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## **Hypothalamic-Pituitary-Adrenal (HPA) function during Health, Major Surgery and Critical Illness**

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### **Key Points:**

- The circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis is composed of 45-60 minute pulses of cortisol, known as an ultradian rhythm.
- The corresponding pulsatility in cortisol-receptor binding is important for normal functioning with varying effects on gene transcription.
- Cortisol binding globulin (CBG) acts as a reservoir and effectively delivers free cortisol to inflammatory sites.
- The value of point assessments of HPA axis function in the Intensive Care Unit is therefore probably of minimal use other than to diagnose *absolute* deficiency.

The basic constituents of the hypothalamic-pituitary-adrenal (HPA) axis will be familiar to most physicians because the “stress response” is seen following any significant illness, injury or surgery. However, this article seeks to highlight the substantial advances in understanding that have been made in the last decade and how these may alter treatment and guide future research.

### **The Hypothalamic-Pituitary-Adrenal Pathway**

A simple schematic of the HPA axis can be seen in Fig 1<sup>1</sup>. The paraventricular nucleus (PVN) of the hypothalamus is the ‘control centre’ of the HPA axis. It receives input from multiple other centres:

*Suprachiasmatic nucleus (SCN):* The body’s “biological clock” provides diurnal information, modulating inhibitory gain to the PVN, resulting in low activation during periods of sleep, increasing in anticipation of awakening and peaking in the morning, the basis of the circadian rhythm.

*Brainstem nuclei:* Delivers information from physiological changes such as hypotension or inflammation.

*Limbic region:* Provides stimulation from cognitive or emotional stressors.

*Sympathetic/Sensory:* In addition to higher centre inputs at the hypothalamus, there is also extensive sensory and sympathetic innervation to the end target, the adrenal glands, via the splanchnic nerves. Both cholinergic pre-ganglionic and catecholaminergic postganglionic sympathetic fibres synapse at the adrenal gland and appear to sensitise it to adrenocorticotrophic hormone (ACTH), increasing cortisol release. This is probably an indirect effect - vasodilation leads to a higher adrenal blood flow which in turn means more cortisol output. Furthermore, the adrenal gland has autonomous clock genes exerting additional circadian control on steroidogenesis and ACTH sensitivity. This effect may be modulated directly by light as well as possibly via splanchnic innervation.

The PVN contains two types of neuroendocrine cells:

Magnocellular neurons synthesise arginine vasopressin (AVP - also known as anti-diuretic hormone, ADH), which is then transported to the posterior pituitary (an embryological down-growth from the hypothalamus), for storage and subsequent release.

Parvocellular neurons synthesise corticotrophin-releasing hormone (CRH), which is secreted from the median eminence of the hypothalamus into the hypophyseal portal circulation. CRH acts upon corticotrophs in the anterior pituitary prompting secretion of ACTH into the systemic circulation, which in turn stimulates cortisol release from the *zona fasciculata* of the adrenal cortex. Cortisol is synthesized *de novo*, secreted and circulating free cortisol then exerts a negative feedback effect at the pituitary to reduce ACTH secretion and inhibit CRH release at the PVN. "Normal" people under unstressed conditions normally produce the equivalent of about 20 – 25mg hydrocortisone per day.

**Fig 1 Near Here**

### **Ultradian Rhythm of ACTH & Cortisol**

The familiar circadian rhythm of cortisol and ACTH (high in the early morning and low in the late afternoon and evening) is in fact composed of an *ultradian* rhythm of pulses lasting around 45 – 60 minutes<sup>2</sup>. The peaks of the circadian rhythm are generated by high amplitude pulses and the troughs by smaller pulses, or non-pulsatile activity (see Fig 2). The term ultradian refers to any biological cycle that repeats more frequently than daily, whereas circadian rhythms follow a one-day cycle. This pulsatility used to be considered to come from a pulse generator within the hypothalamus, but recent studies have concluded that it is more likely generated from the positive feed-*forward* from the pituitary (ACTH) and negative feed-*back* relationship from the adrenal (cortisol)<sup>3</sup>. The driver 'pushing' the system is the hypothalamic CRH. It may be imagined on a simple level like a "Newton's Cradle" system; where ACTH and cortisol are two balls oscillating at alternate ends and CRH is the driving force to maintain and vary propulsion.

