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Hormonal Therapies in Severe Sepsis

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1. Introduction

Endocrine dysfunction is common in severe sepsis and is associated with increased morbidity and mortality risk. Clinical detection of this heterogeneous disorder is challenging, and the accuracy of laboratory diagnosis is complicated by the limitations in methods of hormonal assays and the variable definitions used in its diagnosis. This chapter will review the pathophysiology of neuroendocrine dysfunction during sepsis, the current evidence for hormone supplementation, and the use of hormonal markers and predictors of outcome following severe sepsis. The three hormones that have been most extensively researched and therefore most commonly considered for use in septic shock are corticosteroids, vasopressin, and insulin. We will describe the rationale, explore the controversies and provide recommendations for their use based on the available evidence. We present current recommendations for hormone therapy in adults and children, but caution that further research is needed to better understand the dynamic and complex endocrine responses during septic shock, and to develop improved methods for diagnosis and monitoring of patient response, so that we can determine not only which therapies to use, but how, when, and in which patients.

2. Neuroendocrine dysfunction in severe sepsis

Severe sepsis is characterized by a complex cascade involving widespread inflammation, enhanced coagulation, diminished fibrinolysis, immunomodulation, and release of stress hormones including adrenocorticotrophic hormone, cortisol, vasopressin, glucagon and growth hormone[1]. Endocrine dysfunction plays an important role in the pathogenesis of multiple organ dysfunction that occurs in septic shock, and several studies have correlated the degree of neuroendocrine dysfunction with severity of illness[2]. Neuroendocrine dysfunction is common during critically illness, and can affect multiple neurohormonal pathways in an individual patient[3]. The hypothalamic-pituitary-adrenal (HPA) axis is a key coordinator of the stress response, and involves a series of complex central and peripheral adaptations essential for survival. The HPA axis is functionally related to the sympathoadrenal system, which is responsible for endogenous catecholamine secretion and inflammatory cytokine activation, as well as the neurohypophyseal system, which is responsible for vasopressin release; all pivotal integrative components in the stress response. The response of the anterior pituitary during severe sepsis consists of two distinct phases -

an acute phase, which is likely adaptive and beneficial, and a more prolonged or chronic phase characterized by suppression of the neuroendocrine axes resulting in hypoactivity or hyporesponsiveness of target hormones, which may no longer be beneficial[4]. Disruption of these axes, as we will discuss subsequently, compromises the adaptive response, and potentially survival. Differentiation between beneficial and harmful endocrine responses to septic shock is difficult. Nevertheless, the association between endocrine dysfunction and increased morbidity and mortality risk has fueled investigators to examine the role of hormonal therapy during sepsis. There are numerous adult studies in this area, some of which have revealed conflicting results. Pediatric data is much more limited. The results of these studies have arguably sparked more debate than provided definitive conclusions in the current management of sepsis.

3. Hormonal therapies in severe sepsis

3.1 Corticosteroids

The normal response of the HPA axis to the stress of illness results in the release of cortisol from the adrenal cortex[5, 6]. This activation is crucial for the general adaptation to illness and the physiological response of multiple organs. The mechanism for HPA axis dysfunction in severe sepsis are complex and multifactorial, but can result in decreased production of corticotropin-releasing hormone, adrenocorticotrophic hormone (ACTH), and cortisol, as well as dysfunction of their receptors even in the presence of “adequate” measured serum hormone levels. Inhibition of hormone production by cytokines and other peptides derived from blood cells (known as corticostatsins) may compete with corticotropin and its receptor[7]. Septicemia itself and the medications used in its treatment may result in decreased corticosteroid production and increased metabolism, interfere with receptor signaling, as well as enzymatic and mitochondrial function that are critical in steroidogenesis. Furthermore, hypothalamic, pituitary or adrenal destruction by hemorrhage or ischemia, and the accumulation of nitric oxide, superoxide, or central neuropeptides can contribute to receptor down regulation of HPA hormones in patients with severe sepsis and septic shock[8]. The end-result of this disruption in the HPA axis is a syndrome of adrenal insufficiency.

It has been suggested by the expert panels and consensus from the American College of Critical Care Medicine International Task Force, that the terms absolute or relative adrenal insufficiency be replaced by “critical illness-related corticosteroid insufficiency” (CIRCI)[5]. CIRCI has been defined as inadequate glucocorticoid activity in relation to the severity of the patient’s illness and has been most prominently investigated in cases of sepsis and septic shock[9-11]. It is a heterogeneous disorder that can occur as a result of dysfunction at any point in the HPA axis. CIRCI has been recognized in both adult and pediatric patients with severe sepsis, with an incidence as wide ranging from 10% up to 70% depending on the definition used and the study[3, 12-14]. The diagnosis of CIRCI carries with it prognostic implications. These patients are more likely to require vasopressor support, be refractory to fluid and catecholamine therapy, and are more likely to die[15]. There are several proposed definitions for CIRCI, but the most widely accepted definition in adults and pediatrics is an increment in cortisol of less than 9 µg/dL (250 nmol/L), 30-60 minutes after a 1µg ACTH stimulation test[5, 14]. The traditional dose of 250 µg of ACTH is a very large, supraphysiologic adrenal stimulus, and it is suggested that a low dose (1µg) ACTH stimulation is more appropriate and sensitive in distinguishing primary vs. secondary

