CHAPTER 76

Endocrinology of the Stress Response During Critical Illness

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OBJECTIVES

This chapter will:

1. Provide an overview of the stress response.
2. Review changes in the hypothalamic-pituitary-adrenal axis during critical illness.
3. Review stress hyperglycemia.
4. Review stress hyperlactemia.
5. Describe the sick euthyroid/low T3 syndrome.
6. Describe changes in the hypothalamic-pituitary growth hormone axis during critical illness.

STRESS RESPONSE

The stress system receives and integrates a diversity of cognitive, emotional, neurosensory, and peripheral somatic signals that arrive through distinct pathways. Activation of the stress system leads to behavioral and physical changes that are remarkably consistent in their qualitative presentation (Box 76.1). This observation was first noted by Hans Selye, who in 1936 reported that biologic, physical, or psychologic stressors generally precipitate a similar response, which he named the "general adaption syndrome" or stress response.[1] The stress response is normally adaptive and time limited and improves the chances of the individual for survival.

BOX 76.1

Behavioral and Physical Adaptation During Acute Stress

Behavioral Adaptation
Increased arousal and alertness
Increased cognition, vigilance, and attention
Heightened analgesia
Suppression of reproductive axis

Physical Adaptation
Increased heart rate
Increased blood pressure
Increased cardiac output
Blood flow directed to brain and skeletal muscle
Increased temperature
Increased respiratory rate
Increased gluconeogenesis (stress hyperglycemia)
Increased lactate production (stress hyperlactemia)
Increased lipolysis
Inhibition of digestion
Stimulation of colonic motility
Containment of inflammatory/immune response

Behavioral adaptation during stress includes increased arousal, alertness, and vigilance; improved cognition; and inhibition of vegetative functions, such as appetite, feeding, and reproduction. A concomitant physical adaption also occurs mainly to promote an adaptive redirection of energy. Oxygen and nutrients are shunted to the central nervous system and the stressed body sites where they are most needed. Increases in cardiovascular tone, respiratory rate, and intermediate metabolism (gluconeogenesis, lipolysis) work in concert with these alterations to promote availability of vital substrates. The stress response evolved to be of short or limited duration. The time-limited nature of this process renders its accompanying antigrowth, antireproductive, catabolic, and immunosuppressive effects temporarily beneficial. Critical illness, however, is characterized by a pathologically prolonged stress response, which differs quantitatively and qualitatively from the acute stress response. Box 76.2 outlines the hormonal changes that occur with critical illness.

The acute stress response is mediated primarily by the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathoadrenal system (SAS). Activation of the HPA axis results in increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP).[2] CRH plays

BOX 76.2

"Typical" Hormonal Changes During Critical Illness

Hypothalamic-pituitary-adrenal (HPA) axis
- Initial increased corticotropin (ACTH) followed by low levels, which then normalize
- Decreased cortisol clearance
- Cortisol synthesis increased (may be followed by decreased synthesis)
- Decrease in circulating levels of cortisol-binding globulin (CBG)
- Increase in total and free cortisol (may be followed by decreased levels)
- Tissue glucocorticoid resistance
- Decrease in dehydroepiandrosterone
- Decreased androgen synthesis
- Decreased aldosterone synthesis

Sympathoadrenal system activation
- Increased epinephrine
- Increased norepinephrine

Growth hormone axis
- Increased growth hormone (GH)
- Decreased GH receptor synthesis
- Decreased insulin growth factor-1 (IGF-1)

Thyroid hormone axis
- Decreased triiodothyronine (T3)
- Increased reverse triiodothyronine (rT3)

