CORTICOSTEROIDS
USE IN SEVERE SEPSIS AND SEPTIC SHOCK

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CORTICOSTEROIDS USE IN SEVERE SEPSIS AND SEPTIC SHOCK

INTRODUCTION

In 1914, Schottmueller wrote, “Septicemia is a state of microbial invasion from a portal of entry into the blood stream which causes sign of illness.” (1) This definition has not changed much over the years.

It was only over the last few decades that we now understand the presence of endogenous mediators that coordinate the host response leading to the clinical syndrome of sepsis. The result of which is actually excessive activation of host defense mechanisms rather than the direct effect of microorganisms. Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity.

The use of corticosteroids in sepsis and septic shock has been extensively studied with renewed interest over the last decade. Earlier studies with high dose steroids showed on benefit with increased complications like superinfection. The landmark study by Annane and colleagues using low-dose corticosteroids swung the pendulum back in favour of the use of steroids. However, controversy still loams as conflicting findings in the use of corticosteroids were reported by the largest RCT to date, CORTICUS.

The aim of this talk is to review the latest information regarding cortisosterone use in sepsis and septic shock which is also part an MMed, the aim of which is to evaluate, by use of a questionnaire, the use of corticosteroids for severe sepsis and septic shock by specialists and intensivists in South African ICU’s.


**EPIDEMIOLOGY**

There is no epidemiological data reporting on severe sepsis and septic shock in the South African setting. A 1-day sepsis prevalence study was conducted by Bhagwanjee and co-workers looking at 43 ICU’s with a total sample of 248 patients. Sepsis was reported in 16.5% of patients, with severe sepsis in 4.8% of patients and septic shock in 6.5% of patients. (27) These figures are comparable to a report by Goldwasser and colleague who report the incidence of sepsis at 16.6% in Brazilian ICU’s with an associated mortality of 46.6%. (28)

Smith and colleagues investigated all patients admitted for septic shock in a 15 month period to a Johannesburg hospital and reported an overall mortality rate from septic shock of 40%. (2)

In the United States, 200,000 cases of septic shock and 100,000 deaths per year occur from this disease and this has been an increasing trend since the 1930’s. For example, between 1980 and 1992, the incidence of nosocomial blood stream infection in 1 institution increased from 6.7 cases per 1000 discharges to 18.4 per 1000. The cause for these increased infection rates is probably the increase in immunocompromised patients and an increasing use of invasive diagnostic and therapeutic devices predisposing to infection. (1)

A 2001 article reported the incidence, cost, and outcome of severe sepsis in the United States. Analysis of a large sample from the major centers reported the incidence of severe sepsis as 3 cases per 1000 population and 2.26 cases per 100 hospital discharges. Out of these cases, 51.1% were admitted to an intensive care unit (ICU), and an additional 17.3% were cared for in an intermediate care or coronary care unit.

Severe sepsis resulted in an average cost of $2200 per case, with an annual total cost of $16.7 billion nationally.

The National Center for Health Statistics published a large retrospective analysis using the National Hospital Discharge Survey of 500 nonfederal US hospitals, which included more than 10 million cases of sepsis over a 22-year period. Septicemia accounted for 1.3% of all hospitalizations, and the incidence of sepsis increased 3-
fold between 1979 and 2000, from 83 cases per 100,000 population per year to 240 per 100,000.

A Dutch surveillance study examined the incidence, causes, and outcome of sepsis in patients admitted to a university hospital. The investigators reported that the incidences of sepsis syndrome and septic shock were, respectively, 13.6 and 4.6 cases per 1000 persons.

DEFINITIONS

Many terms were developed to describe different clinical manifestations of varying degrees of severity, from the time of infection to multi-system failure. Terms like sepsis, severe sepsis, and septic shock are often used interchangeably and without a commonly understood definition.

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a consensus conference to establish definitions of these and related terms. (3)

Systemic inflammatory response syndrome (SIRS) is the clinical manifestations that result from the systemic response to infection, trauma, thermal injury or a sterile inflammatory process e.g. acute pancreatitis. Criteria for SIRS are considered to be met if at least 2 of the following 4 clinical findings are present:

- Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart rate (HR) greater than 90 beats per minute (bpm)
- Respiratory rate (RR) greater than 20 breaths per minute or arterial carbon dioxide tension (PaCO₂) lower than 32 mm Hg
- White blood cell (WBC) count higher than 12,000/µL or lower than 4000/µL, or 10% immature (band) forms

In 2001, as a follow-up to the original ACCP/SCCM conference, an International Sepsis Definitions Conference was convened, with representation not only from the ACCP and the SCCM but also from the European Society of Intensive Care Medicine (ESICM), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS). The following definitions of sepsis syndromes were published in order to clarify
the terminology used to describe the spectrum of disease that results from severe infection. \(^{(4)}\)

![Diagram of SIRS, Infection, and Sepsis relationships]

**Figure 1**: The relationship between SIRS, Infection and sepsis. \(^{(2)}\)

**Sepsis** is defined as the presence of infection in association with SIRS. The presence of SIRS is, of course, not limited to sepsis, but in the presence of infection, an increase in the number of SIRS criteria observed should alert the clinician to the possibility of endothelial dysfunction, developing organ dysfunction, and the need for aggressive therapy.

**Severe sepsis** is defined as sepsis complicated by end-organ dysfunction, as signaled by altered mental status, an episode of hypotension, elevated creatinine concentration, or evidence of disseminated intravascular coagulopathy (DIC).

**Septic shock** is defined as a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate fluid resuscitation or by tissue hypoperfusion (manifested by a lactate concentration greater than 4 mg/dL) unexplained by other causes. Patients receiving inotropic or vasopressor agents may
not be hypotensive at the time they manifest hypoperfusion abnormalities or organ dysfunction.

