Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery

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Editor’s key points
- The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in critical illness.
- Levels of cortisol during health and illness are highly dynamic.
- There are gaps in our understanding of secretory patterns and control of cortisol during illness.
- These gaps limit our ability to design optimal therapeutic regimens.

Summary. The hypothalamic-pituitary-adrenal (HPA) axis is a neuro-endocrine system that regulates circulating levels of glucocorticoid hormones. These hormones are vital for normal homeostasis and play a pivotal role in the response to stress. Levels of cortisol fluctuate throughout the day in a diurnal rhythm, underlying which is an ultradian rhythm of approximately hourly pulses, and this pulsatility directly affects transcriptional outcomes. Pulsatility is not the result of a ‘pulse generator’, but is inherent within the system as a result of negative feedback. These patterns of secretion change in both acute and chronic illness as a result of inflammatory mediators, splanchnic nerve output, and central nervous system control. Levels of cortisol in both normal and illness states are highly dynamic and so previously used static assessment tools for diagnosing corticosteroid related critical illness insufficiency (CRI) are not likely to be useful. Therapeutic regimens have also failed so far, to take secretory patterns into account. In this review we look at the dynamic control and effects of glucocorticoids and frame in this context the current evidence surrounding steroid use in critical care and major surgery.

Keywords: adrenal cortex; cortisol binding globulin; critical care; hormones, adrenocorticotropic

The HPA axis is a neuro-endocrine system that regulates circulating levels of glucocorticoid. Endogenous glucocorticoids are essential for normal homeostasis and play a pivotal role in the response to stress. Exogenous glucocorticoid use in major surgery and critical care is still controversial and identification of those who are relatively ‘deficient’ (if they exist at all) has so far not been possible. Changes in our understanding of the HPA axis, such as its highly dynamic pattern of secretion, the role of cortisol binding globulin (CBG) in regulating tissue levels of cortisol, the presence of extracellular receptors and altered genomic and non-genomic signalling render much of the previous clinical work obsolete, while at the same time open up new therapeutic avenues. We look at these recent insights and review in this context the evidence surrounding steroid use in critical illness and major surgery.

HPA control in health

The basic tenets of the HPA axis are relatively well known. The paraventricular nucleus (PVN) of the hypothalamus is the key regulator of HPA activity. In response to a stressor, the PVN releases corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypothalamic-pituitary portal circulation. This then stimulates release of adrenocorticotropic hormone (ACTH) from the pituitary, which in turn increases both the rate of synthesis and secretion of cortisol from the zona fasciculata of the adrenal cortex. Circulating cortisol exerts a negative feedback effect at both the level of the pituitary to reduce ACTH secretion and in the hypothalamus to inhibit CRH release. Higher centres in the CNS (both limbic and brain stem pathways) project to the PVN to provide input from cognitive and physical stressors, while input from another hypothalamic nucleus—the suprachiasmatic nucleus (SCN) provides circadian information. An overview of the inputs and control to the HPA are outlined in Figure 1. The input from the SCN provides the HPA axis with a unique pattern of activity; a circadian rhythm. This is low during periods of sleep and increases in anticipation of wakening to a peak in the morning. The circadian rhythm is actually made up of an ultradian rhythm of discreet pulses¹ (see Fig. 2). Peaks in the circadian rhythm are attributable to large amplitude pulses lasting around an hour and the
night-time nadir reflects little or no pulsatile activity. These pulses result in rapidly changing levels of cortisol in both blood and the tissues and exposure of cells to constant or pulsatile cortisol yields different transcriptional responses, even when the total cortisol exposure is the same.

Although it had previously been assumed that there was a hypothalamic pulse generator, recent work using mathematical modelling has shown that pulsatility is inherent within the pituitary-adrenal system. At a simple level, ACTH and cortisol can be imagined to be two balls in a ‘Newton’s cradle’ system; one ball hits the other and causes movement, while coming to a stop itself and so the cycle continues. In the same way, ACTH stimulates cortisol production, cortisol levels increase and inhibit ACTH, decreasing levels of ACTH reduce the stimulus to cortisol; and the levels decrease. Thus there is a constant cyclical pattern of both ACTH and cortisol. The true picture is slightly more complex than this, with pulsatility only occurring in a ‘goldilocks’ area of moderate to high CRH drive and moderate to high delay in adrenal cortisol production. The greater the adrenal delay, the greater the period of each pulse wave.

In addition to hormonal control of the adrenals, there is also extensive innervation, both from sympathetic and sensory nerves. Both of these are carried in the splanchnic nerves. Sympathetic innervation is from both cholinergic pre-ganglionic fibres and catecholaminergic postganglionic fibres. The nervous supply to the adrenals appears to sensitize them to ACTH, such that they elicit a larger cortisol
response to the same level of ACTH. It may also be that splanchnic neural inputs have a smaller role in the diurnal output of the adrenals.