adrenal failure[14, 16]. The diagnosis of CIRCI in severe sepsis is challenging for the following reasons: firstly, there is debate with respect to the ACTH stimulation test itself. While there is more evidence on the use of the 250 μ g stimulation test, expert panels agree that the 1 μ g stimulation test may be more physiologic, although they concede that there is a moderate grade of evidence supporting this recommendation[5, 17]. Secondly, confounding factors such as variability in sampling and cortisol assays need to be considered. Commercially available assays measure total cortisol, not the biologically active free fraction of the hormone[18]. Circulating cortisol is 90% bound to albumin and cortisol binding globulin, which may be decreased in severe sepsis. Hypoalbuminemic septic patients may therefore have subnormal total cortisol levels but normal free cortisol levels[19]. Defining normal adrenal function can therefore be extremely challenging in the setting of severe sepsis and septic shock, as it needs to consider numerous variables such as the physiologic variation among individuals, the performance of commercially available cortisol assays, levels of free versus bound cortisol, and medications that may interfere with cortisol secretion or regulation.

3.1.1 The evidence for corticosteroid supplementation in severe sepsis

Corticosteroids have been studied extensively as an adjunctive therapy in septic patients for over 40 years and has been a subject of controversy for decades. As corticosteroid insufficiency can occur in severe sepsis, the rationale for steroid use in this setting is to attenuate the exaggerated systemic inflammatory response and cytokine activation, improve hemodynamic function, and reverse the HPA axis suppression and subsequent adrenal insufficiency. Corticosteroids have been shown to improve the vascular response to exogenous catecholamines in the septic state through its up-regulation of adrenergic receptors, and inhibition of vasodilatory stimulants such as nitric oxide synthase, prostaglandin E₁ and prostacyclin[20]. Corticosteroids may also reverse vascular hyporesponsiveness to vasopressin[21].

Clinical trials of corticosteroids date back as far as 1963, and although it may now be recognized that CIRCI is common in septic shock, consensus on how best to treat this phenomenon is yet to be reached. This stems from several challenges – the difficulties in establishing its diagnosis as described above, the controversies on appropriate dosing of corticosteroids and contradictory results from numerous trials on the efficacy of steroid replacement in this setting, and finally, the identification of CIRCI is not predictive of a favourable response to corticosteroids. Nevertheless, meta-analyses, reviews and guidelines have advocated the use of low-dose hydrocortisone in patients with septic shock[9-11, 22]. Arguments in favor of steroid replacement are that CIRCI is common in this population, steroids may result in a more rapid shock reversal and therefore improve survival, and steroids may have additional advantages when septic shock is complicated by acute respiratory distress syndrome. Arguments against its use include the increased risk of adverse effects such as superinfection, critical illness myopathy, hyperglycemia and ultimately increased mortality[11, 23]. Hence, there are multiple questions with respect to CIRCI that pertain not only to should we treat, but who to treat and how to treat.

The earlier sepsis trials of the 1980's evaluated high-dose corticosteroids and found no mortality reduction, but a trend towards harm[24]. Further analyses suggested an inverse relationship with steroid dose and survival - the higher the dose the lower the survival rate. Subsequent trials performed in the 1990's in which lower, more physiologic doses of glucocorticoids were administered for longer courses demonstrated improved shock

reversal, but a more heterogeneous beneficial effect on mortality[22]. The largest of these trials, conducted by Annane et al. demonstrated improved survival with 7 days of 200 mg hydrocortisone and 50 mg fludrocortisone per day when compared to placebo, in patients with evidence of CIRCI (ACTH nonresponders)[25]. There was no significant difference in mortality between groups amongst responders. A criticism of this trial is that 72 of 229 nonresponders received etomidate, an inhibitor of 11 β -hydroxylase and hence cortisol production[26]. 94% of the etomidate treated patients in the Annane trial demonstrated CIRCI. This limitation in generalizability of this study coupled with concerns regarding side effects tempered the initial enthusiasm for steroid use in septic shock. Meta-analyses published in 2004 demonstrated improved shock reversal with steroids at lower doses, dose related adverse effects, but no impact on overall mortality[11, 22].

There have been at least seven prospective randomized controlled trials published since 2004. The largest of these, the multi-center CORTICUS trial, anticipated enrolling 800 patients but recruitment was stopped at 499 patients because of slow enrolment and other logistical reasons[27]. Twenty-eight day mortality was similar between the hydrocortisone (34%) and the placebo groups (31%), however mortality was insignificantly higher in non-responders. Interestingly, steroid treatment accelerated shock reversal more so in responders, but was associated with an increased incidence of nosocomial infection, superinfection, and hyperglycemia. The investigators concluded that routine hydrocortisone should not be routinely used in adults with septic shock, and the ACTH stimulation test does not identify patients who might benefit from hydrocortisone therapy[28]. The discrepant findings of the CORTICUS and the Annane trial have sparked debate as to why their findings differ. Possible contributing factors are that CORTICUS enrolled patients later (up to 72 hours in septic shock), with lower disease severity, as opposed to targeting patients early in their disease (3-8 h) who are poorly responsive to vasopressors, which was the Annane protocol. An updated meta-analysis combining all trials published after 1997 concluded that low-dose corticosteroids consistently improves shock reversal, but decreases mortality only patients with more severe septic shock who are at the highest risk of death[29]. Low-dose steroids appear to increase mortality or have no effect in less severely ill patients with sepsis.

