

## **STRICT BLOOD GLUCOSE CONTROL IN ICU: UPDATE OF THE CLINICAL EVIDENCE**

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Recently, the concept that stress hyperglycemia in critically ill patients is an adaptive, beneficial response has been challenged. Two large randomized studies in adult ICU patients demonstrated that maintenance of normoglycemia with intensive insulin therapy substantially prevents morbidity and reduces mortality. Since then, results from subsequent studies raised questions about the efficacy in general and in specific subgroups, and about the safety of this therapy with regard to potential harm of brief hypoglycemic episodes and of high-dose insulin administration. These issues will be addressed in relation to the available evidence. A recent randomized controlled study investigated the impact of targeting age-adjusted normal fasting blood glucose levels in critically ill infants and children and confirmed a 3 percent absolute reduction in risk of death, reduced severe infections and inflammation, and reduced duration of ICU stay.

Results from translational research suggest that avoiding circulating glucose levels to be higher than what cells are used to deal with during health is the key event. Hence, confounding factors appear the duration of hyperglycemia before the intervention in ICU and the adequacy of identifying the optimal level as well as achieving that target. Inadequate accuracy of glucometers are a major obstacle. Risk of hypoglycemia increases with insulin therapy, but it remains unclear whether this is truly harmful in the setting of critical care. Hyperglycemia on the other hand has shown to cause toxicity in several cell types that take up glucose passively, independent of insulin, including hepatocytes, alveolar cells, endothelial cells, neurons and immune cells. Prevention of glucose toxicity to the mitochondrial compartment in such cells appears important. In addition, insulin may exert direct effects as long as hyperglycemia is avoided. Such insulin effects include partial correction of dyslipidemia and prevention of excessive inflammation.

# **GLUCOCORTICOID TREATMENT IN THE ICU – WHEN AND HOW MUCH.**

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Treating severely sick patients in the ICU with high pharmacologic doses of hydrocortisone (1.0 to 3.0 gr) was popular in the fifties to sixties. It was abandoned after several studies have shown that the risks are higher than the benefits.

## **ACTH tests in the ICU, and the use of “physiologic” stress doses of hydrocortisone -**

In 2000 the term and 2002, Annane et al. described the prognostic classification of outcomes in septic shock patients, based on cortisol levels and cortisol response to corticotropin. A delta response of  $< 9\mu\text{g/dl}$  cortisol was defined as “relative adrenal insufficiency.” The worst prognosis was when basal cortisol level was  $> 34\mu\text{g/dl}$  (934 nmol/L). When  $\Delta$  max was  $< 9\mu\text{g/dl}$ , mortality was higher than in higher  $\Delta$  max. The lowest mortality was encountered when basal cortisol level was  $< 34\mu\text{g/dl}$ , with  $\Delta$  max  $> 9\mu\text{g/dl}$ .

**Measurement of free cortisol** - Serum protein levels in many septic shock patients are low. This is true for both CBG and albumin. It therefore seems reasonable to measure free rather than total cortisol levels, especially when albumin levels are lower than 2.5gr/dL. Measurement of salivary cortisol, which highly correlates with free cortisol, is another option not yet fully validated for this purpose.

**The use of  $\Delta$  max** as a sign of adrenal normalcy is very controversial. The main function of the adrenal cortex is to produce cortisol in quantities that increase in accordance with the body’s needs. If the body needs high serum cortisol levels and the adrenals do not secrete all or nearly all that is needed, yet respond promptly (high delta cortisol) to external ACTH administration, this should be considered adrenal insufficiency and not a normal response. Such a scenario is typical to recent onset secondary adrenal insufficiency. Another explanation may be that the failure of the adrenals to secrete more cortisol spontaneously reflects a non-extreme situation, and that the more favorable outcome in these patients reflects only this fact.

Cooper and Stewart built an algorithm of how to investigate corticosteroid insufficiency in acutely ill patients. A basal cortisol level of  $< 15\mu\text{g}/\text{dl}$  in septic shock makes hypoadrenalism likely and justifies corticosteroid treatment without further testing, while a basal level of  $> 34\mu\text{g}/\text{dl}$  makes this diagnosis unlikely. In the in-between group, a response to ACTH of less than  $9.0\ \mu\text{g}/\text{dl}$  would be considered as RAI, justifying glucocorticoid treatment. In a very recent paper, these authors adjust this algorithm only to ICU patients with septic shock and not to all other critically sick, who should be worked up according to commonly accepted criteria.

A meta-analysis comparing trials of glucocorticoids for sepsis in studies published between 1988 and 2003 found a consistent beneficial effect of glucocorticoids (300 mg daily) on survival from sepsis. These effects were the same regardless of adrenal function. Another study demonstrated that this so called “physiologic” dose of hydrocortisone, is actually 3 times higher than the maximal cortisol secreted normally in septic shock, and should be considered pharmacologic.