**Cortisol binding globulin**

CBG has a major influence on tissue levels of cortisol and acts as both a reservoir and regulator of cortisol. Cortisol is a steroid hormone and is therefore relatively insoluble in plasma and must be carried by other molecules. Approximately 95% of plasma cortisol is bound to proteins; of which 80–90% is bound to CBG and 10–15% to albumin. The remaining 5% is unbound and, therefore, free to cross cell membranes and bind to glucocorticoid and mineralocorticoid receptors. The affinity of CBG for synthetic corticosteroids is negligible apart from prednisolone, which has an affinity about 50% of that of cortisol.

CBG is a 50–60 kDa protein of the serpin (serine proteinase inhibitor) family which is secreted mainly from hepatocytes, but also the lung, kidney, and testes. Its main function is to transport cortisol, although the extra-hepatic sites of production may have a role in locally regulating cortisol levels. Each CBG molecule binds one cortisol molecule and this binding and release occurs by an allosteric method, common to all serpins. This involves a ‘flip-flop’ movement of the reactive loop (binding site) in and out of the body of the molecule. This binding is saturable and CBG has a finite binding capacity, which occurs at plasma cortisol levels of ~400–500 nmol litre⁻¹. This means that at cortisol levels that exceed this, the free and therefore biologically active fraction of cortisol is massively increased. This is important in the context of cortisol pulsatility in that large pulses of cortisol will have their effects exaggerated by exceeding CBG binding capacity.

Serum CBG levels fluctuate slightly in a diurnal manner. The diurnal rhythm of CBG is in opposition to that of cortisol, therefore accentuating the changes in free (and therefore biologically active) cortisol throughout the day. CBG’s affinity for cortisol is altered by both temperature and the activity of neutrophils. These act to enhance cortisol delivery at areas of inflammation. At higher temperatures, the affinity of CBG for cortisol decreases, with a resultant increase in the free fraction. This increase is much more pronounced at lower levels of cortisol when CBG is not saturated and there is not already a relative excess of free cortisol. Activated neutrophils release elastase, which cleaves CBG resulting in the irreversible destruction of the cortisol binding site. Local free cortisol levels will therefore increase significantly at areas of neutrophil activation. Although changes in pH affect the binding of cortisol to albumin, they do not affect the cortisol–CBG interaction.

**Signal transduction**

Glucocorticoids are fat-soluble and can therefore readily traverse the phospholipid bilayer of the cell wall. They bind to and activate intracellular receptors [glucocorticoid receptor (GR)], which can then act as transcription factors. GRs follow a ‘saturable’ pattern of kinetics, although this has only been established in vitro. The complex nature of cortisol delivery in vivo, along with variable GR concentrations between tissues means that we do not currently know what plasma level of cortisol translates to receptor saturation.

Figure 3 summarizes the process of glucocorticoid signal transduction.

The GR-ligand complex was previously thought to be stably bound to chromatin. However, it is now thought that these interactions are much more dynamic. The GR-ligand complex interacts transiently with responsive...
Fig 3  GC signal transduction. Cortisol (CORT) traverses the cell membrane and binds to the GR complex. The stabilizers hsp90 (heat shock protein 90) and p23 hold GR in a conformation that allows cortisol binding. When cortisol is bound, these two proteins dissociate and are recycled. The CORT-GR complex dimerizes and is transported into the nucleus via the nuclear pore complex. This process is achieved by importins, which bind the activated-GR and shuttle it through the nuclear pore. When in the nucleus, activated-GR binds to glucocorticoid response elements (GRE) on the DNA to activate or repress transcription. mGR exists on some cells and exerts its effects via a non-genomic mechanism.
elements at the regulatory site and recruits a secondary set of factors, which then form a complex to interact with chromatin and promote transcription. This process is not the unidirectional, ordered process that was once thought, but a rapid cycling of both GR and transcription factors on and off the chromatin, with each chromatin interaction lasting around 10–20 s.

The interaction of the ultradian rhythm with receptor binding is important for physiological functioning. Real-time, live cell imaging has shown that transcription of GR responsive genes occurs in pulses that tracks the pulses of natural GR ligand (corticosterone in the rat, cortisol in the human). The equilibrium of the GR-ligand complex interaction with DNA allows GR to bind cyclically with DNA. At the peak of each pulse the GR-ligand complex binds to promoter sequences of glucocorticoid responsive genes and then rapidly cycles off the chromatin. It is this rapid cycling that allows HPA output (i.e. gene transcription) to respond quickly to stressors. During the ‘off’ phase of the cycling, the complex comes off the GRE and as the ligand levels decrease in the trough of a pulse, there is an increased likelihood of dissociation of cortisol from the GR. Although unliganded GR can remain in the nucleus, it is unable to bind to DNA. It can however, regenerate into hormone responsive complexes with hsp90 ready to rapidly respond to the next pulse. Therefore, the trough of each pulse is critical to allow regeneration of the GR-complex so that cortisol may bind again and exert its transcriptional effect.