**Fig 2 Near Here**

Ultradian rhythms are relative commonplace in neurological and other neuroendocrine pathways responsible for maintaining homeostasis. Pulsatile signalling affords many benefits including greater signal control, higher energy efficiency and enables receptor recovery between pulses, which is essential for maintaining target responsiveness. Since pulses can vary in amplitude, duration, shape and frequency, pulsatile signalling also transmits much greater information to the target receptor when compared with continuous signalling. This can be illustrated by comparing a colour television image (where each pixel can vary in frequency and amplitude) to that of a black and white television (where pixels may only vary in amplitude). Since the ultradian pattern of ACTH and cortisol release is relatively newly determined, much of the research seeking to accurately quantify HPA activity in health and following injury or surgery may be inaccurate due to insufficient sampling frequency.

Pulsatility is important – patients with absolute cortisol deficiency (Addison's disease), who take physiological cortisol replacement but lack the pulses, are twice as likely to die as their peers<sup>4</sup>. Pulses of cortisol also exhibit characteristics of an effective refractory period - the same stressor applied at different phases of the ultradian cycle appears to elicit differing magnitudes of cortisol response. An exaggerated response occurs if the stressor is applied during the rising cortisol phase, whereas a much smaller or no response is generated when the same stimulus is applied during the falling phase of the cycle. Whether this also applies to humans during sepsis or following surgery remains as yet unstudied.

### **Cortisol Synthesis, Metabolism and Regeneration**

Like the other endogenous steroid hormones, cortisol is synthesised from cholesterol. Since cortisol is lipophilic and will readily pass through membranes, it cannot be packaged in vesicles, but instead must be rapidly manufactured *de novo*. Cortisol steroidogenesis begins with the binding of ACTH to the membrane bound G-protein coupled receptor (the melanocortin 2 receptor - MC2-R) on the surface of *zona fasciculata* cells. This triggers the cAMP - protein kinase A cascade which in turn activates steroidogenic acute regulatory protein (StAR) in the

mitochondria. StAR protein is important since it orchestrates the transportation of cholesterol from the outer to the inner mitochondrial membrane and is the rate-limiting step in steroidogenesis. Once inside the mitochondrion, cholesterol is converted into the steroid precursor, pregnenolone by Side Chain Cleavage enzyme (CYP450<sub>scc</sub>). Cortisol is then constructed via a series of enzyme catalysed steps within the mitochondrion and endoplasmic reticulum, before being released into the circulation.

Cortisol clearance occurs principally by hepatic metabolism via 5 $\alpha$ - and 5 $\beta$ -reductases and is eliminated by the kidneys via 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD) type 2. This is balanced by regeneration of cortisol from cortisone in the liver and adipose tissue by 11 $\beta$ -HSD type 1.

### **Cortisol Binding Globulin (CBG)**

As a steroid hormone, cortisol is fat soluble and thus relatively insoluble in plasma. As a result, it is highly protein bound; 80-90% to cortisol binding globulin (CBG), 10-15% to albumin, with only 5% remaining unbound and free to cross cell membranes and bind to receptors.

Cortisol binding globulin is a 50-60kDa protein, part of the serpin (serine proteinase inhibitor) family and is synthesised mainly in the liver. CBG is also found in small amounts in lung, kidney and testes tissue where it may have a role in regulating local cortisol levels within each organ. CBG is important because as a transporter and reservoir of cortisol in the blood, it plays a significant role in the fraction of free cortisol available to pass into cells. Each CBG molecule binds to one cortisol molecule and thus binding is saturable with a finite binding capacity. This characteristic of the system means it is extremely efficient, since any large pulse of cortisol exceeding the CBG binding capacity or physiological fall in the CBG level, will result in a significant increase in the free fraction of cortisol in the blood, amplifying the signal to the tissues. Serum CBG levels have a diurnal fluctuation, falling slightly in the day and increasing at night and thus accentuating the overall circadian rhythm of cortisol.