In contrast to the adult literature, there are very few clinical trials of corticosteroid use in pediatric septic shock, the majority of which have been conducted in the setting of Dengue shock, and have lead to conflicting conclusions. Min et al in a double-blinded randomized controlled trial (RCT) reported a lower case fatality rate following 3 days of adjunctive hydrocortisone (19%), compared to placebo (44%, $p=0.005$)[30]. However in a subsequent trial by Sumarmo et al, while underpowered ($n=97$), found no benefit following a single dose 50 mg/kg of hydrocortisone within 6 hours of randomization[31]. A Cochrane systematic review evaluated 4 trials that enrolled a total of 284 subjects, and concluded that there was no benefit from adjunctive corticosteroid therapy in children with Dengue shock[32]. There have been two RCTs in the preterm population both of which demonstrated a short term beneficial hemodynamic effect of steroids in the setting of refractory hypotension of unspecified etiology, however no differences in clinical outcomes have been demonstrated.[33, 34] A large retrospective cohort study utilizing the Pediatric Health Information System administrative database ($n=6693$) suggested that adjunctive corticosteroid therapy for pediatric severe sepsis was associated with a variety of worse outcomes (mortality rate of 30% in children who received steroids compared to 18% in those who did not), however the study was criticized for

its lack of severity of illness data in the study population.[35] A post-hoc analysis of the RESOLVE (*RE*searching severe Sepsis and Organ dysfunction in children: a *g*lobal perspective F1K-MC-EVBP) trial of activated protein C for pediatric severe sepsis, which is the largest prospective pediatric sepsis clinical trial to date, found no difference in outcomes (mortality, days requiring vasoactive infusion or mechanical ventilation, organ failure resolution) amongst those who received corticosteroids and those who did not[36]. The evidence in pediatrics is far from conclusive, and further prospective, RCT data evaluating corticosteroids use specifically in pediatric and neonatal septic shock is very much needed.

3.1.2 Recommendations for corticosteroid use in sepsis

The effects of corticosteroids in sepsis are dependent on both the dose used and severity of illness. High-dose steroids during sepsis are harmful, while low-dose steroids improves shock reversal, and may have a mortality benefit in the sickest patients with refractory septic shock. Until further definitive data are available on the population most likely to benefit from therapy, the decision to administer low-dose steroids during sepsis should be individualized, and considered in relation to the patient's severity of illness, and risk factors from their endocrine or corticosteroid history. ACTH stimulation test is not routinely recommended for the purposes of identifying patients who may benefit from steroid therapy. Having considered the controversies and nuances of the current evidence, the 2008 Surviving Sepsis Campaign International Guidelines made the following recommendations, using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) criteria to indicate the strength of the evidence and recommendations[10]: the use of low dose steroids (e.g. < 300 mg/day of hydrocortisone) should be considered for in septic adults (and children) who remain hypotensive despite adequate fluid and vasopressors (Grade 2C); the current ACTH simulation test that assesses total serum cortisol is not recommended to identify the subset of adults with septic shock who might benefit from hydrocortisone (Grade 2B); hydrocortisone is preferred over dexamethasone (Grade 2B); oral fludrocortisone for added mineralocorticoid activity may be considered (Grade 2C); corticosteroid therapy may be weaned once vasoactive support is no longer required (Grade 2D); and the use of corticosteroid supplementation should not be used to treat sepsis in subjects whose shock reverses after fluid and pressors, or in the absence of septic shock unless indicated by the patient's endocrine history(Grade 1D). Despite the lack of evidence supporting the use of short-term steroid therapy in pediatric patients with septic shock, it appears that approximately 50% of pediatric intensivists would empirically treat their septic patients with steroids[13]. Until further data is available, given that CIRCI in pediatric septic shock is associated with a poor prognosis, the guidelines recommend that stress dose steroids (hydrocortisone 50 mg/m²/day) be considered in children with fluid and catecholamine resistant septic shock who have suspected or proven risk factors for corticosteroid insufficiency (purpura fulminans, chronic steroid therapy, pituitary or adrenal abnormalities). These drugs should be weaned off as soon as the hemodynamic status of the patients allows, particularly when vasopressors are no longer required. Potential inhibitors of cortisol secretion such as etomidate or ketoconazole should be avoided in patients with sepsis.

3.2 Insulin

Hyperglycemia is common during severe sepsis and septic shock, due to the presence of circulating counter-regulatory hormones, medications such as catecholamines and

glucocorticoids, and the activation of metabolic pathways such as hepatic glycogenolysis and gluconeogenesis, decreased hepatic glucose utilization, impaired insulin mediated glucose uptake, and cytokine related insulin resistance[37]. The prevalence of hyperglycemia in critically ill patients can be as high as 50% to 75%, depending on the definition used[38]. Historically, moderate hyperglycemia was considered at best to be an adaptive response to critical illness, and at worst, a marker of severity of disease. However, several studies have clearly demonstrated an association between hyperglycemia and mortality in both adult and pediatric non-diabetic critically ill patients[39]. Hyperglycemia has also been associated with an increased risk of sepsis, critical illness polyneuropathy, duration of mechanical ventilation, length of hospital stay[40]. Proposed mechanisms by which hyperglycemia increases morbidity and mortality include pro-inflammatory effects by stimulating reactive oxygen species and interleukin-8, prothrombotic effects, impaired innate immunity, and increased oxidative stress. Reversal of hyperglycemia and its sequelae with insulin therapy therefore has scientific rationale. Insulin in itself may have additional beneficial effects including partial correction of dyslipidemia, prevention of excessive inflammation, and attenuation of the cortisol response to critical illness[41].