**Bacteremia** is defined as the presence of viable bacteria within the liquid component of blood. It may be primary (without an identifiable focus of infection) or, more often, secondary (with an intravascular or extravascular focus of infection). Although sepsis is commonly associated with bacterial infection, bacteremia is not a necessary ingredient in the activation of the inflammatory response that results in severe sepsis. In fact, septic shock is associated with culture-positive bacteremia in only 30-50% of cases.

**PATHOPHYSIOLOGY OF SEPSIS AND SEPTIC SHOCK**

The pathophysiology of septic shock is not precisely understood, but it involves a complex interaction between the pathogen and the host’s immune system. The normal physiologic response to localized infection includes the activation of host defense mechanisms that result in the influx of activated neutrophils and monocytes, the release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways.

These mechanisms are in play during septic shock, but on a systemic scale, leading to diffuse endothelial disruption, vascular permeability, vasodilation, and thrombosis of end-organ capillaries. Endothelial damage itself can further activate inflammatory and coagulation cascades, creating in effect a positive feedback loop, and leading to further endothelial and end-organ damage.

**Mediator-Induced Cellular Injury**

An initial step in the activation of innate immunity is the synthesis de novo of small polypeptides, called **cytokines** that induce protein manifestations on most cell types from immune effector cells to vascular smooth muscle and parenchymal cells. Several cytokines are induced, including tumor necrosis factor (TNF) and interleukins (ILs), especially IL-1. Both of these factors also help to keep infections localized.

The **chemokines** (monocyte chemoattractant protein–1) orchestrate the migration of leukocytes during endotoxemia and sepsis. The other cytokines that have a supposed role in sepsis are IL-10, interferon gamma, IL-12, macrophage migration
inhibition factor, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF).

In addition, cytokines activate the coagulation pathway, resulting in capillary microthrombi and end-organ ischemia.

**Gram-positive and gram-negative bacteria** induce a variety of proinflammatory mediators, including the cytokines just mentioned, which play a pivotal role in initiating sepsis and shock. Various bacterial cell wall components are known to release the cytokines, including lipopolysaccharide (gram-negative bacteria), peptidoglycan (gram-positive and gram-negative bacteria), and lipoteichoic acid (gram-positive bacteria).

Several of the harmful effects of bacteria are mediated by proinflammatory cytokines induced in host cells (macrophages/monocytes and neutrophils) by the bacterial cell wall components. The most toxic component of the gram-negative bacteria is the Lipid A moiety of lipopolysaccharide. The gram-positive bacteria cell wall leads to cytokine induction via lipoteichoic acid.

Additionally, gram-positive bacteria may secrete the superantigen cytotoxins that bind directly to the major histocompatibility complex (MHC) molecules and T-cell receptors, leading to massive cytokine production.

The **complement system** is activated and contributes to the clearance of the infecting microorganisms but probably also enhances the tissue damage. The contact systems become activated; consequently, bradykinin is generated.

Hypotension, the cardinal manifestation of sepsis shock, occurs via induction of nitric oxide (NO). NO plays a major role in the haemodynamic alterations of septic shock, which is a hyperdynamic form of shock.

A dual role exists for neutrophils; they are necessary for defense against microorganisms but also may become toxic inflammatory mediators contributing to tissue damage and organ dysfunction.

The lipid mediators (eicosanoids), platelet-activating factor (PAF), and phospholipase A2 are generated during sepsis, but their contributions to the sepsis syndromes remain to be established.
Figure 2: Schematic representation of immune dysfunction in critical injury. TNF = tumor necrosis factor; IL = interleukin; Schematic representation of immune dysfunction in critical injury. TNF = tumor necrosis factor; IL = interleukin; PMN = polymorphonuclear cells; NK = natural killer; PGE = prostaglandin E; SIRS = systemic inflammatory response (8)
Abnormalities of Coagulation and Fibrinolysis

An imbalance of homeostatic mechanisms leads to disseminated intravascular coagulopathy (DIC) and microvascular thrombosis, causing organ dysfunction and death. Inflammatory mediators instigate direct injury to the vascular endothelium, the endothelial cells release tissue factor (TF), triggering the extrinsic coagulation cascade and accelerating production of thrombin.

The coagulation factors are activated as a result of endothelial damage. Inflammatory cytokines, such as IL-1α, IL-1β, and TNF-alpha, initiate coagulation by activating TF. TF interacts with factor VIIa to form factor VIIa-TF complex, which activates factors X and IX. Activation of coagulation in sepsis has been confirmed by marked increases in thrombin-antithrombin complex and the presence of D-dimer in plasma, indicating activation of the clotting system and fibrinolysis.

Endotoxins increase the activity of inhibitors of fibrinolysis—namely, plasminogen activator inhibitor (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI).

The levels of protein C and endogenous activated protein C (APC) are also decreased in sepsis. Endogenous APC is an important proteolytic inhibitor of coagulation cofactors Va and VIIa. Thrombin, via thrombomodulin, activates protein C, which then functions as an antithrombotic in the microvasculature. Endogenous APC also enhances fibrinolysis by neutralizing PAI-1 and by accelerating tissue plasminogen activator (t-PA)–dependent clot lysis.

The imbalance among inflammation, coagulation, and fibrinolysis results in widespread coagulopathy and microvascular thrombosis and suppressed fibrinolysis, ultimately leading to multiple organ dysfunction and death. The insidious nature of sepsis is such that microcirculatory dysfunction can occur while global hemodynamic parameters such as blood pressure may remain normal.