GR can positively and negatively regulate transcription and the gene response to glucocorticoid is diverse, with some genes induced transiently, continuously, or to a plateau response.

Some effects of glucocorticoids are too rapid to be a result of transcription, with effects seen in seconds or minutes. This led to the discovery that GR can also exist in a membrane associated state, particularly on neuronal and vascular cells. In neuronal cells, the effects of membrane associated GR (mGR) are widespread depending on the area of the brain, but can affect ion channels, receptors and downstream signalling. In the immune system, inhibition of T-cells by dexamethasone occurs within 10 min in a GR dependent manner and this is dynamic, with the number of membrane-GR positive lymphocytes increasing with increasing activation of the immune system and autoimmune disease severity. Physiological doses of hydrocortisone have also been shown to rapidly activate endothelial nitric oxide synthase (eNOS) in neuro-vascular tissue by non-genomic mechanisms.

Epigenetics

Epigenetics refers to changes in the genome, which occur without modifying the DNA sequence. Although previously thought to be long term and heritable, it is emerging that these modifications can be short term and highly dynamic. In this way, genes can be activated or repressed and a genetic output based on previous experience can be generated.

It has long been known that the HPA axis can be programmed by early life events and that previously encountered stress, such as maternal separation, child abuse, or exposure to endotoxin alters the way in which the HPA responds to stressors encountered later in life. Exposure to early life stress appears to sensitize the HPA, such that an exaggerated and more rapid stress response is seen in later life. Epigenetic mechanisms are thought to account for this, particularly DNA methylation of the GR promoter region. There is, however, no work on the influence of epigenetics on the cortisol response and outcome of major surgery and critical care in humans.

Adrenal control in chronic disease

Altered patterns of glucocorticoid secretion occur in chronic disease states including major depression, obstructive sleep apnoea, and immune mediated arthritides. Although patients with inflammatory conditions are often treated with exogenous steroids, pathophysiological levels of glucocorticoid play an important role in modulating inflammation. At a basic level, this can be seen with the inflammatory arthritides, where ‘morning stiffness’ follows the period of overnight low cortisol and in experimental models, adrenalectomized rats show an increase in the disease severity of induced arthritis. The changes in secretory patterns of cortisol seen during chronic illness are that the pulses of cortisol in the ultradian rhythm increase in amplitude and the adrenal glands continue to pulse during the night-time nadir phase. This leads to the well recognized features of an overall increased cortisol levels with ‘blunting’ of the diurnal rhythm. In obstructive sleep apnoea, these patterns return to normal after a period of treatment with night-time continuous positive airway pressure.

Inflammation and inflammatory mediators drive the increased production of the anti-inflammatory glucocorticoids, and despite the activity of the classical negative feedback loop the cytokine induced activation of the HPA overcomes this. However, long-term exposure to these increased levels of glucocorticoid can result in resistance. About one-third of patients fail to respond to exogenous steroids in inflammatory diseases and leukemias. Glucocorticoid resistance can occur because of abnormalities in the GR itself or nuclear importing machinery and may be inherited or induced. Inherited glucocorticoid resistance often leads to raised circulating levels of cortisol, but without the stigmata of Cushing’s disease. Induced glucocorticoid resistance has been most extensively studied in chronic diseases such as asthma, rheumatoid arthritis and inflammatory bowel disease. These inducible changes are attributable to downregulation of GR numbers in those with raised glucocorticoids and changes induced by the pro-inflammatory cytokines of the disease process itself. The clinical effects of these changes in critical illness has still not been established. However, induced changes are beginning to be elucidated in sepsis and critical illness.
via similar mechanisms to those in chronic disease. Teasing out which patients may need increased doses of steroid to overcome resistance and even whether this is useful at all is still to be established.

Endogenous glucocorticoid secretion may be reduced either as a result of feedback from exogenous glucocorticoid therapy or as a result of primary adrenal, pituitary or hypothalamic disease. Studies in patients on adrenal hormone replacement therapy have revealed how important the secretory pattern of glucocorticoids is for health. Not only do patients who are on ‘optimal’ replacement glucocorticoids complain of weariness, fatigue and stress intolerance, but patients with Addison’s disease who are receiving cortisol replacement have double the mortality of the general population of the same age-group. It is clear that these patients on non-pulsatile hormone replacement will have abnormal regulation of GR responsive genes, including those in the immune system. The drive towards less frequent dosing of medicines is not appropriate for glucocorticoids and this is leading to the development of novel drug delivery systems that recreate normal ultradian rhythms.