Cortisol is preferentially delivered to sites of inflammation by CBG. CBG behaves as a “thermocouple”, showing marked decline in affinity for cortisol at higher temperatures, such as during fever<sup>5</sup>. Cortisol is also liberated from CBG by activated neutrophils which release elastase, an enzyme that cleaves and irreversibly destroys CBG. Local inflammatory changes in pH do not affect CBG affinity, but do reduce the affinity of albumin to cortisol and therefore further enhance the effect.

### **Glucocorticoid Receptors**

Since glucocorticoids are lipophilic, they readily cross the phospholipid bilayer of cell membranes and bind to intracellular glucocorticoid receptors (GR). Stabiliser proteins aid the GR-ligand complex formation and cause dimerisation of two GR-ligand complexes. The dimerised GR-ligand complexes can then be transported into the cell nucleus, where they transiently bind to deoxyribonucleic acid (DNA), acting as effective transcription factors. The Glucocorticoid – Receptor complex oscillates on and off the DNA, with each interaction lasting 10-20 seconds. It is this rapid oscillation that allows HPA output to respond quickly to stressors. Although GR follows a ‘saturable’ pharmacokinetic pattern, we do not know at what concentration of cortisol the receptors are saturated in different tissues. The interaction of the ultradian rhythm with receptor binding is important for physiological functioning. Transcription of glucocorticoid responsive genes occurs in pulses that tracks the pulses of cortisol – i.e. pulsatile receptor binding leads to pulsatile gene expression<sup>6</sup>. The genetic output of glucocorticoids can be both positive (cause transcription) and negative (repress transcription) and be transient or continuous. The characteristics of this output is exquisitely sensitive to patterns, with pulsatile glucocorticoid exposure exerting a greater control over certain target genes and a smaller effect on others in comparison to constant presentation as is seen in glucocorticoid based therapeutics.

Some effects of glucocorticoids are too fast to be the result of transcription, with effects seen in seconds or minutes (transcription takes 20 – 40 minutes). Thus some glucocorticoid receptors are membrane bound and act via ion channels and secondary messenger systems. These can cause T-cell inhibition in the immune

system and activation of endothelial nitric oxide synthase (eNOS) in neurovascular tissue.

### **HPA Axis function following Major Surgery or Critical Illness**

Significant stressors, such as major surgery or critical injury or illness, pose significant challenges to the body's homeostasis. They trigger compensatory autonomic and neuro-endocrine mechanisms, some of which are fairly primitive in evolutionary terms. The HPA axis is pivotal to the body's homeostatic response and has evolved to react rapidly, with an amplification of effect: Increased cortisol production, reduced circulating CBG and albumin levels, with a reduced affinity for cortisol, all leads to a net increase in both total and free serum cortisol. Cortisol clearance also seems to be reduced during major stress, such as severe sepsis<sup>7</sup>. This is possibly as a result of the accumulation of circulating bile salts inhibiting the enzymes that breakdown cortisol or a reduction in liver and kidney perfusion. CBG cleavage by neutrophil activity ensures cortisol is optimally targeted at areas of inflammation.

In addition to stimulation of the higher inputs to the hypothalamus, production of pro-inflammatory cytokines; tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukins - 1 and -6 (IL-1 and IL-6) cause direct stimulation of CRH and ACTH. Over the first 24 hours, ultradian pulses in ACTH and cortisol are seen to be significantly magnified<sup>8</sup> (See Fig 3). However, by the first postoperative day, ACTH levels typically return to normal, whereas cortisol pulses remain elevated. This suggests that the mechanisms controlling the adrenal output may be different or sensitised differently in acute systemic inflammation.