Circulatory Abnormalities

Septic shock falls under the category of distributive shock, which is characterized by pathologic vasodilation and shunting of blood from vital organ to non-vital tissues such as skin, skeletal muscle, and adipose. The endothelial dysfunction and vascular maldistribution characteristic of distributive shock results in global tissue hypoxia or
inadequate delivery of oxygen to vital tissues. In addition, mitochondria can become dysfunctional, thus compromising oxygen utilization at the tissue level.

The predominant hemodynamic feature of septic shock is arterial vasodilation. The mechanisms implicated in this pathologic vasodilation are multifactorial, but the primary factors are thought to be (1) activation of adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle cells and (2) activation of NO synthase.

The potassium-ATP channels are directly activated by lactic acidosis. NO also activates potassium channels. Potassium efflux from cells results in hyperpolarization, inhibition of calcium influx, and vascular smooth muscle relaxation. The resulting vasodilation can be refractory to endogenous vasoactive hormones (eg, norepinephrine and epinephrine) that are released during shock.

Diminished peripheral arterial vascular tone may result in dependency of blood pressure on cardiac output, causing vasodilation to result in hypotension and shock if insufficiently compensated by a rise in cardiac output. Early in septic shock, the rise in cardiac output often is limited by hypovolemia and a fall in preload because of low cardiac filling pressures. When intravascular volume is augmented, the cardiac output usually is elevated (the hyperdynamic phase of sepsis and shock).

Although an elevation of cardiac output occurs, the arterial-mixed venous oxygen difference usually is narrow, and the blood lactate level is elevated. This implies that low global tissue oxygen extraction is the mechanism that may limit total body oxygen uptake in septic shock. The basic pathophysiologic problem seems to be a disparity between the uptake and oxygen demand in the tissues, which may be more pronounced in some areas than in others.

This disparity is termed maldistribution of blood flow, either between or within organs, with a resultant defect in capacity to extract oxygen locally. During a fall in oxygen supply, cardiac output becomes distributed so that most vital organs, such as the heart and brain, remain relatively better perfused than non-vital organs are. However, sepsis leads to regional changes in oxygen demand and regional alteration in blood flow of various organs.

The peripheral blood flow abnormalities result from the balance between local regulation of arterial tone and the activity of central mechanisms (eg, the autonomic nervous system). The regional regulation and the release of vasodilating substances
(eg, NO, prostacyclin) and vasoconstricting substances (eg, endothelin) affect regional blood flow.

Increased systemic microvascular permeability also develops, remote from the infectious focus, and contributes to edema of various organs, particularly the lung microcirculation, and to the development of ARDS.

Maldistribution of blood flow, disturbances in the microcirculation, and, consequently, peripheral shunting of oxygen are responsible for diminished oxygen extraction and uptake, pathologic supply dependency of oxygen, and lactate acidemia in patients experiencing septic shock.

**MECHANISMS OF ORGAN DYSFUNCTION**

The precise mechanisms of cell injury and resulting multiple organ dysfunction syndrome (MODS) in patients with sepsis are not fully understood. MODS is associated with widespread endothelial and parenchymal cell injury because of the following proposed mechanisms:

- **Hypoxic hypoxia** - The septic circulatory lesion disrupts tissue oxygenation, alters the metabolic regulation of tissue oxygen delivery, and contributes to organ dysfunction. Microvascular and endothelial abnormalities contribute to the septic microcirculatory defect in sepsis. Reactive oxygen species, lytic enzymes, vasoactive substances (eg, NO), and endothelial growth factors lead to microcirculatory injury, which is compounded by the inability of the erythrocytes to navigate the septic microcirculation.

- **Direct cytotoxicity** - Endotoxin, TNF-alpha, and NO may cause damage to mitochondrial electron transport, leading to disordered energy metabolism. This is called cytopathic or histotoxic anoxia—that is, an inability to use oxygen even when it is present.

- **Apoptosis (programmed cell death)** - This is the principal mechanism by which dysfunctional cells normally are eliminated. The proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, but other tissues, such as the gut epithelium, may undergo accelerated apoptosis. Therefore, derangement of apoptosis plays a critical role in tissue injury in patients with sepsis.
• **Immunosuppression** - The interaction between proinflammatory and anti-inflammatory mediators may lead to an imbalance and an inflammatory reaction, or immunodeficiency may predominate, or both may occur.

• **Coagulopathy** - Subclinical coagulopathy signified by mild elevation of the thrombin time or activated partial thromboplastin time or by a moderate reduction in platelet count is extremely common, but overt DIC is rare. Coagulopathy is caused by deficiencies of coagulation system proteins, including protein C, antithrombin III, and TF inhibitors.
ADRENAL INSUFFICIENCY IN SEPSIS AND SEPTIC SHOCK

HPA physiology

Figure 3: HPA Axis physiology. AVP, vasopressin; PVN, paraventricular nucleus; SON, supraoptic nucleus. (17)

The adrenal glands have 2 distinct zones: (a) medulla- secretes endogenous catecholamines (b) cortex- which secretes steroid hormones. The cortex is further divided (outside to inside) into 3 zones: Glomerulosa (aldosterone), fasciculate (cortisol) and reticularis (adrenal androgens). Experimental removal of the adrenal glands is fatal.

Production of glucocorticoids is stimulated by adrenocorticotropic hormone (ACTH) released from the anterior pituitary. ACTH is controlled by the release of corticotrophin-releasing hormone (CRH) from the hypothalamus. Glucocorticoids inhibit the release of both ACTH and CRH.
In rodents, it has been shown that vasopressin is also released as part of the stress response to sepsis. Vasopressin (secreted from the posterior pituitary) has been shown to increase endogenous ACTH secretion through both V1a and V1b receptors, and aldosterone and cortisol secretion via V1a receptors. Vasopressin is also inhibited by cortisol. Vasopressin has recently been shown to have intrinsic anti-inflammatory effects.

