Critical illness-related corticosteroid insufficiency: What we know and what we don't know

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INTRODUCTION

Glucocorticoids have an important role in the maintenance of vascular tone, endothelial integrity, and vascular permeability in the setting of acute illness.[1] Elevation of plasma cortisol concentrations is part of the adaptive mechanisms in acute illness and inappropriately low plasma cortisol has been linked with increased mortality.[2,3] Based on this, the concept of critical illness-related corticosteroid insufficiency (CIRCI) was first introduced in 2008[4] and refers to inadequate cellular corticosteroid activity for the severity of the patient's illness.[4] This results in neurologic symptoms, such as confusion, delirium and coma, hypotension that is refractory to fluid resuscitation, decreased sensitivity to catecholamines, intolerance to enteral nutrition, hyponatremia, hypokalemia, hypoglycemia, and metabolic acidosis.[5] To date, although the importance of glucocorticoids in the setting of acute illness is well accepted, the concept of CIRCI, its diagnostic criteria, and appropriate treatment are not established, and in 2016, relative adrenal insufficiency was listed by Depuydt et al among "the ten diseases that are not diseases" in a publication in *Intensive Care Medicine*.[6]

PHYSIOPATHOLOGY OF CORTISOL PRODUCTION AND METABOLISM IN ACUTE ILLNESS

In the hypothalamic-pituitary-adrenal (HPI) axis, the "stress response" is initiated at the level of the paraventricular nucleus of the hypothalamus, which senses "stress" and in turn releases corticotropin-releasing hormone (CRH) that activates the release of adrenocorticotropic hormone (ACTH) and subsequently stimulates cortisol synthesis and secretion by the adrenal gland. High cortisol levels in the setting of acute illness were initially thought to be mediated by an activation of the HPI axis through the above mechanism; however, a study comparing cortisol and ACTH levels in acutely ill intensive care unit (ICU) patients and healthy controls showed that critically ill patients actually have lower ACTH levels despite higher serum cortisol concentrations.[7] Similarly, other studies have not found higher ACTH levels in acutely ill patients compared to controls.[8] In addition, it has been shown that the secretion of cortisol in response to ACTH is unaltered during acute illness.[9] In line with this, Boonen et al showed that cortisol production rate measured as "rate of cortisol appearance" in critical illness is increased to less than double compared to matched healthy individuals, not enough to explain higher cortisol concentration in blood seen in acute illness. On the other hand, plasma clearance of cortisol was decreased, as was the enzyme activity of 11B-hydroxysteroid dehydrogenase 1 and 5B-reductase in hepatic and adipose tissue, respectively, which are the enzymes that metabolize cortisol to its inactive form.[7] The latter has now become the most accepted mechanism of cortisol increases in acute illness, but the reason why some patients do not have the capacity to respond to stress as effectively as others remains unexplained. Bile acids, which substantially increase during critical illness, have the ability to inhibit the enzymes that mediate this conversion.[10] Better understanding of inhibitors of such enzymes could help determine factors that might contribute to our understanding of the development of CIRCI.

DIAGNOSTIC MODALITIES OF CIRCI

There are no established diagnostic criteria for CIRCI; proposed diagnostic criteria include a random

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cortisol level of <10 µg/dL or an abnormal response to cosyntropin stimulation test, indicated by a delta cortisol of <9 µg/dL after the administration of 250 µg of cosyntropin.[5] The most recent guidelines by the Society of Critical Care Medicine and European Society of Intensive Care Medicine make no recommendations about which test is superior.[5] In the setting of septic shock, the Surviving Sepsis Guidelines recommend against using any of the above mentioned tests to determine if steroids should be used for the treatment of septic shock, and it is recommended that high dose hydrocortisone be used for shock that is refractory to fluids and moderate to high dose vasopressors without prior laboratory testing.[11]

The use of the cosyntropin stimulation test for the diagnosis of CIRCI is based on the results of a study by Annane et al in 189 patients with septic shock in which a lower mortality was observed in those with a delta cortisol of >9 µg/dL.[12] In a subsequent study in which hydrocortisone and fludrocortisone were used in patients with septic shock, improved survival was observed in patients with an abnormal cosyntropin stimulation test done prior to the initiation of treatment.[13] A criticism of this study is that 30% of the patients who were categorized as "non-responders" based on their responses to cosyntropin stimulation tests had received etomidate within 8 hours of testing. Considering the inhibitory effect of etomidate on cortisol synthesis for at least 24 hours,[14] the results of the study in relation to CIRCI or as proof of validity of the cosyntropin stimulation test for its diagnosis are questioned. The data were never reanalyzed after the exclusion of such patients.[15] Later studies have questioned the utility of a cosyntropin stimulation test for the diagnosis of CIRCI based on the rationale that a suboptimal response of cortisol to ACTH administration is actually the result of negative feedback from the excess cortisol that results from decreased cortisol clearance.[16] A study by Loisa et al suggested that the result of the cosyntropin stimulation test in acutely ill patients with septic shock are inconsistent and not reproducible. These authors performed two consecutive cosyntropin stimulation tests in critically ill patients 24 hours apart. In septic shock no correlation was seen between the cortisol responses on day 1 and day 2. The majority of those patients who had poor cortisol responses on the first day demonstrated preserved adrenal function on the second day. In critically ill patients without septic shock, the results were more consistent.[16]