The prospective CORTICUS study, published in the NEJM in 2008, was aimed to examine whether the response (delta) of cortisol to ACTH in septic shock patients correlated to survival, and to survival rate in response to hydrocortisone treatment. No positive correlation between the two was found. The term “relative adrenal insufficiency” was omitted from this study, as these results prove this term to be invalid.

Two consensus statements on this subject were published recently. The first concludes to consider hydrocortisone when shock responds poorly to fluid and vasopressor, and that ACTH test is not recommended. The second concludes that adrenal insufficiency in critical illness is best diagnosed by a delta cortisol after ACTH of less than  $9\mu\text{g}/\text{dl}$ , however the ACTH test should not be used to identify those patients who should receive glucocorticoids.

### **Conclusions**

The entity of RAI is vague, and ACTH tests in the ICU have not proven to be effective in differentiating those patients who will benefit from pharmacological (240 to 300 mg daily) treatment with hydrocortisone. The only cases who justify HPA workup in the ICU are those in whom clinical suspicion for adrenal insufficiency exists.

## **Thyroid function in stress**

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Two aspects of thyroid function in stress will be discussed: thyroid function alternations in acute stress, a condition that has been called euthyroid sick syndrome (ESS) or non-thyroidal illness syndrome (NTIS), and the connection between chronic stress and thyroid autoimmunity. Thyroid function abnormalities can occur within hours of acute illness, and the magnitude of this alternations correlates with severity of disease with the lowest T3 and T4 values associated with decreased survival. Outlines of specific thyroidal adaptations during several clinical conditions, especially in patients with cardiac dysfunction, will be provided. The controversial issue of thyroxine or triiodothyronine treatment in patients with non-thyroidal illness syndrome will be discussed.

Numerous reports have indicated an association between stress and autoimmunity and that stress may trigger or worsen autoimmune disease. Evidence from experimental and clinical research supporting the hypothesis that stress may influence the clinical expression of thyroid autoimmunity will be briefly overviewed.

## **Neuroendocrine Crisis**

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Neuroendocrine tumors (NETS) are widely distributed throughout the body, with a broad spectrum of varying biologic behavior. Most of these tumors are well differentiated, with variable but often indolent biologic behavior. NETS include carcinoid tumors, pancreatic islet cell tumors (gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma), paragangliomas, pheochromocytomas, and medullary thyroid carcinomas. Regardless of the anatomical location of the NET, these tumors may become clinically evident and even life threatening do to excess hormonal secretion. In this lecture we will discuss some of the rare endocrinological emergencies that may be encountered when dealing with these tumors.

**Carcinoid crisis** Carcinoid tumors may arise anywhere in the gastrointestinal tract, in the bronchi, and occasionally elsewhere. These tumors can secrete various hormonal factors, which are the mediators of the carcinoid syndrome.

Carcinoid crisis is an extreme and life threatening form of the carcinoid syndrome, and may present as profound flushing, extreme changes in blood pressure (hypotension), bronchoconstriction, arrhythmias, and altered mental status. This syndrome may appear spontaneously or may be triggered by different procedures such as induction of anesthesia or palpation of tumor masses during surgery. Octreotide should be given prophylactically to prevent carcinoid crisis. If not given prophylactically and once the carcinoid crisis has developed, intravenous octreotide remains the optimal therapy. Standard therapy with fluids, calcium or inotropic agents may not be helpful and even harmful.

**Pheochromocytoma** is a rare neuroendocrine tumor, occurring in less than 0.2 percent of patients with hypertension. All patients with pheochromocytoma should be operated on after appropriate medical preparation. This preoperative medical therapy is aimed at controlling

hypertension (including a hypertensive crisis during surgery), providing volume expansion and avoiding lethal cardiac tachyarrhythmia. . When patients with undiagnosed pheochromocytomas undergo surgery for other indications without preoperative medical therapy, surgical mortality rates are high secondary to lethal hypertensive crises and multiorgan failure. Acute hypertensive crises may occur before or during an operation, and should be treated intravenously with sodium nitroprusside, phentolamine, or nicardipine.

**PTHrP secreting NET's** A third form of endocrinological emergency which may appear in patients with neuroendocrine tumors is that of life threatening hypercalcemia associated with PTHrP secreting pancreatic NETS. Hypercalcemia in these tumors may be spontaneous, or exacerbated by radioabative therapy which releases preformed hormone into the circulation. Hypercalcemia that is accompanied with changes in mental status or serum calcium concentration  $>14$  mg/dL (3.5 mmol/L) require treatment, regardless of symptoms. Therapy under these circumstances is based on the regular measures of treating hypercalcemia including aggressive saline hydration, potent intravenous bisphosphonates, intramuscular calcitonin (and gallium nitrate). In addition, intravenous octreotide is given simultaneously in order to reduce PTHrP secretion from the pancreatic tumor.

In conclusion, the endocrine emergencies that may accompany NETS are by and large preventable by means of specific and non-specific measures.