Increased prolactin
Increased glucagon

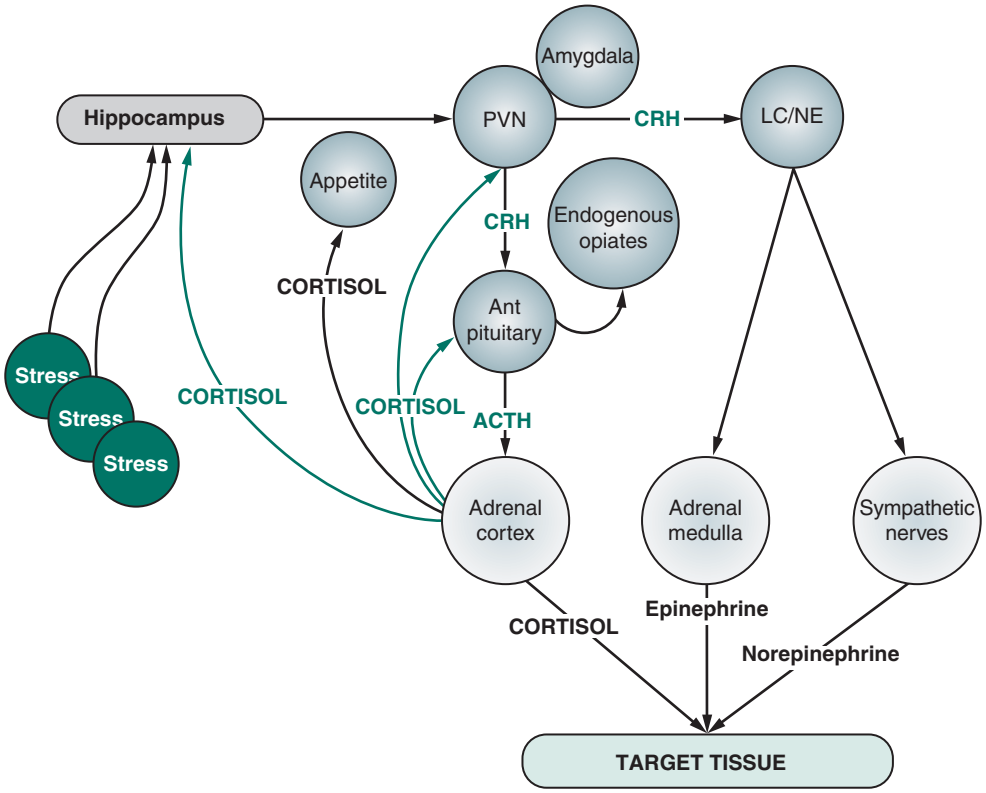

FIGURE 76.1 Activation of the stress response. *ACTH,* Adrenocorticotrophic hormone; *CRH,* corticotrophin-releasing hormone; *LC/NE,* locus ceruleus norepinephrine system; *PVN,* paraventricular nucleus.

a major role in orchestrating and coordinating the stress response (Fig. 76.1). CRH stimulates the production of adrenocorticotrophic hormone (ACTH) by the anterior pituitary, causing the zona fasciculata of the adrenal cortex to produce more glucocorticoids (cortisol in humans).[3] Activation of the SAS results in the secretion of epinephrine and norepinephrine from the adrenal medulla and sympathetic nerves and to an increased production of inflammatory cytokines such as interleukin-6 (IL-6).[2]

The acute stress response results in increased circulating levels of cortisol, epinephrine, and norepinephrine. The combined effects of these hormones increase cardiac output blood, blood pressure, and blood flow to vital organs with an increase in circulating levels of glucose (stress hyperglycemia) and lactate levels (stress hyperlactemia). In general, there is a graded response to the degree of stress with cortisol and catecholamine levels correlating with the intensity of the stressor.[3] An intact HPA axis is required to protect the host against diverse stressors (fight-and-flight response) and to ensure survival.

Cortisol Physiology

ACTH stimulates steroidogenesis by binding to the melanocortin-2 receptor on adrenocortical cells. ACTH upregulates expression of this receptor and mediates cholesterol release from lipid droplets. In addition, ACTH activates the expression of genes encoding cholesterol uptake and synthesis as well as key enzymes responsible for cortisol synthesis.[4] Cortisol (hydrocortisone) is the major endogenous glucocorticoid secreted by the adrenal cortex. More than 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with less than 10% in the free, biologically active form. CBG is the predominant binding protein with albumin binding a lesser amount. The adrenal gland does not store cortisol; increased secretion arises because of increased synthesis under the control of ACTH. Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue. In a series of sequential enzymatic steps, cholesterol is converted to pregnenolone and then to the end products of adrenal biosynthesis, namely, aldosterone, dehydroepiandrostenedione, and cortisol. At rest and during stress about 80% of circulating cortisol is derived from plasma cholesterol, the remaining 20% synthesized in situ from acetate and other precursors. High-density lipoprotein (HDL) is the preferred cholesterol source of steroidogenic substrate in the adrenal gland.[5] In healthy individuals the circulating half-life of cortisol varies from 70 to 120 minutes, with a biologic half-life of about 6 to 8 hours. The principal route of cortisol clearance occurs in the liver (through A-ring reductases) and the kidney, where 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) converts cortisol to cortisone.