Angiotensin II also regulates the HPA axis, via the AT1 receptors, causing release of CRH and vasopressin.

Apelin, a neuropeptide discovered in rodents, released from the paraventricular and supraoptic nuclii, acts to stimulate release of CRH and decreases plasma vasopressin, although human data is lacking.

Cortisol secretion follows a circadian rhythm with pulsatile periods. The average daily cortisol production is 55umol/day. Ninety percent of the circulating cortisol is inactive because it is carried in the plasma bound to corticosteroid-binding globulin (CBG) and albumin since free cortisol is the only active form of cortisol.

During acute illness, inflammatory cytokines like IL-6, TNF-α, and IL-1β stimulate the production and release of CRH and ACTH. These cytokines are also sensed by vagal afferent fibres also active the HPA-axis. Other substances like noradrenaline, vasopressin, serotonin, angiotensin and vasoactive intestinal peptide also upregulate ACTH synthesis. This results in increased cortisol secretion from the adrenal glands.

Critical illness and chronic stress has shown to cause dissociation between ACTH and glucocorticoid levels. This results in raised cortical levels without a change in ACTH. There is also an intra-adrenal shift towards increased glucocorticoid synthesis, even to the detriment of mineralocorticoid and androgen production. The activation of these non-ACTH driven pathways are explained by:

1) The vast variety of receptors for modulating ACTH-independent adrenal glucocorticoid release (e.g. neuropeptides, neurotransmitters, opioids, growth factors, cytokines, adipokines)
2) An extensive intra-adrenal paracrine regulation
3) Gonadal steroid down-regulation

As mentioned above, most of the cortisol is bound and unavailable to target tissues. However, elastases, secreted by neutrophils, release cortisol from CBG allowing
localized delivery of cortisol. Cortisol may either enter the cell or interact with specific membrane binding sites (see below).

The increased cortisol released also stimulates increased conversion to cortisone (inactive cortisol) by 11β-hydroxysteroid dehydrogenase-type 2 (11β-HSD-type2).

ADRENAL FUNCTION TESTING

Relative adrenal insufficiency has previously been defined as a rapid clinical and haemodynamic improvement in catecholamine-dependent patients after 200-300mg of hydrocortisone per day. Measurement of basal cortisol levels and adrenal stimulation tests has contributed in tailoring this definition.

1) Basal cortisol levels in critically ill patients
Cortisol levels in critically ill patients are usually normal or high from ACTH-adrenal uncoupling. Therefore, baseline cortisol levels are unhelpful in diagnosing RAI. They have, however, been shown to predict mortality, with studies suggesting that higher cortisol levels are associated with higher mortality.

Another problem with basal cortisol levels is that the test measures total cortisol (bound and free). Because 90% of the cortisol is bound to carrier proteins, changes in these proteins can alter total cortisol without changes in free cortisol concentrations. Measuring true free cortisol may be useful in further understanding the pathophysiology of RAI. Studies based on baseline total cholesterol concentration are now questionable.

2) Stimulated cortisol levels in critically ill patients
Stimulation tests of the adrenal gland by use of an ACTH analogue (synacthen) have been used for the diagnosis of adrenal insufficiency and to assist in the decision to start and/or continue corticosteroid therapy. There are 2 types of tests commonly used based on the dose of ACTH: 250ug which is the more commonly used test and the 1ug test. The cortisol rise expected 30-60mins after a 250ug stimulation test is >9ug/dL (“Delta 9” rule). Patients not achieving a >9ug/dL are termed: non-responders. Reference values of the ACTH stimulation test, determined under standardized conditions, cannot be extrapolated to the stressed critically ill patient. Additionally, the usually high unstimulated cortisol
levels are associated with a relatively small increase in cortisol without a clear association between basal and stimulated levels.

This blunted response may be due to: (1) the already maximally stimulated HPA-axis, (2) the disruption of pituitary-glucocorticoid feedback, (3) because the adrenal glands are already maximally stimulated by the increased secretion of peptides with corticotrophin-like activity (e.g. cytokines), or (4) the adrenals have been damaged by the disease process.\(^{(11)}\)

Dimopoulou et al. \(^{(29)}\) investigated the value of low-dose (1ug) corticotrophin stimulation test in predicting outcome and mortality in ICU patients with acute traumatic and non-traumatic brain injury. The mortality rates for responders were higher than in non-responders. A logistic regression analysis showed that increase in cortisol after ACTH stimulation was no predictor of death.

A recent meta-analysis, by Moran and colleagues \(^{(10)}\), was unable to show treatment efficacy with respect to mortality and shock-reversal based upon corticotrophin responsiveness. This is a reaffirmation of the findings by Minneci et. al in their meta-analysis where they also question the usefulness of ACTH testing to aid diagnosis and direct management with corticosteroids. \(^{(30)}\)

**MECHANISMS OF ADRENAL INSUFFICIENCY IN SEPSIS AND SEPTIC SHOCK**\(^{(6)}\)

There are 2 main reasons from glucocorticoid insufficiency: (1) decreased synthesis and (2) reduced access to target tissues.

1) **Decreased synthesis**

Glucocorticoids (GC) are synthesized from cholesterol (20% endogenous from acetate, 80% exogenous) in the adrenal cortex. GC’s are not stored in any significant amount, so the rate of secretion is directly proportional to the rate of biosynthesis, therefore any disruption of GC production will immediately result in GC insufficiency. Adrenal insufficiency may be primary or secondary.

a) **Primary**

Bilateral necrosis and haemorrhage of the adrenals has been reported in sepsis. The rich blood supply from the multitude of arterial plexuses that
supply the cortex and sinuses of the medulla, all drain into one medullary central vein. This limited venous drainage predisposes the gland to haemorrhage. Bilateral adrenal haemorrhage may be found in 1-1.8% of autopsied patients and up to 30% in septic shock patients.