3.2.1 The evidence for insulin therapy

The landmark RCT by Van den Berge et al. provided the first clinical evidence that maintaining strict glycemic control with intensive insulin therapy (IIT) in an adult postsurgical intensive care unit (ICU) (target glucose range 80 to 110 mg/dL) provided a mortality, and in some instances, a morbidity benefit, with the greatest mortality reduction of the subgroup of patients with an ICU stay of > 5 days[42]. The IIT group also experienced reductions in duration of mechanical ventilation, ICU stay and critical illness-associated polyneuropathy. This study was criticized for its lack of generalizability as it was conducted in a single center, and participants were mainly cardiothoracic surgical patients, many of whom were receiving total parenteral nutrition. In a subsequent study conducted in adult medical ICU patients by Van den Berghe, IIT did not reduce mortality, but resulted in reductions in length of ICU and hospital stay, duration of mechanical ventilation, and incidence of new renal injury, particularly in the group of patients with an ICU stay of 3 or more days[43]. In fact, mortality was actually greater among those receiving IIT with ICU stay less than 3 days. Since the original Van den Berghe trials, IIT has not been shown to improve outcomes in subsequent multicenter studies involving patients with severe sepsis or in a general ICU population[44, 45]. Two large multi-center trials (VISEP and GLUCONTROL) were both stopped early for safety reasons because of adverse events related to hypoglycemia in the IIT arm, and no mortality difference[44, 46]. In the VISEP study, IIT increased the rate of severe hypoglycemia (17.0% vs. 4.1%) and serious adverse events (10.9% vs. 5.2%, $p = 0.01$) in critically ill adults with sepsis[44]. In the GLUCONTROL trial, treating to achieve a moderately hyperglycemic goal (140-180 mg/dL) yielded similar survival, length of stay with fewer hypoglycemic reactions compared with IIT[46]. The authors of both studies concluded that tight glycemic control with IIT offered no apparent benefits, but increased the risk of hypoglycemia.

The Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR), and international multicenter trial involving 6104 patients, is the largest trial of intensive insulin therapy to date[45]. This trial compared conventional glucose control (≤ 10.0 mmol/L or 180 mg/dL) to intensive glucose control (4.5 to 6.0 mmol/L or 81 to 108 mg/dL) in critically ill patients, and concluded that using insulin to

achieve a conventional glucose control resulted in lower 90 day all cause mortality. However, the subgroup analysis did not reveal a significant difference in treatment effect in the subgroup of patients with severe sepsis (21% of patients). Subsequent meta-analyses incorporating the results of all trials of this nature reveal that IIT significantly increases the risk of hypoglycemia while conferring no overall mortality among critically ill patients, compared to conventional insulin therapy. However, there may be benefits of IIT in the subset of patients treated in surgical ICU's[47, 48]. As corticosteroid therapy induces potentially detrimental hyperglycemia in septic shock, the benefit of intensive insulin therapy in patients treated with hydrocortisone was evaluated (COITSS Study), but did not improve mortality in patients with septic shock when compared to conventional insulin therapy[49].

As expected, the data in pediatrics is limited. While a relationship between hyperglycemia and poor outcomes have also been identified in this population, hypoglycemia in the absence of insulin therapy, and increased glucose variability in particular appear to have an even stronger association with mortality and length of stay[38, 50]. To date, there is only one prospective randomized controlled trial to date by Vlasselaers et al, published in 2009.[98] This trial randomized 700 critically ill children (317 infants aged 1 year, and 383 children aged ≥ 1 year) to an age-adjusted intensive insulin group (i.e. target glucose range of 2.8-4.4 mmol/L in infants, and 3.9-5.6 mmol/L in children), or a conventional group where insulin was initiated only when blood glucose exceeded 11.9 mmol/L. The investigators found that intensive insulin therapy in this trial of predominantly cardiac surgical patients, resulted in a significant decrease in PICU stay, reduced mortality and an attenuated inflammatory response on day 5, as indicated by lower C-reactive protein values. The risk of secondary infections was also significantly lower in the intensive insulin group. The risk of hypoglycemia however, was significantly higher in the intensive insulin group. They also observed that patients who developed hypoglycemia had a higher risk of death than those who were not hypoglycemic, although this difference was not statistically significant. It has been suggested that glucose reperfusion after hypoglycemia may trigger neuronal death, rather than hypoglycemia itself.[99] As the excess neurological deaths in this trial occurred in the conventional and not the intensive insulin arm, the authors conclude that the short-term benefits of preventing hyperglycemia in critically ill children may outweigh those of hypoglycemia, provided that hypoglycemia is recognized and treated promptly.

3.2.2 Limitations of insulin therapy in sepsis

The limitations of insulin therapy for glucose control in critically ill patients with sepsis are primarily three-fold. Firstly, blood glucose variability, especially in children, may be a more important marker of poor outcome than isolated blood glucose levels per se[51]. Secondly, blood glucose monitoring in critically ill patients is notoriously inaccurate by nature of intermittent testing as opposed to real-time results, and the variable methods of measurement and levels of quality control[52]. Furthermore, symptomatic monitoring is also hindered as counter-regulatory responses in critically ill septic patients are often impaired, and ICU therapies like sedation may mask symptoms of severe hypoglycemia. The third and most obvious limitation is the risk of hypoglycemia, which has been clearly identified in the multiple large adult RCTs, as well as the pediatric observational studies. In fact, the rate of hypoglycemia is highest in children with sepsis (28.6%), in the absence of insulin therapy[50]. While there may be subgroups of adult patients who may benefit from IIT[48],

there is clear evidence that children are more susceptible to developing hypoglycemia, and the risks of mortality, morbidity, and irreversible neurological sequelae of hypoglycemia in the developing brain is greater[38].

