypotension and vascular collapse
  - Death occurs within 3-14 days with total loss of aldosterone unless the patient is given mineralocorticoid
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## Adrenal Insufficiency

- ❑ Two types: primary and secondary
- ❑ Primary (Addison's disease) is caused by the inability of the adrenal gland to produce cortisol, aldosterone or both (HPA axis remains intact)
- ❑ Characterized by orthostatic hypotension, hyponatremia, hyperkalemia, mild metabolic acidosis and hyperpigmentation of the skin

## Adrenal Insufficiency

- ❑ Secondary is caused by dysfunction of the hypothalamus, pituitary gland or both (with a normal adrenal gland)
- ❑ May result in hypotension and hyponatremia with normal potassium and hydrogen ion levels

## Relative Adrenal Insufficiency

- ❑ Cortisol level is either insufficient or high in absolute terms but too low to respond to the level of stress
- ❑ Increases the risk of death during severe illness
- ❑ May result from catecholamine receptor desensitization or downregulation and/or chronic secretion of cytokines and other substances that suppress the HPA axis
- ❑ Also known as adrenal exhaustion syndrome

## Causes

- ❑ The most common causes in critically ill patients are thought to be sepsis and systemic inflammatory response syndrome
- ❑ Probably related to decreased synthesis and/or decreased release of ACTH, CRH (corticotropin releasing hormone) and cortisol by cytokines and other inflammatory mediators released during sepsis

## Causes

- ❑ Several drugs have been implicated with the primary drug being oral corticosteroids which decrease the endogenous ACTH secretion and in turn may induce adrenal atrophy that may persist for weeks or months even after discontinuation of the drug
- ❑ Other drugs include ketoconazole, megestrol, medroxyprogesterone, aminoglutethimide, mitotane, metyrapone, etomidate and high dose fluconazole (>400mg)
- ❑ Patients should be monitored with the ACTH stimulation test

## Signs and Symptoms

- ❑ Fatigue, weakness, joint pain, dizziness, depression, GI symptoms such as nausea, vomiting, abdominal cramps, weight loss and anorexia nervosa
- ❑ Hyponatremia
- ❑ Symptoms are more severe in primary adrenal insufficiency

## The Critically Ill Patient

- ❑ Difficult to recognize in the ICU
- ❑ Must watch for important clues such as hyponatremia, hyperkalemia, hypoglycemia (rare), and hemodynamic instability despite adequate fluid and vasopressor therapy (the most common feature)

## Diagnosis

- ❑ Several testing methods available
- ❑ Insulin tolerance test measures response to insulin induced hypoglycemia
- ❑ Considered as a Gold Standard because it tests the entire HPA axis

## Diagnosis

- ❑ Metyrapone test
- ❑ The drug interferes with cortisol synthesis when given to the patient
- ❑ Corticotropin-releasing hormone stimulation test
- ❑ Measures the ability of the pituitary gland to secrete ACTH in response to exogenous CRH with an increase in cortisol secretion by the adrenal gland

## ACTH Stimulation Test

- ❑ Standard ICU test for diagnosing adrenal insufficiency
- ❑ Based on the inability of the diseased adrenal gland to secrete cortisol after corticotropin is given
- ❑ Quick, simple, insensitive to interferences, reliable and relatively free of side effects

## ACTH Stimulation Test

- ❑ Corticotropin is a synthetic agent which consists of the first 24 amino acids of human ACTH
- ❑ Blood is drawn for cortisol level as a baseline
- ❑ Corticotropin is then given any time of day (dose may vary from a low dose of 1 µg or a high dose of 250 µg)

## ACTH Stimulation Test

- ❑ This simulates the adrenocortical steroidogenesis
- ❑ Blood is then drawn for cortisol levels at 30, 60 and sometimes 90 minutes

## Random Cortisol Levels

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- For critically ill patients, the random level can be drawn at any time of the day as they lose the diurnal variation
  - Rivers et al. (Chest 2001) reported that a cortisol level of less than 690nmol/L in a group of surgical patients is associated with steroid responsive hypotension
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- Marik et al. (Chest, 2002) suggested that ACTH testing is not necessary in critically ill patients as they are already severely stressed and should have maximal cortisol secretion
  - They also stated that a random cortisol level provides enough information on the function of the entire HPA axis
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## Interpretation of the Results