The activities of glucocorticoids are mediated by the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The GR and MR share functional and structural homology.[6] Aldosterone and glucocorticoid hormones bind to the GR and MR. At low basal levels cortisol binds to the high-affinity, low-capacity MR. However, with increased cortisol secretion the MRs are saturated and cortisol then binds to the low-affinity, high-capacity GR. In addition, the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes play an important role in preventing glucocorticoid access to cells that express the MR.[7,8] This enzyme has two isoforms, a NAD+-dependent form (11β-HSD-2) and a NADP+ dependent form (11β-HSD-1). 11β-HSD-2 is found in tissues with high levels of MR activity such as the kidney, sweat and salivary

glands, placenta, and colon. 11β-HSD-2 converts cortisol to cortisone, its inactive reduced metabolite, which is unable to bind to the GR and MR. 11β-HSD-1, which is found in glucocorticoid target tissues, catalyzes the conversion of cortisone to the active glucocorticoid cortisol.

Cortisol diffuses rapidly across cell membranes binding to the GR. Two isoforms of the GR have been isolated, namely GR-α and GR-β. The GR-β isoform fails to bind cortisol and activate gene expression and thus functions as a negative inhibitor of GR-α.[9] Seven isoforms of GR-α have been reported; these isoforms may be selectively expressed by different tissues with each isoform eliciting a distinct response.[10,11] Through the association and disassociation of chaperone molecules the glucocorticoid-GR-α complex moves into the nucleus, where it binds as a homodimer to DNA sequences called glucocorticoid-responsive elements (GREs) located in the promoter regions of target genes, which then activate or repress transcription of the associated genes. In addition, the cortisol-GR complex may affect cellular function indirectly by binding to and modulating the transcriptional activity of other nuclear transcription factors, such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1). Overall, glucocorticoids affect the transcription of thousands of genes in every cell of the body. It has been estimated that glucocorticoids affect 20% of the genome of mononuclear blood cells.[12]

Cortisol has several important physiologic actions on metabolism, cardiovascular function, and the immune system. Cortisol increases the synthesis of catecholamines and catecholamine receptors, which are partially responsible for its positive inotropic effects. In addition, cortisol has potent antiinflammatory actions, including the reduction in number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils at sites of inflammation. Cortisol is the most important inhibitor of the transcription of proinflammatory mediators (inhibits NF-κB and AP-1 by multiple mechanisms).[3]

Hypothalamic-Pituitary-Adrenal Axis in Critical Illness

Classically the stress response is short lived, allowing the host to successfully deal with the acute threat, after which the stress response rapidly dissipates with cortisol and catecholamine levels returning to baseline. Critically ill and injured patients, however, have a prolonged stress response that may last for weeks. It previously has been assumed that the stress response of critical illness was an extension of the acute stress response. However, recent data suggest that the chronic stress response differs qualitatively and quantitatively from the acute stress response. Although the changes of the hypothalamic-pituitary-thyroid axis with critical illness have been well characterized (euthyroid sick syndrome), the changes of the HPA axis have been less well studied. Furthermore, although a number of studies have evaluated the HPA axis early in the course of critical illness (i.e., on ICU admission), very few studies have investigated the temporal trends of CRH, ACTH, and cortisol over time. These studies have demonstrated that the pattern of the HPA activation during critical illness differs considerably from the classic short-lived acute stress response.[13] Most strikingly there appears to be a dissociation between the serum cortisol and ACTH levels, known as the "cortisol-ACTH dissociation."[14] In addition, there is a marked hourly variability in plasma cortisol levels with loss of the circadian rhythm.[15] Annane et al. performed a cosyntropin stimulation and metyrapone test within 24 hours of ICU admission in critically ill patients with sepsis, critically ill patients without sepsis, and healthy volunteers.[16] In this study the mean basal cortisol was 17.8 ug/dL, 27.8 ug/dL, and 12.6 ug/dL, respectively, whereas the simultaneous ACTH levels were 8 pg/mL, 6 pg/mL and 33 pg/mL, respectively. This study demonstrated that, although the basal cortisol was elevated in the majority of critically ill patients, the ACTH levels were subnormal. In addition, the basal cortisol levels were lower in the critically ill septic as compared with nonseptic patients.