3.2.3 Recommendations for insulin and glycemic control in sepsis

Although current guidelines from the American Diabetes Association, the American Association of Clinical Endocrinologists and other organizations such as the Surviving Sepsis Campaign currently recommend tight glycemic control with insulin therapy, more recent meta-analyses of the largest trials to date suggest that these recommendations should be revised for septic patients who are critically ill[48]. Less restrictive target glucose values in the range of 140-180 mg/dL appear safer than 80-100 mg/dL in critically ill adults, although it is unclear whether there may be specific subgroups of adult patients who may benefit from IIT and be at lower risk of hypoglycemic events. We recommend that hypoglycemic and variable glucose episodes should be avoided in all patients with sepsis. The risk-benefit ratio for insulin therapy in critically ill children with sepsis remains unclear. While there is a suggestion from the pediatric literature that glycemic control may be beneficial in reducing morbidity and mortality, the optimum blood glucose targets in children remain uncertain. Until further prospective data is available specifically in this population, it is reasonable to target blood a glucose control of ≤ 10 mmol/L as defined by the definitive adult trial. However, further research on this subject in critically ill children is needed, and the long-term sequelae of both hypo- and hyperglycemia in this population should be further investigated. Well-developed, detailed and user-friendly protocols and extensive education of caregivers are essential to any insulin therapy and glucose monitoring protocol. Until a more accurate and reliable continuous blood sensor is available, the most reliable method of blood glucose measurement (i.e. arterial point-of-care) is recommended, particularly in the patient at risk, and capillary blood samples should be interpreted with caution.

3.3 Vasopressin

Vasopressin is a neurohypophyseal peptide hormone that is an attractive adjunctive agent in vasodilatory septic shock for the following reasons:

1. Vasopressin inactivates the key mechanisms responsible for the pathogenesis of vasodilatation and catecholamine resistance[53].
2. Although it is a potent systemic vasoconstrictor, vasopressin demonstrates organ specific vasodilator effects in the pulmonary, cerebral and coronary circulations, potentially preserving vital organ perfusion. It also has been shown to increase urine output and creatinine clearance in patients with septic shock, when compared to norepinephrine[54].
3. Vasopressin influences multiple other hormone responses including ACTH, and consequently cortisol release, important considerations in the setting of HPA axis dysfunction during septic shock[54, 55]. Vasopressin also stimulates prolactin secretion, an important mediator of cellular immune response during sepsis[56].
4. Vasopressin insufficiency, either absolute - as a result of depletion or impaired release from neurohypophyseal stores; or functional - as a result of cytokine mediated receptor down regulation, has been demonstrated in both adults and perhaps children with septic shock[57].

3.3.1 Assessing the vasopressin axis

There is a surge in endogenous vasopressin levels during sepsis, however inappropriately low levels to the order of 3-10 pg/mL have been identified in septic shock. The detection of endogenous deficiency by measuring circulating vasopressin levels is limited by the fact that the mature hormone is unstable, has a short half-life, and circulates largely attached to platelets. Copeptin, a stable vasopressin precursor, has recently been identified as a stable and sensitive surrogate marker for vasopressin release, and has been proposed as a more sensitive and potential prognostic biomarker in sepsis[58]. Others have suggested that the ratio of vasopressin to norepinephrine levels should be considered a reflection of adequacy of vasopressin homeostasis relative to adrenocorticoid homeostasis. The vasopressin/norepinephrine ratios in sepsis and severe sepsis are similar (1/175) while they are much lower when shock ensues (1/1000)[21].

3.3.2 The evidence for vasopressin supplementation in severe sepsis

Numerous adult trials suggest short term benefits of vasopressin, the Vasopressin and Septic Shock Trial (VASST) conducted by Russell et al. evaluated the effect of low dose arginine vasopressin (0.01-0.03 U/min) as an adjunctive agent compared to norepinephrine alone, on mortality in 779 adult patients in septic shock[59]. There was no difference in 28-day mortality between groups (35.4% vs. 39.3%, $p = 0.26$). Although the authors had predicted that based on its vasoconstrictor potency, vasopressin would be more efficacious in the stratum of patients with more severe septic shock (baseline requirement of $\geq 15 \mu\text{g/kg/min}$ norepinephrine), they observed a significant reduction in mortality in the subgroup of patients with less severe septic shock (baseline of 5-14 $\mu\text{g/kg/min}$ norepinephrine). While the authors conclude that these subgroup findings should be hypothesis generating only, it has sparked further debate as to whether higher doses of vasopressin should be used in patients with more severe shock, and should be thus evaluated in future studies. A post hoc analysis of the VASST trial suggested that combined vasopressin and corticosteroid therapy was associated with decreased mortality and organ dysfunction than norepinephrine and corticosteroids[60]. A subsequent open-label trial by Torgersen and colleagues demonstrated that higher doses of vasopressin (0.067 IU/min) resulted in improved hemodynamic control without increased adverse effects, compared to lower doses of 0.033 IU/min in patients with vasodilatory septic shock[61].