Sepsis may exacerbate chronic known or latent primary adrenal insufficiency, which is usually caused by autoimmune adrenalitis (in developed countries) and tuberculous adrenalitis (in developing countries). Less common causes include genetic disorders, tumoral and non-tumoral infiltration and bilateral adrenalectomy’s.

Many drugs used in the critically ill patient are known to decrease cortisol production. Etomidate inhibits steroidogenesis by blocking mitochondrial cytochrome P450 enzymes and may persist for up to 24 hours after a single bolus. Dexmedetomidine is an imidazole compound that has been shown to inhibit cortisol synthesis (in animal studies) in high doses. Short post-operative sedation in ICU with dexmedetomidine has not shown to affect adrenal function.

Circulating pro-inflammatory cytokines (e.g. TNF-a) may inhibit ACTH-induced cortisol release. Neutrophil corticostatins compete with ACTH binding sites and inhibits the effects of ACTH on adrenal cells. Cortisol metabolism may be accelerated by drug competition e.g. ketoconazole, cyclosporine, clarithromycin and antiepileptic drugs such as phenytoin and phenobarbitone.

b) Secondary
Sepsis may induce irreversible anatomical damage to the hypothalamus or the pituitary gland. Pituitary necrosis is well known complication of dramatic cardiovascular collapse. Necrosis or haemorrhage of the hypothalamus or pituitary gland have been reported in sepsis as a result of prolonged hypotension or severe coagulopathy.

Sepsis may exacerbate chronic known or latent secondary adrenal insufficiency which may be due to hypothalamic or pituitary tumors, chronic inflammation or congenital ACTH deficiency. Secondary adrenal insufficiency may also follow drug therapy. Suppression of CRH and ACTH
result in a slow onset of suppression that may outlast the exposure. (see table below)

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<td><strong>Mechanisms</strong></td>
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<td>Primary adrenal insufficiency</td>
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<td>Haemorrhage</td>
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<td>Cortisol synthesis enzyme inhibition</td>
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<td>Cortisol metabolism activation</td>
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<td>Peripheral resistance to glucocorticoids</td>
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<td>Interaction with glucocorticoids receptor</td>
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<td>Inhibition of the glucocorticoid-induced gene transcription</td>
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ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Opiate receptors are known to modulate ACTH/cortical synthesis. High doses of diazepam and fentanyl inhibit the early increase in ACTH and cortisol that occurs in response to surgery. This suggests that they act at the level of the hypothalamus. Since these drugs may be used for sedation in the critically ill, likely that they contribute partly to adrenal insufficiency.

Neuronal apoptosis may also cause suppression of CRH synthesis that is triggered by elevated levels of substance P or inducible nitric oxide synthase (iNOS) in the hypothalamus. Proinflammatory mediators like TNF-α may block CRH-induced ACTH release and local expression of TNF-α and IL-1β may interfere with CRH and ACTH synthesis.

2) Decreased delivery and action

   a) Decreased access to tissues
CBG acts as a substrate for neutrophil elastase which cleaves off a 5kDa segment resulting in more than 80% release of cortisol ensuring local delivery and avoiding systemic side effects. CBG also inversely correlates with cortisol disappearance rate, suggesting that CBG actively modulates the disposition of cortisol. Sepsis following trauma and burns results in reduced activity and quantity of CBG. Although the free fraction is increased, the decreased CBG levels result in reduced distribution and delivery to the site of inflammation or infection.

Cortisol is converted to the inactive cortisone by 11β-HSD type 2 enzyme, while 11β-HSD type 1 converts cortisone back to cortisol. Sepsis is usually associated with an increase in the cortisol/cortisone ratio that is proportional to the increase in acute phase protein concentration. It has also been shown that IL-1β and TNF-α upregulated 11β-HSD type 1 activity. Thus, in the early phase, mediators derived from the recruitment of T-helper-1 cells increase the conversion of cortisol from cortisone. In the second phase, cortisol enhances T-helper-2 cells that release cytokines such as IL-2, IL-4 and IL-13 that stimulate 11β-HSD type 2 resulting in the conversion of cortisol to cortisone. This immune-cortisol crosstalk results in increase levels of cortisol initially to control the proinflammatory phase, while the second phase has decreased cortisol activity thus preventing local immunosuppression.

b) Decrease receptor numbers or affinity
Cortisol freely crosses the cell membrane and interacts with specific glucocorticoid receptors (GR) in the cytosol. There is no evidence to suggest the GC entry into the cell is affected by sepsis, although endotoxin and lipopolysaccharide (LPS) has been shown to decrease GR affinity. Studies investigation GR expression showed heterogenous findings. Some treatments produced upregulation of GR while others produced a downregulation of GR.

Potential mechanisms for cytokine-induced reduction in GR function and affinity may include inhibition of GR translocation to the nucleus and reduction in GR-mediated gene transcription. One example is TNF-α that binds to the nuclear receptor binding domain or GR-interacting protein-1,
thereby preventing GR transactivation. Thus, TNF-α induces GC resistance upstream and independently of NF-κB.

CORTICOSTEROID MECHANISMS OF ACTION

Glucocorticoids (GC) act on carbohydrate, protein and lipid metabolism, as well as modulate vascular tone and have variable mineralocorticoid activity. GC’s also decrease the synthesis and release of antibodies from lymphocytes, reduce inflammatory cell recruitment and inhibit the production of cyclo-oxygenase II and phospholipase A2. The binding of cortisol to its cytoplasmic receptor releases heat shock proteins, which have important stress protective abilities. The cortisol-receptor complex moves to the nucleus where it promotes production of anti-inflammatory cytokines like IL-6, TNF-a, IL-1b, as well as vasopressin and noradrenaline. Vasopressin release has not been shown to correspond to ACTH levels.