Only a few studies have evaluated the course of serum cortisol and ACTH levels over time. Vermes et al. measured the cortisol and ACTH levels daily for 8 days in 30 critically ill patients and 15 matched hospitalized controls.[17] The plasma cortisol levels were elevated in the critically ill patients and remained high during the whole observation period. In contrast, plasma ACTH levels decreased between days 3 and 5, reaching significantly lower levels on day 5 compared with those in the control group. Vassiliadi et al. measured cortisol, ACTH, and stimulated cortisol levels every 3 to 4 days until day 30, recovery, or death in 51 critically ill patients with sepsis.[18] In this study basal cortisol was elevated and remained elevated throughout the duration of the study. The ACTH levels, however, were low on presentation and normalized after day 10. In the most comprehensive study to date, Boonen et al. evaluated the time course of the HPA axis and cortisol metabolism over 7 days in 158 ICU patients.[13] Similar to the study of Vassiliadi et al., plasma cortisol levels were elevated on presentation and remained elevated over the 7 days of the study; however, ACTH levels were reduced on presentation (lower than controls) and tended to increase over the next 6 days. This dissociation between ACTH and cortisol suggested that non–ACTH-mediated mechanisms regulate cortisol availability during critical illness.[19] The authors of this study quantified cortisol production with the use of the deuterated cortisol tracer technique in addition to evaluating cortisol metabolism.[13] This analysis demonstrated that daytime cortisol production was only twice that of healthy subjects, whereas cortisol breakdown was reduced substantially, which resulted in a fivefold longer half-life of cortisol.

The calculated plasma clearance after the administration of 100 mg of hydrocortisone was 60% lower in patients than in controls. Furthermore, patients with a cortisol response to corticotropin less than 21ug/dL had a substantially reduced plasma clearance of cortisol than patients with a normal response to corticotrophin. The reduced cortisol breakdown was explained by suppressed expression and activity of A-ring reductases in the liver and by suppressed activity of 11β-HSD2 in the kidney. The results of this study suggest that impaired cortisol clearance contributes to the increased cortisol levels found during critical illness. It is postulated further that the increased cortisol levels via negative feedback inhibit ACTH release accounting for the low ACTH levels.[13,20,21] The increased cortisol levels do not appear to be due to increased adrenocortical sensitivity to ACTH.[14] In addition, these authors have demonstrated that pulsatile ACTH secretion was 31% lower in critically ill patients than controls, largely because of decreased ACTH burst mass.[14]

ACTH levels are subnormal during critical illness and ACTH plays an important role in steroidogenesis and has tropic effects on the adrenal cortex. Therefore it has been postulated that the low ACTH levels would lead to atrophy of the adrenal gland and decreased ACTH responsiveness. Boonen et al. harvested the adrenal glands from long-stay ICU patients, short-stay ICU patients, and controls within 24 hours of their death.[22] These authors demonstrated 78%

less cholesterol ester and at least 58% less mRNA expression of ACTH-regulated steroidogenic enzymes in the long-stay ICU patients as compared with the controls and short-stay patients. This finding may contribute to "relative adrenal insufficiency," which may occur in chronically critically ill patients.