There are at present at least 18 published observational studies reporting on a collective total of only 145 children, that arginine vasopressin and its longer lasting synthetic analogue, terlipressin increase systemic blood pressure, decreases inotrope or vasopressor requirement, and increases urine output in children with catecholamine-resistant shock[57, 62]. The doses used in these studies varied substantively, ranging from 0.00002 U/kg/min to 0.002 U/kg/min of vasopressin, and terlipressin dosing administered anywhere from every four hourly, to continuous infusion. The Vasopressin in Pediatric Vasodilatory Shock trial which evaluated the safety and efficacy of low dose vasopressin as an adjunctive agent found no difference in the time to hemodynamic stability, organ free failure days or magnitude of vasoactive agent use between the vasopressin and placebo groups[63]. While there was no statistical difference in the adverse event rates, there was a trend towards increased mortality in the vasopressin group.

3.3.3 Adverse effects of exogenous vasopressin

Because of its potent vasoconstrictor action, potential adverse effects of low dose vasopressin include increase in myocardial after-load, reductions in oxygen delivery,

impaired tissues perfusion and ischemic tissue injury. Thrombocytopenia and increases in aminotransferases activity and bilirubin concentrations have also been reported. These adverse effects appear to be dose-dependent, and more commonly noted with doses of greater than 0.04 U/min of vasopressin or 2 µg/kg/h of terlipressin[21]. However, some of the data is conflicting, and it is yet unclear whether the hemodynamic alterations represent adaptive response to stabilized blood pressure, or the impaired tissue perfusion is an epiphenomenon of the severity of underlying disease rather than a specific side effect of vasopressin or concurrent catecholamine pressor administration.[64] Both the VASST and Vasopressin in Pediatric Vasodilatory Shock trials reported no significant difference in adverse event rates between the vasopressin and control groups[59, 63].

3.3.4 Recommendations for vasopressin use in sepsis

There are currently no recommendations for routine testing for endogenous vasopressin levels in the setting of sepsis. Catecholamine infusions remain the first line vasopressor agents of choice in adults with septic shock[10]. Based on the results of VASST, low dose vasopressin infusion may be considered as an adjunctive agent, however, with the anticipation of an effect equivalent to that of norepinephrine alone. Higher doses of vasopressin may have short-term beneficial hemodynamic effects in septic shock refractory to traditional vasopressor therapy, however its effect on clinically important patient outcomes is unknown. As with any vasopressor therapy, close monitoring of end-organ perfusion, awareness of potential side effects, and measurement of tissue flow where possible are essential. Pediatric recommendations are based on limited evidence and one should be aware that children more commonly present with low cardiac output, high systemic vascular resistance during septic shock, and commonly evolve from one hemodynamic state to another[65]. Vasoactive therapy should therefore be tailored according to the patient's clinical status. There is no evidence that adjunctive vasopressin therapy is beneficial in pediatric sepsis at the present time.

4. Hormonal markers and predictors of outcome in sepsis

The clinical diagnosis of sepsis is made in the presence of a systemic inflammatory response syndrome (SIRS) and a proven or suspected source of sepsis. Our ability to accurately and promptly diagnose sepsis is limited due to the lack of a definitive test in this setting. Positive cultures may account for only 10% of all blood culture results reported, of which up to 50% may be due to contamination. This in turn has significant potential financial and healthcare costs to the patient and the healthcare system[66, 67]. Despite the expanding research on treatment modalities in this field, the mortality rate in sepsis remains unacceptably high, often due to delayed diagnosis and treatment. According to United States data, the incidence of sepsis and number of sepsis-related deaths continue to rise, although there is a slight decrease in the age-adjusted mortality rate among patients with sepsis in recent years[68]. In view of this diagnostic and therapeutic dilemma, the search of an unequivocal and rapid confirmatory test to distinguish septic from non-septic causes of SIRS is paramount. There have been enormous attempts to identify prognostic markers of early sepsis and accurate risk prediction that may better direct therapy and diagnosis and thus improve mortality and morbidity in septic patients. In this context, several endocrine markers and mediators of sepsis have been investigated as potential early indicators and potential predictors of outcome in sepsis. Many of these hormonal assays are still under

investigation and are not commercially available. We discuss some of the current research on hormonal markers of sepsis in the remaining section of this chapter.

4.1 Procalcitonin

Procalcitonin is a 116 amino acid peptide with a sequence identical to that of prohormone calcitonin but devoid of hormonal activity. During sepsis, circulating levels of procalcitonin, increase several-fold to several thousand-fold. Procalcitonin is released into the circulation within 3 hours of endotoxin injection, plateaus at 6 hours, and remains elevated for 24 hours, making it an attractive and sensitive hormonal marker of early sepsis[69]. Procalcitonin measurement was first described by Assicot et al to differentiate between bacterial and non-bacterial causes of sepsis, and while it is now increasingly used as an early marker of bacterial infection, procalcitonin can be increased in noninfectious conditions, and remain low in certain bacterial infections, such as bacterial pulmonary aspiration[70-72]. Procalcitonin appears to offer better specificity over other biomarkers such as C-Reactive Protein, in differentiating between viral and bacterial causes of fever, and in distinguishing invasive from noninvasive infections[73, 74]. More recently, procalcitonin has been advocated as a clinical tool to guide antimicrobial therapy in patients with suspected infections. Several randomized controlled trials have reported a significant reduction in antibiotic exposure and duration based on serial procalcitonin measurements, compared to a standard approach[75-77]. An association between decreasing levels of procalcitonin and favourable outcomes has been suggested by several investigators, however further validation studies are required before any firm conclusions can be made[72, 78].