Glucocorticoids (GC) bind to specific glucocorticoid receptors (GR) in the cytosol. The GR is a 94 kDa protein and a member of the nuclear receptor family. Upon activation, it dissociates from a multiprotein complex, dimerizes, and enters the nucleus to bind to specific DNA regions termed Glucocorticoid responsive elements. At homeostasis, the GR forms a multiprotein complex with numerous members of the heat shock protein family, immunophilins and possibly other proteins not yet known. Upon activation, the GR translocates to the nucleus.

Transcriptional activation or repression of specific target genes occurs and subsequent levels of regulated proteins change. GR interactions with other proteins of the complex are still poorly understood. Although, it is these interactions that may account for a number of rapid nongenomic biological effects of GC. These effects are too rapid to be explained by transcriptional and translational events and they are insensitive to appropriated inhibitors. So the effects of GC can be genomic or non-genomic.

1) Genomic Effects

GR directly activates or represses target genes by binding to specific hormone response elements. Regulation of gene transcription requires recruitment of coregulators like the p160 steroid receptor coactivator (SRC) gene family. These are responsible for chromatin remodeling, assembly of general transcription
factors and transcription of target genes. Glucocorticoids (GC) have been shown to transactivate genes for cytokines, chemokines and complement family members and newly discovered innate immune-related genes, including scavenger and Toll-like receptors. GC’s also transrepress adaptive immune-related genes. GC may simultaneously transactivate and transrepress inflammatory T-helper subsets and apoptosis-related gene clusters. Development of GR agonists that favour transrespression over transactivation is an exciting new field.

Glucocorticoids play a major role in regulating the activity of NF-κB, which plays a crucial, though generalized, role in inducing cytokine gene transcription. The NF-κB protein family forms a complex that is maintained in its inactive form in the cytosol by a specific inhibitor – IκB-α. On stimulation by LPS, double-stranded DNA, physical and chemical stresses, and inflammatory cytokines, the latent NF-κB/IκB complex is activated by phosphorylation and proteolytic degradation of IκB with exposure of NF-κB. NF-κB initiates the transcription of targets genes that result in the production of cytokines, cell adhesion molecules, and other mediators of inflammation.

The interaction of GC, NF-κB and activator protein-1 represents the main GR-induced, DNA-independent mode of transrepression. GR prevents activator protein-1 from interacting with its binding site within the promoters. Glucocorticoids also induce IκB which further inhibits NF-κB dependent gene transcription. GC’s can also directly inhibit NF-κB as well as increasing the transcription of IκB’s.

Glucocorticoids may also regulate inflammatory mediators by acting at the post-transcriptional level, on mRNA or on proteins.

2) Nongenomic effects
Specific nongenomic effects are mediated by membrane bound receptors. Membrane binding sites for GC have been described in many tissues including liver and neuronal synaptic membranes with classic receptors and non-classic receptors. Nonspecific, nongenomic effects are thought to result from physicochemical membrane interactions, and to occur within seconds to minutes but only at high doses of glucocorticoids.

a) Nonspecific nongenomic effects
Direct membrane effects of GC in the hypothalamic synaptosomes have been suggested as the mechanism for plasma cortisol-induced negative feedback. The loss of this effect may partly explain the disruption of circadian rhythm of cortisol production during sepsis. Nonspecific nongenomic effects may explain the rapid restoration of the sympathetic modulation of heart rate and vasomotor tone, as well as the potentiation of exogenous catecholamine action that can be seen within minutes after a 50mg bolus of hydrocortisone in septic shock.

b) Specific nongenomic effects
Some of these effects account for glucocorticoid-induced rapid anti-inflammatory and cardiovascular effects. The p38 mitogen-activated protein kinase (MAPK) participates in intracellular signaling cascades resulting in inflammatory responses. The classic GR may directly interfere with Raf-1 which is downstream of the Ras in the MAPK cascade. The anti-inflammatory effects from the interaction between GR and MAPK remains to be investigated.

It has been recently shown that GC, through activation of phosphatidylinositol 3-kinase and protein kinase Akt, could exert perfusion-independent protective effects in a model of ischaemic brain injury. Phosphatidylinositol 3-kinase and protein kinase Akt activate endothelial NOS resulting in NO dependent vasorelaxation. This results in vascular inflammation and reduced myocardial infarct size following ischemia/reperfusion injury in mice.
CORTICOSTEROID COMPARATIVE PHARMACOLOGY

CHARACTERISTICS OF CORTICOSTEROIDS

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Mineralocorticoid activity</th>
<th>Relative inflammatory potency</th>
<th>Approx. IV or oral doses</th>
<th>Approx. plasma half-life (hrs)</th>
<th>Biological half-life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>20mg</td>
<td>1-2</td>
<td>8-12</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.8</td>
<td>0.8</td>
<td>25mg</td>
<td>0.5-1.5</td>
<td>8-12</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.8</td>
<td>4</td>
<td>5mg</td>
<td>2.1-3.5</td>
<td>18-36</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.8</td>
<td>4</td>
<td>5mg</td>
<td>3.4-3.8</td>
<td>18-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.5</td>
<td>5</td>
<td>4mg</td>
<td>3.5</td>
<td>18-36</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0</td>
<td>30</td>
<td>0.75mg</td>
<td>3-4.5</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0</td>
<td>25-40</td>
<td>0.75mg</td>
<td>3-5</td>
<td>36-54</td>
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<tr>
<td>Fludrocortisone</td>
<td>125-250</td>
<td>10</td>
<td>-</td>
<td>3.5</td>
<td>10-36</td>
</tr>
</tbody>
</table>

ROLE OF CORTICOSTEROIDS FOR SEPTIC SHOCK

The effect of stress response attenuation, and the improving knowledge of anti-inflammatory and immunosuppressive effects, has lead to the use of glucocorticoids in many sepsis trials over the years. Earlier randomized, controlled, high-dose glucocorticoid trials failed to improve outcomes, leading to skepticism and the avoidance of using any glucocorticoids in septic patients. However, recent randomized, controlled trials with low doses of hydrocortisone in septic shock have evoked a renewed interest.