Finally, total cortisol, as is the case with total level of any other hormone, does not reflect the actual steroid effect, which is mostly mediated by free cortisol and its interaction with cortisol receptors at the tissue level. The affinity of cortisol binding globulin (CBG) for cortisol and the expression of cortisol receptors are altered in acute stress as an adaptation for survival.[2] Because most of the circulating cortisol in human serum is protein-bound, changes in the binding proteins can alter measured serum total cortisol concentrations without necessarily influencing free concentrations of this hormone. Not uncommonly, critically ill patients present with low proteins, and when this is the case, the correlation of free and total cortisol has been described to be as low as 50%.[5] In a study by Hamrahian et al, baseline serum total cortisol concentrations were found to be lower in patients with hypoproteinemia than in those with normal protein levels (defined as albumin ≤2.5 and >2.5 g/dL respectively), while baseline serum free cortisol concentrations were similar in the two groups of patients. Cosyntropin-stimulated serum total cortisol concentrations were subnormal in 14 of the patients, all of whom had hypoproteinemia and had normal or high stimulated serum free cortisol concentrations. Acknowledging the limitations of total cortisol, some experts suggest that the cutoff for normal total cortisol levels should depend on the albumin levels that indirectly indicate the amount of protein available for cortisol binding. They suggest using a cutoff of 15 µg/dL when albumin levels are >2.5 g/dL and 10 µg/dL when albumin is ≤2.5 g/dL.[15] Free cortisol levels could help better assess adrenal response to stress in acute illness, but normal values are not well defined.[2] The processing of the sample is time consuming, and, therefore, the test is not widely available, making it an impractical tool in the setting of acute illness. When available, cutoff levels of 2.0 µg/dL have been recommended to identify patients who would benefit from steroid use.[17] Formulas have been established to calculate free cortisol levels based on total cortisol

levels, CBG and protein levels, but studies of the use of these formulas have shown that they are not precise and result in up to 66 percent error when compared to actual measured free cortisol.[18]

Therapeutic approach of CIRCI

After the study mentioned above by Annane et al,[13] several subsequent studies have examined the benefits of steroids in sepsis and septic shock patients without finding reduced mortality with the use of steroids.[19,20,21] In 2008 the "Corticosteroid Therapy of Septic Shock Study" (CORTICUS) group found no survival benefits in patients with septic shock treated with hydrocortisone 50 mg every 6 hours, regardless of their responses to cosyntropin stimulation.[19] Similarly, the "Hydrocortisone for Prevention of Septic Shock" (HYPRESS) study, in which patients with severe sepsis were assigned to receive a continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 or placebo, found no reduced occurrence of septic shock with the use of hydrocortisone.[20] Finally, a study by Venkatesh et al that compared use of hydrocortisone for 7 days to placebo in septic shock patients also found no survival benefit with the use of steroids; reduction in time for shock resolution and ICU length of stay were the only benefits of steroids in this study.[21] Two major differences between the above studies and the Annane study[13] are that patients in the latter were more severely ill and received fludrocortisone along with hydrocortisone. A recent study in which a 7-day treatment with a 50-mg intravenous bolus of hydrocortisone every 6 hours and a daily dose of 50 µg of oral fludrocortisone resulted in lower mortality at day 90 and ICU and hospital discharge than placebo among adults with septic shock.[22] The Surviving Sepsis Guidelines recommend using hydrocortisone 200mg per day for shock refractory to fluid resuscitation and vasopressors and advise tapering the steroids once vasopressors are no longer needed.[11]

Finally, the benefits of using steroids in acute patients not in septic shock are less clear. In pneumonia there seems to be a mortality benefit in using steroids in cases of severe pneumonia when using hydrocortisone 200mg daily for five to seven days. In addition, steroids seem to reduce time to clinical stability and the length of hospital stay.[23,24] Steroid benefit does not seem to correlate to the response to a cosyntropin stimulation test in this setting.[25] The benefits of the use of hydrocortisone and fludrocortisone in patients with major trauma are not well established at this time.[5] Relative adrenal insufficiency has also been described in patients with ischemic stroke[26] and has been found to be highly prevalent in patients with liver disease,[27] and burn patients.[28] In these groups, patients with adrenal insufficiency are thought to have worse outcomes,[29] but studies assessing treatment outcomes are lacking.

Conclusion

So, what do we know and what don't we know about the concept of CIRCI? We certainly know that cortisol levels increase in the setting of acute illness as an adaptive response for better survival; this is achieved to a large extent through decreased metabolism of cortisol and to a lesser extent through increased cortisol production. We know that inability to maintain high cortisol levels in the setting of acute illness is associated with increased mortality in scenarios, like sepsis, septic shock, pneumonia, ischemic stroke, and liver disease among others. But we have not identified risk factors for CIRCI in patients who develop these conditions. We don't have clear diagnostic criteria that allow us to recognize those patients who fail to increase cortisol levels in acute illness; an assay to measure free cortisol that is readily available would possibly help us better assess cortisol status in acutely sick patients. We also know that when measuring serum total cortisol levels, albumin levels should be taken into consideration to account for the changes in bound cortisol when proteins are low. We know that patients with septic shock and severe pneumonia benefit from glucocorticosteroid treatment; in septic shock the benefits have been reported only when used with fludrocortisone.

Keywords: Adrenal insufficiency, cortisol, hydrocortisone

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