EVIDENCE-BASED CORTICOSTEROID THERAPY IN CRITICAL ILLNESS

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There is a general tendency in veterinary medicine towards the non-critical acceptance of new advances, often because of the pressure to emulate human medicine. Corticosteroid therapy for critically ill patients represents no exception to this general trend. Besides, there are some cogent theoretical arguments for the use of corticosteroids in critically illness – a state usually characterised by an exuberant pro-inflammatory response, where several factors, such as infectious agents, trauma or tissue inflammation challenge the immune system and alter the hypothalamic-pituitary-adrenal (HPA) axis. Indeed, corticosteroids appears to be a perfect panacea, in that they induce the synthesis of Annexin 1, a binding protein, which is responsible for inhibiting phospholipase A2 and eicosanoid formation. Furthermore, they blocks leucocyte migration, increase IL-10 release and induce apoptosis of inflammatory cells. Moreover, glucocorticoids play a major role in regulating the activity of nuclear factor kappa B, which plays a crucial role in cytokine gene transcription after exposure to an invading pathogen. Lastly, corticosteroids have a myriad of other anti-inflammatory actions, among others, the activation of endothelial nitric oxide synthetase. All of the above, ostensibly, justify corticosteroid use in the face of severe and overwhelming inflammation.

The erroneous attribution of hypotensive shock to inherent adrenal failure, rather than to drug-induced reduction of serum cortisol at the Glasgow Royal infirmary in 1982\(^1\), sparked a plethora of studies addressing this issue in human critical care. This fervour in search of the golden bullet in critical care was undimmed, e.g., such as etomidate\(^2\). As a result, a condition coined relative adrenal insufficiency entered the literature, purporting to represent a state of normal to elevated basal cortisol with a blunted response to ACTH. Subsequently, numerous studies have investigated the diagnosis of this condition and the risks and benefits of corticosteroid supplementation in critical illness.

Yet, despite more than 30 years of investigation and more than 20 meta-analyses, the use of glucocorticoids in patients with critical illness remains controversial with resultant conflicting recommendations\(^3\). Nevertheless, there is at least consensus that a condition, that manifests clinically as systemic hypotension, refractoriness to fluid loading and vasopressor use, yet eminently responsive to corticosteroid therapy, does exist.

This systemic hypotension may be due to down-regulation of smooth muscle adrenergic receptors; the expression of which is modulated by corticosteroids. The above condition has later been termed critical illness related corticosteroid insufficiency (CIRCI) and its definition was somewhat refined to represent a state of insufficient corticosteroid-mediated down-regulation of inflammatory transcription factors\(^4\). However, its aetiology remains only partially elucidated and several cytokines have been implicated in this reversible dysfunction of the HPA axis. As an example, TNF alpha has been shown to impair both pituitary CRH-mediated ACTH release and ACTH-stimulated cortisol synthesis in the adrenal.

Lately, however, several of the assumptions regarding a so-called “adequate” cortisol response to critical illness and its diagnosis are in the process of being debunked:

1. The body is able to regulate intracellular glucocorticoid concentrations, irrespective of circulating concentrations, thus rendering circulating plasma levels highly problematic as indicators of glucocorticoid action.
2. There is high variability in hourly cortisol concentration in critically ill patients.
3. There is a large variation in the time points of assessment after onset of illness in the different studies (from 8 hours up to 61 days).
4. There is marked gender differences in response.
5. There is high variability in the currently available cortisol assays.
6. Many studies had pharmacological confounders, such as etomidate, used on patients.

As a result of further evidence, yet another name has lately been proposed for this condition, analogous to the sick euthyroid syndrome - namely, sick euadrenal syndrome, rather than a sick adrenal indicating adrenal insufficiency\(^5\).
Diagnosis
The diagnosis of adrenal insufficiency in critical illness, with the aid of an ACTH stimulation test is very problematic. Firstly, the dose of ACTH and the appropriate response to ACTH in critical illness is controversial and almost impossible to predict, given the ill-defined magnitude of stress and inflammation and the nature and scope of individual response to critical illness. Second, the test’s reproducibility is very poor in critically ill human patients. Thirdly, interpretation of the test is generally based on total plasma cortisol concentrations, which has been shown to correlate very poorly with free cortisol and even less with interstitial cortisol. Lastly, since we have no clinical test that quantifies corticosteroid activity at tissue level, the diagnosis of CIRCI remains elusive at this time. To get any closer to a definitive answer, future studies should measure markers of glucocorticoid receptor nuclear density, annexin 1, PLA2 or NF kappa B levels and correlate them with survival and other clearly defined outcome measures. In sum, corticosteroid therapy should not be based on the results of an ACTH stimulation test, because its mechanism of hastening shock reversal seems to have very little to do with adrenal insufficiency and much more with vascular hypo-reactivity.