High doses of glucocorticoids mainly refer to 30 mg/kg methylprednisolone or equivalent steroid preparations administered up to four times during a short course of 1 or 2 days. Recent low-dose glucocorticoid trials refer to a daily dose of 200–300 mg of hydrocortisone (or equivalent) administered for 5–7 days or longer. The terminology is poorly defined with low-dose synonyms including: (a) stress dose, (b)
supraphysiologic dose, (c) physiologic dose, and (d) moderate dose. Early investigations of high dose corticosteroids proved no benefit and sometimes harmful.

Subsequently, in a multi-center trial, with 300 patients with septic shock refractory to volume resuscitation and vasopressors, Annane and colleagues found that the administration of hydrocortisone 50 mg intravenously every 6 hours and fludrocortisone 50 mcg per day reduced 28-day mortality by 10% in patients with relative adrenal insufficiency. At the time of publication (2002), this was the most definitive trial of stress-dose steroids in septic shock, greatly influencing clinical practice and rapidly became the standard of care.

The Corticosteroid Therapy of Septic Shock (CORTICUS) study evaluated the efficacy and safety of low-dose hydrocortisone therapy in a broad population of patients with septic shock, including patients who responded to a corticotropin test, in whom a benefit was unproven. Patients were enrolled if they had clinical evidence septic shock with onset within 72 hours of enrollment. Shock was defined by a systolic blood pressure (SBP) <90 mmHg despite fluid resuscitation or a vasopressor requirement for at least one hour.

All patients underwent a corticotropin stimulation test. Somewhat surprisingly, the use of low-dose hydrocortisone had no significant effect on 28-day mortality, regardless of the patients’ adrenal responsiveness to corticotropin. The proportion of patients in whom reversal of shock was achieved was similar in the two groups, though this goal was achieved earlier in patients who received hydrocortisone. New infection, hypernatremia and hyperglycemia occurred more frequently in the hydrocortisone group compared to the placebo group.

CORTICUS is the largest study to date to address the role of corticosteroids in septic shock. Yet, the study has limitations, the most important of which is inadequate power. The study was stopped prematurely due to slow recruitment, termination of funding, and time expiry of the trial drug. Only 500 of the intended 800 patients were enrolled. This, coupled with a lower control death rate than anticipated, resulted in the trial having less than 35% power to detect a relative risk reduction of 20% for the primary outcome.

Selection bias is another potential limitation. Physicians who were convinced of the benefit of steroids may have been reluctant to withhold this therapy from their sickest patients, thereby excluding the group of patients that theoretically had the most to
gain. The lower than expected mortality rate in the control group supports this notion. To better understand the potential influence of this limitation, it would have been useful for the authors to have provided information about the patients who were screened but not included in the study, such as those who were excluded because they were already receiving corticosteroids.

In comparing CORTICUS and the study by Annane and colleagues, there are important methodological differences, which may explain their differing findings. In the Annane study, patients were enrolled within eight hours of onset of shock and were still hypotensive (SBP <90 mmHg for at least one hour) despite fluid resuscitation and vasopressor therapy. In contrast, CORTICUS enrolled patients with evidence of shock within the previous 72 hours, as manifest by either hypotension after fluid resuscitation or a vasopressor requirement for at least 1 hour. This led to a disparity in severity of illness between the trials, with Annane and colleagues enrolling a sicker group of patients as measured by SAPS II scores and control group mortality.

These observations bring into question not only the issue of timing, but also whether sicker patients might be more likely to benefit. CORTICUS patients more commonly had post-surgical, hospital acquired, and abdominal infections. Patients with these characteristics may respond differently to steroid therapy than the primarily medical sample studied by Annane and colleagues. Finally, the trials also employed different steroid treatment protocols. The Annane trial used a fixed dose of hydrocortisone along with fludrocortisone for a total of 7 days, whereas in CORTICUS, a tapering dose of hydrocortisone (without fludrocortisone) for a total of 11 days was used.

The contradictory findings of these two large multicenter studies creates uncertainty in using corticosteroids for: any septic patient, patients with septic shock or only for those patients in septic shock not responsive to conventional therapy. In the last few years, 4 recent meta-analyses were performed in an attempt to help clear the uncertainty and guide clinical practice. However, they too show conflicting results.
The meta-analyses of Annane et al and Minneci et al analyzed patients with both sepsis and septic shock. Although many of the mechanisms of disease are similar, the severity, morbidity, mortality and response to therapy are very different in patients with septic shock. Both analyses found differences in mortality between the high-dose and low-dose steroid treatment and reversal of shock in the steroid treated patients. However, overall mortality was not different between steroid treated patients (both high and low doses) and the control patients. The lower mortality found in the low dose steroid treated group included a disproportionately large number of small studies demonstrating beneficial steroid effects with a potential publication bias.