Adrenal control in major surgery and critical illness

Major surgery and critical illness are both significant challenges to homeostasis. They both activate compensatory autonomic and neuro-endocrine systems, of which a pivotal one is the HPA axis. Total levels of cortisol increase, as does CBG, although tissue levels of free cortisol are difficult to calculate as CBG saturation, increase in body temperature, acidosis, and neutrophil activity all act to increase the free fraction of cortisol. It is likely that this may result in differential levels of free cortisol in different tissues.

Initially, production of the pro-inflammatory cytokines; tumour necrosis factor α (TNF-α) and interleukins-1 (IL-1) and IL-6 cause direct stimulation of CRH and ACTH from the hypothalamus and pituitary respectively. This drives an overall increase in plasma cortisol levels. While plasma levels of cortisol remain persistently elevated after major surgery, by the first postoperative day, ACTH has returned to normal or below preoperative levels. This implies that the mechanisms controlling cortisol output from the adrenal are different, or are at least sensitized differently in those with acute systemic inflammation. It is possible that some of the increased adrenal sensitivity comes from increased splanchnic nerve firing and in response to inflammatory mediators.

The inflammatory mediators TNF-α, IL-1 and IL-6 have disparate effects on adrenal production of cortisol. TNF-α and IL-6 work directly via receptor mediated mechanisms, while IL-1 appears to mediate its effects indirectly by local release of prostaglandins. Although not fully elucidated, it appears that TNF-α has both inhibitory and stimulatory effects on the adrenal production of cortisol. Overall, it has been shown that at low concentrations of TNF-α the inhibitory effects dominate and at higher concentrations the stimulatory effects dominate. However, much of this work is in adrenal cell culture and not in vivo. IL-6 has been well studied and has universally been found to increase cortisol secretion in a dose dependent manner, with a high density of receptors in both the zona fasciulata and pituitary. It is somewhat slow to exert this effect on the adrenals; requiring between 12–24 h of stimulation for zona fasciulata cells to produce more cortisol. IL-1 has been less well studied, but again, also appears to increase cortisol production.

Stimulation with stressors at different phases during the ultradian pulse cycle results in different outcomes. Animal models that were stressed during the rising phase of a pulse showed an exaggerated glucocorticoid response compared with their response during the decreasing phase of a pulse—an effective refractory period. The mechanisms controlling this are unclear but computational modelling suggests that it is the coupling between the stress induced hypothalamic input and the rhythmicity of pituitary-adrenal network that governs the response to a stressor. The impact of acute stressors such as surgery during different phases of the pulse cycle in humans has not been studied. Both characterizing and elucidating the control and impact of ultradian rhythms in this situation is the subject of ongoing work.

HPA control in those taking exogenous steroids

It is relatively well known that patients on corticosteroids have a reduced basal secretion of cortisol and a reduced response to stress as a result of negative feedback. Normal ultradian pulsatility is blunted by even small doses of exogenous steroid, such as that found in skin treatment creams.