4.2 Thyroid

Thyroid hormones play an important role in the adaptation of metabolic function to stress and critical illness. Thyroid function abnormalities are often observed during critical illness but are transient and may not represent underlying thyroid disease. There is evidence that lower baseline thyroid hormone values, including triiodothyronine (T_3), thyroxine (T_4), and thyroid stimulating hormone (TSH) can be substantially lower in septic compared to non-septic patients of similar critical illness severity, and that these abnormalities are associated with a worse outcome in patients with sepsis or septic shock[79]. Low T_3 can be attributed to increased de-iodination of T_4 to reverse T_3 (rT_3), rather than T_3 , and increased catabolism of T_3 to 3,3-diiodothyronine. Low total and free T_4 and low TSH levels can be observed in severe sepsis and septic shock due to decrease in plasma T_4 -binding globulin or transthyretin as well as accumulation of substances that lower the plasma thyroid hormone-binding capacity[80]. However, the pattern of abnormal thyroid profiles are not consistently observed between studies, with more pediatric studies reporting thyroid function abnormalities. Reasons for discordant findings may be attributed to age related hormonal differences - plasma thyroid hormone levels are higher than older children and adults in the first few months of life, due to the TSH surge that occurs in the immediate postnatal period, and elevated TBG levels secondary to maternal estrogen. Other reasons for variable findings may be attributed to differences in the hemodynamic response to septic shock in children, and thus the type of vasoactive support; dopamine can suppress the pituitary release of TSH and thus potentially the production of T_3 , while norepinephrine is believed to stimulate the secretion of TSH. It is however, generally accepted that alterations in thyroid hormone observed during septic shock constitute part of an adaptive metabolic response, and that the

majority of patients recover normal thyroid function once their critical illness subsides[81]. Nevertheless, thyroid disorders are relatively common in the general population, with an estimated prevalence of 1% to 10%, and hence a subset of patients with septic shock can have true underlying hypothyroidism. High TSH or reduced rT_3 may be suggestive of such a diagnosis.

The hypothesis of relative thyroid insufficiency and its association with a worse outcome has led to several studies on thyroid supplementation during sepsis. However, despite early animal studies showing beneficial effects of thyroid supplementation particularly on lung mechanics and vasoactive requirements during sepsis[82], human studies have failed to demonstrate a beneficial effect from thyroid hormone replacement in this setting[79]. Thyroid hormone supplementation during sepsis can lead to a reciprocal decrease in TSH, which in turn can adversely effect the adaptive immune response.

In summary, thyroid hormone abnormalities are very common in septic patients and hence future studies are required to establish the strength of this association, or if a causal relationship exists between thyroid hypofunction and adverse outcome. The role of thyroid hormone abnormalities as an adjunctive predictor of outcome warrants further evaluation. Follow-up thyroid function tests are recommended if abnormal levels are measured during severe sepsis, as the majority of these abnormalities are transient.

4.3 Growth hormone

Activation of the HPA axis in critical illness results in an alteration in pulsatile release of growth hormone (GH) from the somatotropes. Down regulation of insulin-like growth factor 1 (IGF1) and GH binding proteins result in an acquired peripheral GH resistance during severe sepsis which in turn promotes protein catabolism and negative nitrogen balance[83]. There is evidence that GH resistance and the resultant increase in circulating GH concentrations have deleterious effects in critically ill patients. Increased GH levels has been shown to correlate with poor outcome in children with meningococcal sepsis and septic shock[84]. Increased GH has also been found to correlate with severity of disease and appears to be an independent predictor for mortality in critically ill adults but does not discriminate between septic and non-septic patients[85]. It is also unclear how GH is influenced by difference metabolic factors such as glucose control, insulin administration, and nutrition. Unfortunately, trials with recombinant GH targeted at overcoming the GH resistance induced catabolism have not been promising but in fact have demonstrated potential harm due to emergence of uncontrolled infections and the development of multiple organ failure[86]. At this point in time, the potential benefits of GH measurements in sepsis remain unclear and is therefore not recommended.

4.4 Copeptin

As discussed earlier, measuring circulating vasopressin levels is challenging as the mature hormone is unstable, has a short half-life and is largely attached to platelets. Copeptin, a stable peptide of the vasopressin precursor, is secreted in an equimolar ratio and thus mirrors the production of vasopressin[87]. Copeptin measurements have been shown to be much more stable and easy to determine than vasopressin, and has therefore been proposed as a sensitive and potential prognostic marker in patients with sepsis. Copeptin levels do appear to be increasingly elevated according to severity of illness from patients with sepsis, to severe sepsis and septic shock, however the optimal cut-off level has a sensitivity of 61.5%

and a specificity of 83.8%[88]. Copeptin is not specific to sepsis, and increased levels are also a marker of heart disease and ischemic stroke. Furthermore, copeptin levels may be affected by exogenous corticosteroid therapy, and in renal insufficiency[88].