Marik et al and Sligl et al in their analyses only included patients who were in septic shock. These analyses showed a benefit of corticosteroids in reversing shock, but no benefit in overall mortality nor increased adverse events like superinfection. These findings are in keeping with those of CORTICUS and come back to the unanswered question: If corticosteroids do indeed improve shock reversal, why is this not translated into improved survival?
RECOMMENDATIONS FOR THE USE OF CORTICOSTEROIDS IN SEPTIC SHOCK

In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis. The guideline has since been updated in 2008. The following are the updated recommendations regarding the use of corticosteroids for septic shock.

Surviving sepsis campaign recommendations (2008) and grading the evidence

1. **The Surviving Sepsis Campaign suggests intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy (Grade 2C).**

   **Rationale:**

   One French multi-center, randomized, controlled trial (RCT) of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors) showed a significant shock reversal and reduction of

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**Steroids**
- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C).
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B).
- Hydrocortisone is preferred to dexamethasone (2B).
- Fludrocortisone (50 μg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone if optional if hydrocortisone is used (2C).
- Steroid therapy may be weaned once vasopressors are no longer required (2D).
- Hydrocortisone dose should be ≤300 mg/day (1A).
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it (1D).
mortality rate in patients with relative adrenal insufficiency (defined as post-adrenocorticotropic hormone [ACTH] cortisol increase of 9 µg/dL or less). Two additional smaller RCTs also showed significant effects on shock reversal with steroid therapy. However, a recent large, European multicenter trial (CORTICUS) failed to show a mortality benefit with steroid therapy of septic shock. CORTICUS did show a faster resolution of septic shock in patients who received steroids.

The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. Importantly, unlike the French trial, which only enrolled shock patients with blood pressure unresponsive to vasopressor therapy, the CORTICUS study included patients with septic shock, regardless of how the blood pressure responded to vasopressors.

Although corticosteroids do appear to promote shock reversal, the lack of a clear improvement in mortality--coupled with known side effects of steroids such as increased risk of infection and myopathy--generally tempered enthusiasm for their broad use. Thus, there was broad agreement that the recommendation should be downgraded from the previous guidelines (Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32:858-873).

2. The Surviving Sepsis Campaign suggests the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B).

Rationale:

Although one study suggested those who did not respond to ACTH with a brisk surge in cortisol (failure to achieve or > 9 µg/dL increase in cortisol 30-60 mins post-ACTH administration) were more likely to benefit from steroids than those who did respond, the overall trial population appeared to benefit regardless of ACTH result, and the observation of a potential interaction between steroid use and ACTH test was not statistically significant.

Furthermore, there was no evidence of this distinction between responders and nonresponders in a recent multicenter trial. Commonly used cortisol immunoassays measure total cortisol (protein-bound and free) while free cortisol is the pertinent measurement. The relationship between free and total cortisol varies with serum protein concentration. When compared to a reference
method (mass spectrometry), cortisol immunoassays may over- or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders. Although the clinical significance is not clear, it is now recognized that etomidate, when used for induction for intubation, will suppress the HPA axis.

3. The Surviving Sepsis Campaign suggests that patients with septic shock should not receive dexamethasone if hydrocortisone is available (Grade 2B).

Rationale:

Although often proposed for use until an ACTH stimulation test can be administered, we no longer suggest an ACTH test in this clinical situation. Furthermore, dexamethasone can lead to immediate and prolonged suppression of the HPA axis after administration.

4. The Surviving Sepsis Campaign suggests the daily addition of oral fludrocortisone (50 µg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (Grade 2C).

Rationale:

One study added 50 µg of fludrocortisone orally. Since hydrocortisone has intrinsic mineralcorticoid activity, there is controversy as to whether fludrocortisone should be added.

5. The Surviving Sepsis Campaign suggests clinicians wean the patient from steroid therapy when vasopressors are no longer required. (Grade 2D).

Rationale:

There has been no comparative study between a fixed duration and clinically guided regimen, or between tapering and abrupt cessation of steroids. Three RCTs used a fixed duration protocol for treatment, and in two RCTs, therapy was decreased after shock resolution. In four RCTs steroids were tapered over
several days, and in two RCTs steroids were withdrawn abruptly. One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids. It remains uncertain whether outcome is affected by tapering of steroids or not.

The above category 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects case series data or expert opinion.

6. **The Surviving Sepsis Campaign suggests doses of corticosteroids comparable to >300 mg hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A).**

   **Rationale:**

   Two randomized prospective clinical trials and a meta-analysis concluded that for therapy of severe sepsis or septic shock, high-dose corticosteroid therapy is ineffective or harmful. Reasons to maintain higher doses of corticosteroid for medical conditions other than septic shock may exist.

7. **The Surviving Sepsis Campaign recommends that corticosteroids not be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress-dose steroids if the patient’s endocrine or corticosteroid administration history warrants (Grade 1D).**

   **Rationale:**

   No studies exist that specifically target severe sepsis in the absence of shock that offer support for use of stress doses of steroids in this patient population. Steroids may be indicated in the presence of a prior history of steroid therapy or adrenal dysfunction. A recent preliminary study of stress dose level steroids in community-acquired pneumonia is encouraging but needs confirmation.
Evidence grading: The above category 1 recommendations are strong recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects case series data or expert opinion.

CONCLUSION

While the Surviving sepsis campaign guideline maybe the best all round document for managing patients with sepsis and septic shock, there are still many unanswered diagnostic and therapeutic dilemmas. There is a call for larger, more focused clinical trials. However, with the lack of funding from uninterested pharmaceutical companies, this is a problem even in developed countries. Meta-analyses are probably helpful in this setting, though publication bias and heterogeneity give conflicting results that are difficult to interpret and translate in clinical practice.

The management of sepsis and septic shock is a dynamic process. With newer treatment strategies coming to the fore and being evaluated, established strategies may need to be modified. The next few years will be an exciting time, with hopefully a positive impact on reducing the mortality rate from sepsis and septic shock.
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