Patients having major surgery who are taking supplementary steroids have traditionally been given increased doses during the perioperative period to cover the ‘stress’ response. A number of studies have shown that in terms of haemodynamic and mortality outcomes, this is probably not required (this does not apply to those on physiological replacement for Addison’s disease, who are unable to produce any cortisol). Converting patients’ regular steroids to an i.v. equivalent if they are unable to take medication by mouth is all that is needed, even for major surgery. This is in contrast with what happens in critical illness, where supplementary hydrocortisone appears to improve haemodynamic, but not mortality outcomes (see Table 1). This highlights the gap in our understanding between the physiology of the HPA under ‘stress’ and what happens in clinical randomized controlled trials. All studies used patients taking <15 mg day⁻¹ prednisolone (or equivalent) and many had abnormal responses to synthetic ACTH. Until we characterize ‘normal’ responses, we do not know if it is the combination of supplementary steroids and endogenous production that meets the patient’s need, or if it is the exogenous steroids alone. Stopping or reducing a patient’s steroids abruptly in
<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>Bolus / Infusion</th>
<th>Duration of drug</th>
<th>Patients = n</th>
<th>Shock reversal</th>
<th>Mortality effect</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprung 2008</td>
<td>Hydrocortisone</td>
<td>50 mg 6 h</td>
<td>Bolus</td>
<td>5 days full dose</td>
<td>499</td>
<td>Total numbers of patients with shock reversed similar (hydrocortisone 79.7%, placebo 74.2%, (P = 0.18)). Shock reversed faster in those receiving hydrocortisone ((P &lt; 0.001))</td>
<td>No difference at 28 days (hydrocortisone 34.3%, placebo 31.5%, (P = 0.51))</td>
<td>Increased superinfections, hyperglycaemia and hypernatraemia in hydrocortisone group</td>
</tr>
<tr>
<td>Cicarelli 2007</td>
<td>Dexamethasone</td>
<td>0.2 mg kg(^{-1}) 36 h</td>
<td>Bolus</td>
<td>3 doses</td>
<td>29</td>
<td>Duration of vasopressors less in dexamethasone group (71.9 h vs 91 h, (P = 0.042))</td>
<td>Higher mortality in placebo group at 28 days (dexamethasone 50%, placebo 80%, no (P)-value)</td>
<td>Nil</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>Hydrocortisone</td>
<td>200 mg load then 10 mg h(^{-1})</td>
<td>Infusion</td>
<td>7 days</td>
<td>46</td>
<td>Not assessed</td>
<td>Survival to hospital discharge 100% in hydrocortisone group and 70% in placebo ((P = 0.009))</td>
<td>Nil</td>
</tr>
<tr>
<td>Oppert 2005</td>
<td>Hydrocortisone</td>
<td>50 mg load then 0.18 mg kg(^{-1}) h(^{-1}) then 0.06 mg kg(^{-1}) h(^{-1}) after shock reversal</td>
<td>Infusion</td>
<td>Until shock reversal</td>
<td>41</td>
<td>Duration of vasopressor shorter in hydrocortisone group (53 h vs 120 h, (P = 0.02))</td>
<td>No difference at 28 days (hydrocortisone 39% vs placebo 48% (P = 0.06))</td>
<td>Nil</td>
</tr>
<tr>
<td>Annane 2002</td>
<td>Hydrocortisone/Fludrocortisone</td>
<td>Hydrocortisone 50 mg every 6 h and fludrocortisone 50 mcg once a day</td>
<td>Bolus</td>
<td>7 days</td>
<td>300</td>
<td>Duration of vasopressor shorter in hydrocortisone group (7 days vs 9 days, (P = 0.01))</td>
<td>No difference at 28 days (hydrocortisone 55%, placebo 61%, (P = 0.09))</td>
<td>Nil</td>
</tr>
<tr>
<td>Yildiz 2002</td>
<td>Prednisolone</td>
<td>5 mg at 0600 2.5 mg at 1800</td>
<td>Bolus</td>
<td>10 days</td>
<td>40</td>
<td>Not assessed</td>
<td>No difference at 28 days (prednisolone 40%, placebo 60%, (P = 0.34))</td>
<td>Nil</td>
</tr>
<tr>
<td>Briegel 1999</td>
<td>Hydrocortisone</td>
<td>100 mg load then 0.18 mg kg(^{-1}) h(^{-1}) then 0.08 mg kg(^{-1}) h(^{-1}) after shock reversal</td>
<td>Infusion</td>
<td>6 days then taper</td>
<td>40</td>
<td>Duration of vasopressor shorter in hydrocortisone group (2 vs 7 days, (P = 0.005))</td>
<td>No difference at discharge from ICU (hydrocortisone 20%, placebo 30%, (P = 0.072))</td>
<td>Hypernatraemia and raised serum alanine transferase levels</td>
</tr>
<tr>
<td>Chawla 1999</td>
<td>Hydrocortisone</td>
<td>100 mg every 8 h</td>
<td>Bolus</td>
<td>3 days then taper</td>
<td>44</td>
<td>Duration of vasopressor shorter in hydrocortisone group (74 vs 122 h, (P &lt; 0.005))</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Bollaert 1998</td>
<td>Hydrocortisone</td>
<td>100 mg every 8 h</td>
<td>Bolus</td>
<td>5 days</td>
<td>41</td>
<td>Seven-day reversal of shock higher in hydrocortisone group (68 vs 21%, (P = 0.007))</td>
<td>Mortality was higher in the placebo group (63 vs 32%, (P = 0.045))</td>
<td>Nil</td>
</tr>
</tbody>
</table>
or near the perioperative period is associated with hypoten-

d sion and haemodynamic compromise.76

**Therapeutic use of glucocorticoids in major surgery and critical care**

The use of glucocorticoids in major surgery and critical illness is still controversial. The research can be framed into two questions: first, is there a group of patients among the critically ill who are in a state of relative adrenal insufficiency (and how is this diagnosed) and secondly, do therapeutic glucocorticoids improve outcome in major surgery and critical illness?