Alternative Mechanisms for Altered HPA Function During Critical Illness

The finding that critically ill patients have reduced cortisol metabolism, resulting in increased cortisol levels with low concomitant low ACTH levels, recently has gained much attention.[13,19–21,23] However, it is likely that other derangements of the HPA axis as well as abnormal glucocorticoid signaling occur in the critically ill. It is therefore probable that a variety of phenotypic patterns exist and that these patterns may change over time. It has been demonstrated that an increased concentration of proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin factor-1β (IL-1β) can impair directly CRH-stimulated ACTH release.[24] Increased expression of inducible nitric oxide synthase (iNOS) and suppressed orexin levels during experimental sepsis are associated with suppressed ACTH synthesis.[25] In addition, abnormities in steroidogenesis may contribute to the adrenal insufficiency of critical illness. Festti et al. evaluated the HPA axis in 34 patients within the first 24 hours of the onset of septic shock.[26] In this study 32% of patients had adrenal insufficiency (Δ cortisol < 9 mg/dL) with the baseline ACTH being significantly higher in the nonresponders compared with the responders (55.5 pg/mL vs. 18.3 pg/mL, $p = .01$). In this study, the high ACTH in the nonresponders may be a consequence of abnormalities in steroidogenesis. Although the baseline cortisol levels were increased in the studies by Boonen et al. and Vassiliadi et al., other studies have demonstrated low cortisol levels (<10 ug/dL) in approximately 20% of ICU patients.[16,27] In the study by Annane et al. 18% of the septic patients had a basal cortisol less than 10 ug/dL.[16] Kwon et al. evaluated the HPA axis in 82 patients critically ill patients.[27] In this study 16 (20%) patients had a basal cortisol less than 10 ug/dL, whereas an additional 20 (24%) patients had a delta cortisol of less than 9 ug/dL after a cosyntropin stimulation test.

Tumor necrosis factor-alpha (TNF-α) has been shown to reduce adrenal cortisol synthesis by inhibiting the stimulatory actions of ACTH and angiotensin II on adrenal cells.[28–30] In addition, a strong body of evidence suggests that substrate deficiency (HDL) may lead to inadequate cortisol synthesis during acute illness. HDL is an important lipoprotein present in human plasma and plays a major role in reverse cholesterol transport.[31] The major apoprotein present in HDL is apolipoprotein A1 (Apo-A1), which provides structural stability to the spherical molecule. Free cholesterol is esterified by lecithin-cholesterol acyl-transferase (LCAT), which then combines with the disk-shaped pre-HDL complex forming a spheric structure, HDL_3.[32] HDL_3 molecules continue to engulf additional lipid molecules and apoproteins, thereby forming mature HDL_2. HDL_2 is removed from the circulation by the liver, where it binds to the scavenger receptor class B type I (or the human homolog Cla-1) and Apo-A1 receptors. HDL has been shown to be reduced substantially in patients with many acute illnesses, including sepsis and burns, after myocardial infarction and in patients undergoing surgical interventions.[33,34] Proinflammatory cytokines, particularly IL-6, appear to decrease the synthesis of Apo-1.[35,36] In addition, during the acute phase response, Apo A1 is replaced by serum amyloid A (SAA) in the HDL particle.[31] Ly et al. demonstrated that plasma LCAT activity and hepatic LCAT mRNA levels are decreased by lipopolysaccharide and TNF-α treatment.[37] Similarly, Ettinger et al. demonstrated that TNF-α, IL-1, and IL-6 decreased synthesis of LCAT in cultured Hep G2 cells.[38] It is likely that LCAT levels are reduced in critically ill and injured patients contributing to the reduced HDL_2 levels. Low HDL levels have been demonstrated to have important prognostic implications.[39,40] HDL is believed to modulate the inflammatory process by a number of mechanisms, including binding and neutralization of bacterial toxins, inhibition of adhesion molecule expression, and stimulation of endothelial nitric oxide synthase (eNOS) production. [31] However, HDL may have a major role in modulating the inflammatory response in its role as the major precursor of cortisol.