### **Fig 3 Near Here**

The inflammatory cytokines TNF- $\alpha$ , IL-1 and IL-6 have varied effects on the adrenal gland. There is a high density of IL-6 receptors in the *zona fasciculata* of the adrenal gland and the *corticotroph cells* of the pituitary. They increase cortisol production in cell culture, in animal models and in humans. IL-1 also increases cortisol synthesis, but to a lesser extent. TNF- $\alpha$  has different effects on cortisol



synthesis depending on the concentration; at low concentrations inhibitory effects appear to dominate and at higher concentrations stimulatory effects predominate.

### **Modulation of the HPA axis response to Surgery**

HPA axis activation and elevated cortisol levels should be regarded as a response to the inflammation rather than a driver. Therefore, in broad terms, the greater the tissue damage, the greater the levels of activation of the HPA axis and the higher the cortisol level. However, this is a rather one-dimensional way of looking at the HPA axis after surgery – the timing of the rise and patterns are also important. For example, laparoscopic cholecystectomies have an earlier rise in cortisol than open cholecystectomy, although overall levels are higher and persist longer in the open cholecystectomies.

Multiple strategies have been tried to modulate HPA axis activity around the time of surgery, although it is difficult to see what benefit reducing cortisol production in response to the same operation brings. An *appropriate* amount of corticosteroid is required to protect the body from uncontrolled inflammation at one end of the spectrum and circulatory failure at the other – high-dose corticosteroids are associated with a poor outcome, as is too little. It must be remembered that the high-dose exogenous steroids associated with poor outcomes (methylprednisolone in sepsis<sup>9</sup> and head injury<sup>10</sup>) have potencies many times more than is physiologically possible.

Effective neuraxial anaesthesia can block the somatic and autonomic innervation to both the hypothalamus and directly at the adrenals, and so could potentially reduce HPA activation. Systemic analgesics can directly and indirectly affect the HPA axis - for example, opioids suppress the hypothalamic-pituitary-gonadal-adrenal pathway. Chronic opioid use is well recognised to cause hypogonadism and occasionally adrenal suppression. Use of non-steroidal-anti-inflammatory drugs prior to surgery can reduce levels of inflammatory mediators, but has no *direct* effect on the HPA axis. Reducing the inflammatory response to surgery is

best achieved by adjusting surgical technique to minimise tissue damage, for example by using minimally invasive surgery.

### **HPA Axis Dysfunction and Critical Illness**

The link between adrenal dysfunction and circulatory failure has been recognized for over a century. In patients with septic shock who are resistant to standard treatment (antibiotics, fluids, vasopressors and inotropes), a syndrome of relative adrenal insufficiency has been postulated – Critical Illness Related Corticosteroid Insufficiency (CIRCI). This has also been postulated to exist in many other syndromes of systemic inflammation, such as burns. However, crystallisation of this phenomenon has proved elusive, with measurements of serum, urine and salivary cortisol, ACTH responsiveness and eosinophil count all seeming of little value. This was reflected in the consensus guidelines produced by the American College of Critical Care Medicine in 2008<sup>11</sup>. Given that cortisol (and ACTH) may vary by up to 600nmol/l during the ultradian pulse, any test involving infrequent cortisol measurement or ACTH responsiveness is unlikely to be useful in this set of patients. Whether in fact this group of patients does really exist and how to diagnose and treat them is yet to be established.

### **Therapeutic use of Corticosteroids during Critical Illness**

The use of exogenous corticosteroids during critical illness and their benefits is a different and equally contested debate. Use of high dose corticosteroids (>400mg hydrocortisone or equivalent per day) at immunosuppressive doses in sepsis has been discarded since the mid 1990's when multiple studies and two meta-analyses revealed no outcome improvement and a potential increase in the incidence of superinfection. Over the last two decades, attention has focused on lower doses of corticosteroids (<400mg hydrocortisone or equivalent per day). The first major randomised controlled trial was published by Annane *et al.* in 2002<sup>12</sup>. It concluded that there was no overall mortality benefit with the use of corticosteroids in sepsis, although perhaps there was a benefit in those failing an ACTH stimulation test. CORTICUS, the largest randomised control trial to date, recruited 600 patients and showed no mortality benefit with corticosteroid use even in that cohort of patients considered to have 'adrenal insufficiency'<sup>13</sup>. Use of

random cortisol levels or the ACTH stimulation test as a marker of adrenal insufficiency in sepsis has subsequently been discredited and is no longer advocated. The latest and largest RCT to compare hydrocortisone with placebo in septic shock, called ADRENAL ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT01448109), aims to recruit 3800 patients and started in 2012, with a proposed completion date of late 2016.