Sub-optimal adrenal function has been recognized as a cause of circulatory failure since 1911,79 and interest in testing for relative adrenal insufficiency (now termed Critical Illness Related Corticosteroid Insufficiency—CRII80) in the context of septic shock since the 1950s.81 82 Despite multiple attempts to identify who these patients are using point measurements and changes in cortisol83 and free,83 –85 synthetic ACTH tests,83 –86 eosinophil counts,83 urinary,87 and salivary cortisol,88 none have been shown to be functionally useful at detecting this subset of the population.80 Ultradian pulsing of cortisol shows that cortisol can vary in the same patient by up to 600 nmol litre\(^{-1}\) within an hour.89 Therefore, any test that uses a small number of cortisol measurements is likely to be unhelpful in diagnosis.

**Therapeutic glucocorticoids in sepsis and critical care**

The question of whether glucocorticoids in major surgery and critical illness are useful is separate to that of those who are ‘relatively deficient’. Despite consensus statements80 and large-scale reviews,90 –92 there is no robust evidence that glucocorticoids reduce mortality or other measures of outcome in the critical care unit, although there is a trend towards a shorter duration of vasopressor use and ventilator times. These reviews and meta-analyses all include disparate studies using different synthetic glucocorticoids, given at different doses, using both continuous infusions and boluses for differing time periods. This is important, as not all exogenous steroids have the same transcriptional or physiological effect93 and in chronic disease, it appears to be both the amount and pattern of glucocorticoid that affect outcome.61

Most recent studies have used hydrocortisone at ‘low-dose’ (<300 mg day\(^{-1}\)). CORTICUS96 is the largest of these (499 patients) and used 6 hourly bolus doses of 50 mg. CORTICUS showed no difference in terms of death, although shock was reversed more rapidly in those receiving hydrocortisone. It was however underpowered, with only 62% of the number of patients recruited required to achieve adequate power. As CORTICUS was published in 2008, we could find no new randomized controlled trials of corticosteroids alone vs placebo in sepsis.

Five randomized trials comparing low-dose hydrocortisone alone to placebo were published before 2008 (see Table 1)—the sum total of patients in all of these other studies is significantly less than the number of patients in CORTICUS. Again, they are methodologically disparate, with some using bolus doses95 96 and some using infusions.97 –99 As we have seen previously, associating these in the same group may not be helpful, as different patterns of GR-ligand binding may lead to quantitatively and qualitatively different transcriptional outcomes.90 –92 The one study comparing bolus doses to continuous infusions assessed outcome in terms of blood-glucose control, not mortality.100 Other studies of so-called ‘low-dose’ corticosteroids in sepsis have included prednisolone101 and dexamethasone.102 The heterogeneous nature of the dosing regimes and drugs associated with small sample sizes makes real conclusions from any study or meta-analysis fraught with uncertainty.

Studies of high-dose (immunosuppressive) corticosteroids in sepsis halted in the late 1980s, when a number of studies showed that high-dose steroids effected little difference in outcome at the expense of higher rates of superinfection.103 –105 106 –108 This was with the exception of Schurner and colleagues,109 where there was a remarkably lower mortality in those receiving steroids (see Table 2).

The clinical bottom line is that evidence for the use of any corticosteroids in critical care is lacking, mainly because of disparate, underpowered trials and heterogenous meta-analyses. There is a consistent trend that using low-dose hydrocortisone improves physiological parameters (time on ventilator, time on vasopressors), although not mortality, without deleterious effects. However, as we still have no accurate model for ‘normal’ adrenal function and control in critical illness, it is likely that the optimal therapeutic regimen is still some way off.

**Therapeutic glucocorticoids in cardiac surgery**

Steroids theoretically offer benefits in cardiac surgery, as it is a large, sterile physiological insult. The effect of supplemental steroids in cardiac surgery is similar to other interventions that have attempted to reduce the inflammatory response; there is robust evidence for biochemical improvement, but this does not translate to a survival benefit. Evidence for the use of corticosteroids in cardiac surgery also suffers from many of the problems of their use in critical care; heterogeneity and small sample sizes using differing steroids and dose regimens. Small sample sizes are a particular problem when studying cardiac surgery; UK survival rates for cardiac surgery are >98%110 and therefore large trials are required to achieve adequate power to detect even small changes in mortality.