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- Both low and high cortisol levels are associated with poor prognosis
  - Some authors have stated that a cortisol level of < 414nmol/L is indicative of adrenal insufficiency
  - Others feel that ICU patients with a level < 550-690nmol/L is more appropriate
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## Results

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- Maximum cortisol levels have been used with values of < 500, 550 and 690-828nmol/L after ACTH stimulation
  - A cutoff of < 250nmol/L incremental response after ACTH stimulation is another method
  - Cooper et al. (N Engl J Med, 2003) suggested that adrenal insufficiency is unlikely when a random cortisol level is > 889nmol/L and likely if the level is < 414nmol/L and suggest performing the ACTH stimulation test if the level is between 414 and 889
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## Results

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- Another author added a recommendation of the use of a peak cortisol level of < 550nmol/L or an incremental response of < 250nmol/L after the high dose ACTH stimulation test to diagnose adrenal insufficiency in critically ill patients
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- Annane et al. (JAMA, 2000) showed in septic shock patients :
    - 3 groups of patient prognoses by using the ACTH stimulation test
    - Baseline cortisol level of > 889nmol/L and an increase of 250nmol/L or less after ACTH are associated with the highest mortality
    - Baseline level > 889nmol/L with an increase of > 250nmol/L
    - Lowest mortality risk was in those with baseline levels of 889nmol/L or lower and an increase of > 250nmol/L
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- ❑ Moran et al. (Intensive Care Med, 1994) found that there was a greater mortality rate with a lower response to the stimulation test
  - ❑ The magnitude of change after ACTH may have a predictive value for mortality
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## What's the Consensus?

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- ❑ Several authors agree that the strongest evidence supports a baseline cortisol level of < 414nmol/L with an increase of < 250nmol/L after ACTH or a random level of < 690nmol/L as the best values to diagnose adrenal insufficiency
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## Treatment

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- ❑ IV hydrocortisone, methylprednisolone and dexamethasone are the three glucocorticoids most commonly administered to critically ill patients with adrenal insufficiency due to stress
  - ❑ Hydrocortisone is the synthetic equivalent of cortisol and has both glucocorticoid and mineralocorticoid activities
  - ❑ Fludrocortisone is a mineralocorticoid but its use remains controversial in the ICU
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## Treatment

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- ❑ The recommended dosage of hydrocortisone is 200-300 mg/day in 3 or 4 divided doses (50 mg every 6hr or 100 mg every 8hr)
  - ❑ A continuous infusion may also be used with a 50-100 mg bolus followed by a 10 mg/hr infusion
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- ❑ Dexamethasone does not cross-react with the cortisol level and should be used if adrenal insufficiency is suspected but an ACTH stimulation test cannot be performed right away
  - ❑ Once the test results are available, therapy can be continued, if necessary, using hydrocortisone
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- (Kwame, Pharmacotherapy, 2007)

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- ❑ Marik et al. (Crit Care Med, 2008) state that although treatment with dexamethasone has been suggested in patients with septic shock until an ACTH stimulation test is performed, this approach can no longer be endorsed
  - ❑ Dexamethasone leads to immediate and prolonged suppression of the HPA axis, therefore, limiting the value of ACTH testing
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- ❑ Hemodynamic improvement should be noticed in about 24 hrs in septic shock patients
  - ❑ Discontinuation can be considered as the patient improves clinically
  - ❑ The dosage is usually tapered at the end of therapy and should be restarted if shock recurs
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## Things to consider

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- ❑ Routine blood glucose monitoring should be performed as hyperglycemia is common
  - ❑ The liver is where cortisol is broken down so with decreased blood flow to the liver the clearance will be altered
  - ❑ Corticosteroids are excreted mainly in the urine (75%) as well as bile and feces (25%)
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## Conclusion

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- ❑ Adrenal insufficiency can be life threatening
  - ❑ Diagnosing it is always a challenge
  - ❑ It should be suspected in ICU patients with persistent hypotension despite therapy
  - ❑ It can occur at any time during an illness
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## Conclusion

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- ❑ Most of the research is focused on septic shock patients and ARDS
  - ❑ Treatment with glucocorticoids should be considered in these patients
  - ❑ Adrenal function tests are not routinely required for these patients
  - ❑ More research is required in other critically ill patients
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Questions?

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