4.5 Leptin

Leptin is an adipose-derived hormone known for its contribution to energy metabolism and satiety signaling in the hypothalamus. Elevated baseline levels of leptin are found in obese patients, and obesity appears to be an independent, “dose-dependent” risk factor for sepsis morbidity and mortality[89]. There is evidence that leptin is also involved in cell-mediated immunity and cytokine crosstalk. Human septic patients have evidence of increased circulating leptin concentrations which correlate with severity of illness, and hence it has been postulated that leptin may play a critical role in the pathogenesis of sepsis-associated multi-organ dysfunction[90]. It has also been suggested that elevated leptin levels may aid in distinguishing between sepsis and non-infectious SIRS[91]. However, research in this area is in its infancy, and further studies are required to determine the pathogenic mechanisms of leptin, and the diagnostic and therapeutic potential of leptin family molecules in human sepsis.

4.6 Age and sex hormone related phenomena during sepsis

Differences in hormonal profiles have been suggested as the cause of gender-based differences in the incidence and outcomes from severe sepsis. The incidence of sepsis appears to be 15% to 28% higher in males than in females in both the pediatric and adult populations[68, 92]. Among septic patients, even microbes may have a predilection for certain sexes. In a large cohort study of septic patients admitted to US hospitals, men were more likely than women to be infected with Gram-positive organisms after controlling for source of infection[93]. Whether gender related differences in sepsis translates into a higher mortality risk remains unclear[68, 94]. Sex hormones or sex-related gene polymorphisms may protect women against sepsis and death from sepsis. Estrogens and prolactin may confer some protection in women however there are additional non-hormonal based factors such as a differential immune response, sociocultural, racial background, economic or personal health-related behaviours between men and women, that account for the gender-related differences in incidence and outcomes from sepsis[94].

Neuroendocrine dysfunction appears to differ significantly between children and adults and hence it is suggested that age related differences may contribute to variations in disease course, physiologic response and clinical outcomes in these populations[95]. Mortality from pediatric septic shock is significantly lower than in adults[96]. The hemodynamic profile during severe sepsis in children more commonly presents as cardiogenic dysfunction as opposed to the vascular failure seen in adults[97]. As a result, children with fluid-refractory septic shock are frequently hypodynamic and respond to inotrope and vasodilator therapy, while vasopressor therapy is recommended as the first line agent in adult patients[10, 97]. These differences in physiologic response therefore call for a diagnostic and therapeutic approach that is tailored dependent on the patient’s age.

5. Conclusion

Severe sepsis and septic shock remains one of the most challenging problems in medicine today, and in our search for potential therapies to reverse end-organ sequelae of infection,

we are eager to embrace the concept of endocrine support to supplement the antimicrobial and cardiorespiratory support during the management of the sickest of these patients. While hormonal therapy may play an important role in the management of severe sepsis for hormone therapy in sepsis, we have yet to fully understand the dynamic compensatory mechanisms, signaling pathways and complex interdependence of multiple hormonal responses, such that replacement therapy with exogenous hormone with the rationale of restoring normal or “physiologic” values, or to reverse target organ receptor resistance, may be too simplistic a therapeutic approach. We have yet to fully understand the precise mechanisms by which these hormones participate in sepsis and non-infectious SIRS, and the complex role each may play in modulating the inflammatory and immune responses during severe infection, and whether these responses are adaptive or maladaptive. Limitations in predicting who may respond and potentially benefit from such therapies, together with how to define or diagnose dysfunction within a hormonal axis, add further challenges. There are many stress hormones that mirror the severity of illness during sepsis, however with the possible exception of prolactin, none are specific enough to consistently discriminate between infectious and non-infectious causes of SIRS such that one can currently be recommended for routine use as an early diagnostic and independent prognostic marker. Nevertheless based on emerging research, it is likely that hormonal assays may become adjunctive to the predictive capacity of validated prognostic scoring tools in the future. There is evidence that corticosteroid and insulin therapy in specific subgroups of critically ill septic patients can be beneficial. The many controversies and ongoing debates ensure that this area of research will continue to evolve, which will hopefully enhance our ability to not only detect hormone dysfunction, but also predict outcome, and ultimately refine our diagnostic, therapeutic and prognostic approaches in septic patients.

6. References

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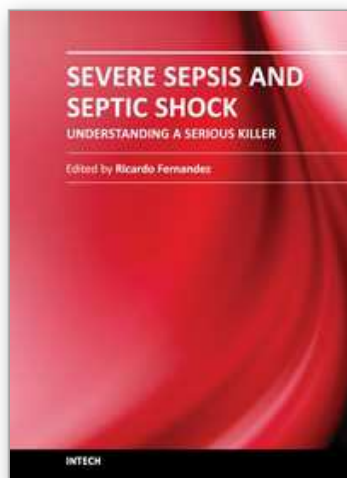
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Severe Sepsis and Septic Shock - Understanding a Serious Killer

Edited by Dr Ricardo Fernandez

ISBN 978-953-307-950-9

Hard cover, 436 pages

Publisher InTech

Published online 10, February, 2012

Published in print edition February, 2012

Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Karen Choong (2012). Hormonal Therapies in Severe Sepsis, Severe Sepsis and Septic Shock - Understanding a Serious Killer, Dr Ricardo Fernandez (Ed.), ISBN: 978-953-307-950-9, InTech, Available from: <http://www.intechopen.com/books/severe-sepsis-and-septic-shock-understanding-a-serious-killer/hormonal-therapies-in-severe-sepsis>

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