The profile of clinical studies in cardiac surgery is also slightly different to that in sepsis, in that the vast majority of studies investigate the effects of methylprednisolone and dexamethasone. This may reflect investigators perceptions that improvements in outcome will come from suppressing the inflammatory response of cardiac surgery rather than treating a group of patients who are relatively deficient in endogenous corticosteroids or utilizing their permissive effects on vasculature as suggested by the use of low-dose hydrocortisone, the prevalent drug in recent sepsis trials.
**Table 2. Trials of ‘high-dose’ glucocorticoids (>300 mg day\(^{-1}\) hydrocortisone equivalent) in sepsis and critical care**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>Bolus/infusion</th>
<th>Duration of drug</th>
<th>Patients = n</th>
<th>Shock reversal</th>
<th>Mortality effect</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luce 1988(^{105})</td>
<td>Methylprednisolone</td>
<td>30 mg kg(^{-1}) every 6 h</td>
<td>Bolus</td>
<td>4 doses</td>
<td>87</td>
<td>Not assessed</td>
<td>No difference (methylprednisolone mortality 57 vs 54%)</td>
<td>Nil</td>
</tr>
<tr>
<td>Bone 1987(^{116})</td>
<td>Methylprednisolone</td>
<td>30 mg kg(^{-1})</td>
<td>Bolus</td>
<td>4 doses</td>
<td>382</td>
<td>No difference</td>
<td>Mortality at 14 days higher in the methylprednisolone group (34 vs 25%)</td>
<td>Higher rate of secondary infection in methylprednisolone group</td>
</tr>
<tr>
<td>VASSCSG 1987(^{103})</td>
<td>Methylprednisolone</td>
<td>30 mg kg(^{-1}) load then 5 mg kg(^{-1}) h(^{-1})</td>
<td>Infusion</td>
<td>9 h</td>
<td>223</td>
<td>Not assessed</td>
<td>No difference at 14 days (methylprednisolone 21 vs 22%, (P=0.97))</td>
<td>Resolution of secondary infection lower in methylprednisolone group</td>
</tr>
<tr>
<td>Sprung 1984(^{108})</td>
<td>Methylprednisolone (MP) Dexamethasone (D)</td>
<td>MP 30 mg kg(^{-1})</td>
<td>Bolus</td>
<td>2 doses</td>
<td>59</td>
<td>Shock reversal at 24 h: M 19%, D 32%, placebo 0%, (P&lt;0.05) steroid vs placebo</td>
<td>No difference hospital mortality (MP 76%, D 77%, placebo 69%)</td>
<td>Higher rate of superinfection in steroid groups</td>
</tr>
<tr>
<td>Lucas 1984(^{107})</td>
<td>Dexamethasone</td>
<td>6 mg kg(^{-1})</td>
<td>Infusion</td>
<td>48 h</td>
<td>48</td>
<td>Not assessed</td>
<td>No difference (dexamethasone 22 vs 20%)</td>
<td>Nil</td>
</tr>
<tr>
<td>Schumer 1976(^{109})</td>
<td>Dexamethasone (D) Methylprednisolone (MP)</td>
<td>D 3 mg kg(^{-1}) MP 30 mg kg(^{-1})</td>
<td>Bolus</td>
<td>Up to 2 doses</td>
<td>172</td>
<td>Not assessed</td>
<td>Mortality: D 9.3%, MP 11.6%, placebo 38.4%, no (P)-value given</td>
<td>No difference</td>
</tr>
<tr>
<td>Klastersky 1971(^{106})</td>
<td>Betamethasone</td>
<td>0.5 mg kg(^{-1}) every 12 h</td>
<td>Bolus</td>
<td>3 days</td>
<td>85</td>
<td>Not assessed</td>
<td>No difference (betamethasone 48 vs 46%)</td>
<td>Higher rate of superinfection in steroid treated (24% vs 15%)</td>
</tr>
</tbody>
</table>
Three large meta-analyses have been published in the previous 5 years.\textsuperscript{91 111 112} None of them could demonstrate a survival benefit. Two of them showed benefits with regard to morbidity (atrial fibrillation and length of stay), which was not offset by side-effects.\textsuperscript{111 112} The Cochrane analysis,\textsuperscript{91} which included somewhat more detailed statistics, showed a reduction in atrial fibrillation only, but at the expense of an increase in gastrointestinal bleeding.

It is again difficult to discern a clinical conclusion from studies of steroid use in cardiac surgery in the face of available evidence. Huge, multicentre trials are required to demonstrate a survival benefit from supplementary steroids. However, smaller numbers would be needed to elucidate a clinically (and financially) important difference in critical care stay and vasopressor use if there were one. This is currently happening, with two randomized controlled trials; The Dexamethasone for Cardiac Surgery (DECS) Trial\textsuperscript{113} (n=4,494) which has recently reported and the SIRS (Steroids In CaRdiac Surgery: http://www.clinicaltrials.gov: study number NCT00427388) which has a n=7500 patients and has currently recruited around one-third of these. The DECS trial gave single bolus, high-dose (1 mg kg\textsuperscript{-1}) dexamethasone to patients having cardiac surgery with cardiopulmonary bypass. It did not show any significant difference in a composite outcome of death, myocardial infarction, stroke, renal or respiratory failure within 30 days. There was a reduction in length of mechanical ventilation, intensive care unit, and hospital stays in the dexamethasone group, and post-operative infection and at the expense of higher glucose levels. The SIRS trial is using methylprednisolone and is still to finish recruiting. A focus switch from immunosuppression to augmentation of cardiovascular effects using low-dose hydrocortisone may also provide an important area of investigation.