Treatment
Fortunately for patients, high-dose steroid therapy in critical care has been sufficiently discredited to allow for its discontinuation, yet the new “low dose corticosteroid” regimens found immediate appeal and piqued the interest of clinicians desperate to improve the lives of their critically ill patients. The problem when deciding on appropriate treatment, in essence, is one of chasing moveable set points; since effective regulatory systems are capable of adjusting set points according to changing demands and hence the appropriate dose of corticosteroid therapy for each individual patient at a given time point will remain elusive for some time to come.

However, a degree of consensus has emerged regarding low-dose corticosteroid therapy in humans:

1. It is part of the standard of care or so-called “treatment bundle” in septic shock that is unresponsive to fluid and vasopressor therapy (i.e. only those patients whose systolic blood pressure does not increase to 90 mmHg or above after 1 hour of aggressive fluid resuscitation and vasopressor therapy).
2. It is associated with a more rapid recovery from unresolved, severe acute respiratory distress syndrome (ARDS) of > 7 days duration; but NOT in early ARDS and not in ARDS that has been ongoing for > 14 days.
3. It should NOT be used in H1N1-induced ARDS.
4. In bacterial meningitis its use decreases hearing loss and other neurological sequelae, but NOT mortality.
5. There is NOT enough evidence to support its use in severe community-acquired pneumonia, nor in acute spinal cord injury.

So, what does this all mean for the critically ill small animal patient?

Currently, there are no evidence-based guidelines for the treatment of CIRCI or indeed whether the condition even exists in critically ill veterinary patients; however the following can be deduced after carefully extrapolating from human medicine and learning from their mistakes and considering one recent experimental canine study.

1. It seems reasonable to use supplemental doses of corticosteroids in volume-resuscitated patients in which it is difficult to maintain their blood pressure, despite the use of high doses of vasopressors.
2. The optimal dosage, duration and type of corticosteroid therapy are currently unknown, but a 3 - 5 mg/kg/day (or 200 – 250 mg/day for 7 days) equivalent of hydrocortisone seems to be the dose and duration settled on for humans. Since dogs tend to have roughly half of the basal serum concentration of humans; one would tend to suggest that a dose of 1 – 2.5 mg/kg/day of hydrocortisone equivalent be used. Since prednisolone and methylprednisolone both have approximately 5 times the glucocorticoid potency of hydrocortisone, they should be used at 5 times lower doses of 0.2 – 0.5 mg/kg/day. Since dexamethasone is about 6 times more potent than prednisolone, its dose should be roughly 6 times lower, at 0.03 – 0.08 mg/kg/day.
3. In a lethal, canine S. aureus pneumonia model, it was found that constant rate intravenous infusion of dexamethasone at 0.014 mg/kg/hr, started immediately after bacterial intra-bronchial challenge, was associated with improved outcome. In addition, dexamethasone therapy appeared to reduce cortisol levels in survivors, but not in non-survivors, thereby increasing the ability of total and free cortisol, ACTH and delta cortisol after ACTH stimulation to discriminate between survivors and non-survivors. However, although this study is very interesting from a mechanistic point of view, it is not readily translated into clinical practice, given that therapy was commenced immediately after experimental challenge, patients were not randomized and repeated, serial measurements and provocative testing
over a well-defined experimental timeline was necessary to establish which patients might benefit from glucocorticoid therapy.  

4. There is NO evidence in veterinary medicine showing treatment benefit after basing the decision on the results of an ACTH stimulation test, especially since the results of this test is often at variance with the interpretation of the cortisol/ACTH ratio and noting that this approach has been sufficiently debunked in human critical care.  

5. Moreover, a recent veterinary review has concluded that treatment should be based on clinical judgement and confirmed by subsequent response to corticosteroid therapy.  

6. Lastly, abruptly stopping corticosteroid therapy will likely result in rebound of pro-inflammatory mediators with a resultant recurrence in the features of sepsis and tissue injury. Therefore, indications are that initial dosage should be continued for 7 days and then reduced every 3 days and stopped after 14 days.

In sum, it is important to highlight what we do NOT know concerning glucocorticoid therapy in critical illness, so that we as clinicians can realise the limitations and constraints under which we attempt to practice evidence-based medicine:

- Apart from the fluid and vasopressor unresponsive septic human subgroup, we do NOT know which patients with other forms of critical illness should be treated with glucocorticoids.
- We do not know what the optimal treatment window is.
- We are unsure of the optimal dosing strategy.
- We do not know which glucocorticoid should be used.  

Consequently, until more data become available, veterinary practitioners will have to base their diagnosis and treatment of CIRCI on clinical judgement in patients with vasopressor-resistant hypotension and septic shock.

References