Large scale reviews and meta-analyses have regularly been undertaken to assess the role of steroids in sepsis of which the latest, the Cochrane review was published in December 2015<sup>14</sup>. All have included a disparate collection of smaller studies, which have used different synthetic corticosteroids, at a variety of doses and treatment durations, by bolus and continuous infusion - all factors which may result in very different physiological and transcriptional effects and outcome. Overall, the use of low-dose corticosteroids in sepsis may only have a small positive impact on all-cause mortality, but they do consistently appear to reverse shock more rapidly, reduce the number of ventilation days and length of stay on the ICU.

### **Corticosteroid Therapy in Cardiac Surgery**

Cardiac surgery evokes a significant acute inflammatory response both from use of cardiopulmonary bypass and tissue destruction from the surgery itself. There is a theoretical benefit of supplemental corticosteroids to obviate some of the inflammatory response. However, since survival rates following cardiac surgery are greater than 98%, extremely large trials are required to be of adequate power to demonstrate statistically significant changes in mortality. The vast majority of studies have looked at large, immunosuppressive doses of methylprednisolone and dexamethasone rather than the low-dose hydrocortisone predominant in sepsis. The two largest placebo controlled randomized trials have only recently been published; the DECS trial<sup>15</sup> in 2012, using a single dose of dexamethasone (n=4,494 patients) and the SIRS trial<sup>16</sup> in 2015, using methylprednisolone (n=7,507 patients). Neither study has revealed any significant difference in mortality or major morbidity and thus the routine use of corticosteroids in adult cardiac surgery is currently not justified.

### **Patients on Long-term Corticosteroids and Surgery**

There is no evidence that anything other than *absolute* corticosteroid deficiency is associated with circulatory failure after surgery. Traditionally, surgical patients likely to have a suppressed HPA axis from long-term steroid therapy would receive an increased dose of steroid during the perioperative period - the theory being to replicate the endogenous stress response following surgery. However, converting patients' regular steroids to an IV equivalent (see table 1) whilst they are not eating and drinking is probably all that is required, although many guidelines do not yet reflect this. The caveat to this are patients with Addison's disease, who are unable to produce ANY endogenous cortisol and thus **do** require larger steroid doses during the surgical period<sup>17</sup>.

### **Conclusion**

The HPA axis is a dynamic system that has evolved to rapidly respond to stressors. Cortisol secretion is pulsatile and this pulsatility has a real impact on physiological functioning in both health and disease. Normal function and control of the HPA axis after major surgery and critical illness is still not yet fully understood – nor is its place as an avenue of therapy for these conditions. Too much corticosteroid is associated with an excess mortality and morbidity, too little is associated with circulatory failure and death. Where the transition points are, we are still to find out.

**Table 1**

**Dose equivalency of corticosteroids**

<b>Corticosteroid</b>	<b>Equivalent Dose</b>
Hydrocortisone	40mg
Prednisolone	10mg
Triamcinolone	8mg
Methylprednisolone	8mg
Dexamethasone	1.5mg
Betamethasone	1.2mg

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## **Figure Legends**

Fig 1. Basic hypothalamic-pituitary-adrenal axis control. Arrows indicate positive feed-forward. Blocks indicate negative feedback. CNS – Central nervous system. SCN – supra-chiasmatic nucleus. PVN – paraventricular nucleus. CRH – Corticotrophic releasing hormone. ACTH – Adrenocorticotrophic hormone. (Reproduced with permission from reference 1)

Fig 2. 24 hour ACTH and cortisol profile of a healthy volunteer. The ultradian rhythm is seen underlying the diurnal rhythm. Diurnal highs are generated by large amplitude pulses and lows by smaller, or minimal activity. ACTH is seen to precede cortisol.