**Therapeutic glucocorticoids in major non-cardiac surgery**

Glucocorticoids have wide-ranging effects and as such, form part of the therapeutic regimen for numerous other areas of surgery. The heterogenous nature of this area, in both the type of drugs and outcomes for which they are used make review of this subject well beyond the scope of this article. Although not immediately obvious, characterizing the HPA axis response in minor surgery may be important for our understanding of major surgery and critical illness. It provides a natural model of an acute insult without high concentrations of systemic inflammatory mediators and without marked changes in plasma proteins.

**Future directions**

The key to improving care is to understand the pathophysiology of the HPA axis in critical care and major surgery. We still have no truly detailed model of ‘normal’ adrenal functioning in these situations. Until we have done this, we cannot hope to move forward with diagnostic and therapeutic studies.

Simple questions that need answering are: does ultradian pulsatility persist in this context? Is the pattern of secretion important in terms of morbidity and mortality outcomes? If a ‘normal’ response is pulsatile what are the downstream effects and does this translate to fluctuating levels of free cortisol? Further downstream, what is the effect at a receptor and transcriptional level? Moving upstream, to what extent do ACTH, the splanchnic nerves and inflammatory mediators each drive the adrenal glands in critical illness (if at all)? Once we begin to answer these questions we can use that knowledge to design meaningful tests of HPA function in critical illness and begin to offer an optimal therapeutic regimen.

**Conclusions**

The HPA axis is a system that has multiple effects on almost all tissues of the body and plays a crucial role in regulating inflammation. Levels of cortisol fluctuate throughout the day in a diurnal rhythm, underlying which is an ultradian rhythm of approximately hourly pulses, which affects transcriptional outcomes. Pulsatility is not the result of a ‘pulse generator’, but is inherent within the system. These patterns of secretion change in both acute and chronic illness as a result of inflammatory mediators, splanchnic nerve output and central nervous system control. Levels of cortisol in both normal and illness states are highly dynamic and so static assessment tools for diagnosing corticosteroid related critical illness insufficiency not likely to be useful. Knowledge of ‘normal’ adrenal output in different states of critical illness and major surgery are likely to be required before the optimal dosing regimen is found.

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**Declaration of interest**

None declared.

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**References**

molecules CBP/p300 during ultradian ligand treatment. Mol Endocrinol 2011; 25: 944–54


27. Bartholome B, Spies CM, Gaber T, et al. Membrane glucocorticoid receptors (mGCR) are expressed in normal human peripheral blood mononuclear cells and up-regulated after in vitro stimulation and in patients with rheumatoid arthritis. Faseb J 2009; 150: 70–80


inflammation during sepsis and acute respiratory distress syn-
drome. Evidence for inflammation-induced target tissue resist-

health status in 256 patients with adrenal insufficiency on
standard therapy based on cross-sectional analysis. *J Clin Endo-
crinal Metab* 2007; 92: 3912–22

61 Berghorsdottir R, Leonsson-Zachrisson M, Oden A,
Johannsson G. Premature mortality in patients with Addison's
disease: a population-based study. *J Clin Endocrinol Metab*
2006; 91: 4849–53

62 Caputo M, Alwair H, Rogers CA, et al. Myocardial, inflammatory,
and stress responses in off-pump coronary artery bypass graft
surgery with thoracic epidural anesthesia. *Ann Thorac Surg*
2009; 87: 1119–26

63 Roth-Isiggkeit AK, Schmucker P. Postoperative dissociation of
blood levels of cortisol and adrenocorticotropin after
corona artery bypass grafting surgery. *Steroids* 1997; 62:
695–9

64 Vermes I, Beisluizen A, Hampsink RM, Haenen C. Dissociation
of plasma adrenocorticotropin and cortisol levels in critically ill
patients: possible role of endothelin and atrial natriuretic
hormone. *J Clin Endocrinol Metab* 1995; 80: 1238–42

65 Martich GD, Boujoukos AJ, Suffredini AF. Response of man to

66 Judd AM, Call GB, Ranney WJ, et al. Possible function of IL-6 and
TNF as proinflammatory factors in the regulation of adrenal steroid

67 Winter JS, Gow KW, Perry YS, Greenberg A. A stimulatory effect of
continuous positive airway pressure therapy. *Am J Respir Crit
Care Med* 2000; 162: 134–41


79 Waterhouse R. Case of suprarenal apoplexy. *Lancet* 1911; 1: 577


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