Fig 3. Stylised ultradian rhythms of cortisol in Healthy subjects and in those having cardiac surgery.

## **Table Legends**

Table 1. Dose equivalency of corticosteroids



## MCQ's : Hypothalamic-pituitary-adrenal (HPA) function during major surgery and critical illness

### Question

1.	Regarding the hypothalamic-pituitary-adrenal axis and the ultradian rhythm	
(a)	The suprachiasmatic nucleus (SCN) has an inhibitory effect on the paraventricular nucleus (PVN) and forms the basis of the circadian rhythm.	
(b)	Neurons in the paraventricular nucleus of the hypothalamus synthesise, oxytocin, arginine vasopressin and corticotrophin releasing hormone.	
(c)	The ultradian rhythm consists of hourly cortisol pulses which begin in the early morning and peak mid-morning.	
(d)	Loss of cortisol pulsatility is thought to be a factor in the increased mortality seen in patients with Addison's disease.	
(e)	The pulsatility of cortisol causes pulsatile gene expression within cells with varying transcriptional effects, but this system is inherently energy inefficient.	

### Answers

1.	(a)	True	The suprachiasmatic nucleus is the brain's "biological clock" providing diurnal information to the paraventricular nucleus and inhibiting hormone release.
	(b)	True	Oxytocin and arginine vasopressin are synthesised by magnocellular neurons in the paraventricular nucleus (PVN) and stored in the posterior pituitary. Corticotrophin releasing hormone (CRH) is synthesised by parvocellular neurons in the PVN and released from the median eminence of the hypothalamus.
	(c)	True	In health, pulses of ACTH and cortisol last 45-60 minutes and begin at about 2am or 3am in preparation for awakening. Pulses diminish after lunchtime. See fig. 2.
	(d)	True	The age related mortality for patients with Addison's disease is between two or three times higher than seen in the general population.
	(e)	False	Pulsatile signalling is believed to be highly energy efficient since it enables greater signal control, intricately varying gene transcription as well as allowing receptor recovery and optimising responsiveness.

### Question

2.	Cortisol	
(a)	Is stored in vesicles within the zona fasciculata of the adrenal cortex.	
(b)	Cortisol steroidogenesis is stimulated by binding of corticotrophin releasing hormone (CRH) to the membrane bound melanocortin 2 receptor (MC2-R) on the surface of zona fasciculata cells.	
(c)	The rate determining step in the production of cortisol is the transportation of cholesterol through the mitochondrial membrane by steroidogenic acute regulatory protein (StAR).	
(d)	Glucocorticoid receptors may be intracellular or membrane bound.	
(e)	Is metabolised predominantly by plasma 11 $\beta$ -hydroxylases.	

### Answers

2.	(a)	False	Cortisol is lipophilic and so not amenable to storage in vesicles, instead it is synthesised <i>de novo</i> .
	(b)	False	Cortisol steroidogenesis is stimulated by binding of adrenocorticotrophic hormone (ACTH) not corticotrophin releasing hormone (CRH).
	(c)	True	
	(d)	True	Glucocorticoid receptors (GR) may be intracellular, the GR-ligand complexes dimerising before binding to DNA within the cell nucleus and affecting gene transcription. Some GR's are membrane bound, G-protein coupled receptors or ion-gated ion channels and this binding accounts for the more rapid effects of corticosteroids.
	(e)	False	Cortisol is hepatically metabolised by 5 $\alpha$ - and 5 $\beta$ - reductases before being renally excreted. Cortisol is regenerated from cortisone by 11 $\beta$ -hydroxysteroidal dehydrogenase type 1 in the liver and fat cells.

### Question

3.	Cortisol binding globulin (CBG)	
(a)	Is synthesised predominantly in the liver.	
(b)	As a serpin (serine proteinase inhibitor), it is a larger protein than albumin with a molecular weight of 150-160kDa.	
(c)	Has a finite binding capacity which is typically exceeded during times of severe physiological stress.	
(d)	More than 75% of serum cortisol is bound to CBG.	
(e)	CBG affinity for cortisol alters with pH and temperature.	

### Answers

3.	(a)	True	Globulins are made in the liver, immunoglobulins by the immune system.
	(b)	False	Cortisol binding globulin has a molecular weight of 50-60kDa, Albumin is 60-70kDa. However, generally globulins have a larger molecular weight than albumins.
	(c)	True	Acting as a carrier and reservoir for cortisol in normal health and optimising delivery of free cortisol to target tissues in times of physiological stress.
	(d)	True	Typically 80-90% of cortisol is bound to cortisol binding globulin (CBG), 10-15% to albumin.
	(e)	False	CBG affinity for cortisol reduces with increasing body temperature, behaving as a "thermocouple", however it is unaffected by pH. The affinity of albumin to cortisol is reduced by reducing pH.

### Question

4.	Commencing a patient on intravenous hydrocortisone would be an appropriate treatment	
(a)	At a dose of 50mg four times daily until eating and drinking, in a 57 year old female presenting for laparoscopic cholecystectomy with rheumatoid arthritis, usually taking prednisolone 20mg daily.	
(b)	Urgently in a hypotensive 35 year old patient with Addison's disease presenting with acute severe abdominal and lower back pain, syncope, confusion, agitation and seizures and fever, with biochemistry results revealing hyponatraemia, hyperkalaemia and hypercalcaemia.	
(c)	For 3 to 5 days duration in a 70 year old male following routine aortic valve replacement surgery, to reduce the system inflammatory response to surgery and cardiopulmonary bypass.	
(d)	As an infusion at a rate of 20mg/hr in a 51 year old man with severe sepsis secondary to pneumonia, who is ventilated, with multiorgan dysfunction requiring noradrenaline, dobutamine and vasopressin infusions.	
(e)	100mg at induction and then four times daily until eating and drinking normally, in a 42 year old lady with Addison's disease having a total knee replacement, who usually takes 20mg oral hydrocortisone twice daily and 100 micrograms oral fludrocortisone daily.	

### Answers

4.	(a)	False	In this patient presenting for elective intermediate surgery, increasing the steroid dose to replicate the endogenous stress response is not necessary. One should plan to continue the patient's regular oral prednisolone regime. If they are unable to eat and drink, one might consider conversion to an intravenous equivalent. Prednisolone 5mg is equivalent to IV hydrocortisone 20mg.
	(b)	True	The symptoms and signs described are characteristic of acute adrenal crisis (Addisonian crisis). A life-threatening condition resulting from sudden cortisol insufficiency. Management includes HDU/ICU care, ventilatory support if necessary, IV fluids, vasopressors and inotropes, correction of electrolyte disturbances and hypoglycaemia, baseline cortisol + ACTH levels and treatment with hydrocortisone 100mg IV stat followed by 100mg four times a day and treating the precipitating cause.
	(c)	False	Two recent placebo controlled randomised trials have shown

		no major morbidity or mortality benefit associated with the use of corticosteroids following cardiac surgery. Thus routine use of hydrocortisone in this setting is not appropriate.
(d)	False	Commencement of hydrocortisone either via infusion or divided bolus doses might be considered appropriate treatment in a patient in septic shock resistant to treatment with vasopressors and inotropes. However, a rate of 20mg/hr (480mg/day) would be considered high-dose which is associated with an increased incidence of superinfection and no improvement in outcome.
(e)	True	Patients with Addison's disease, primary adrenal insufficiency, are unable to mount a stress response following surgery. They therefore require an increase in dose and frequency of their hydrocortisone regime. For further information consult the Addison's Disease Self Help Group (ADSHG) surgical guidelines, as recommended by NICE.