Experimental studies suggest that HDL is the preferred cholesterol source of steroidogenic substrate in the adrenal gland.[5] Mouse SR-B1 (scavenger receptor, class B, type 1) and its human homolog (Cla-1) have been identified as the high affinity HDL receptor mediating selective cholesterol uptake.[41–45] These receptors are expressed at high levels in the parenchymal cells of the liver and the steroidogenic cells of the adrenal glands, ovary, and testis.[44] Cai et al. demonstrated that SR-B1 knockout mice had marked glucocorticoid insufficiency and higher mortality in LPS shock compared with control mice.[45] In this study SR-B1–null mice showed a lack of inducible glucocorticoid synthesis in response to LPS, bacterial infection, stress, or ACTH. Decreased production of cortisol during acute illness therefore may occur because of substrate deficiency (HDL). Polito et al. demonstrated diffuse lipid depletion in the zona fasciculata of the adrenal glands in patients who died of septic shock as well as in experimental endotoxemia and sepsis models.[46] van der Voort et al. demonstrated that in critically ill patients low HDL levels were associated with an attenuated response to cosyntropin.[47] In this study the mean HDL level was 27 mg/dL in cosyntropin responders as compared with 12.7 mg/dL in the nonresponders. Furthermore, a low HDL was the strongest predictor of nonresponsiveness after a cosyntropin test. Low HDL is common in patients with liver disease and may predispose these patients to adrenal insufficiency. We have reported previously that adrenal insufficiency is common in patients with liver disease, with a low HDL being the only variable tested that was predictive of adrenal insufficiency.[48] Similarly, in a cohort of 164 critically ill patients with liver disease, Atogo-Asse et al. reported that 52% had adrenal insufficiency (Δ cortisol < 9 mg/dL) with the increment in the cortisol after a cosyntropin test being inversely related to the HDL level.[49]

Tissue Glucocorticoid Resistance

Tissue corticosteroid resistance is a well-known manifestation of chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD), severe asthma, systematic lupus erythematosus (SLE), ulcerative colitis, and rheumatoid arthritis. Defective GR nuclear translocation and altered histone acetylation has been described in people with corticosteroid-resistant asthma.[50,51] Increased expression of the beta isoform of the GR has been reported in patients with glucocorticoid-insensitive asthma and patients with idiopathic pulmonary fibrosis.[52,53] It is likely that patients with acute inflammatory diseases such as sepsis, acute lung injury (ALI), pancreatitis, traumatic injuries, and burns may develop tissue resistance to glucocorticoids during the course of their disease. In a mouse fibroblast cell line

model, Pariante et al. demonstrated that IL-1 reduced GR translocation and function.[54] In cell culture as well as in ex vivo human lymphocytes, Webster et al. demonstrated that TNF-α disproportionately increased the levels of the GR-β over the GR-α isoform, and that this was associated with the development of glucocorticoid resistance.[55] Guerrero et al. demonstrated increased expression of the GR-β isoform in mononuclear cells from septic patients.[56] In a murine *Staphylococcus aureus* sepsis model Bergquist et al. demonstrated markedly decreased GR expression and decreased nuclear translocation of the GR-complex into the nucleus.[57] In this study GR expression decreased with time, which paralleled the time-dependent decreased efficacy of glucocorticoids in preventing weight loss in the animals. Similarly, in an LPS model, these authors demonstrated decreased GR nuclear translocation compared to control animals.[58] In this study, glucocorticoid treatment improved survival only when started early (2 hr) after LPS administration. van den Akker et al. demonstrated that neutrophils from pediatric patients with sepsis had decreased expression of GR mRNA, with the GR levels inversely related to the level of IL-6.[59] Similarly, Indyk et al. demonstrated lower total and cytoplasmic GR levels in critically ill children.[60] In an ex vivo model Meduri et al. compared the cytoplasmic to nuclear density of the GR-complex in patients with ARDS who were improvers with those of nonimprovers.[61] These authors demonstrated a markedly reduced nuclear density of the GR-complex in nonimprovers, whereas the cytoplasmic density was similar between improvers and nonimprovers. This experiment provides further evidence that the nuclear GC-GR activity may be impaired in critically ill patients despite adequate cytoplasmic (serum) levels of cortisol.

Rheumatoid arthritis and systemic lupus erythematosus are more prevalent in females with greater disease activity in premenopausal women. Gene expression studies suggest that the antiinflammatory actions of glucocorticoids are more effective in males. In an endotoxin sepsis model glucocorticoids are significantly more effective in abrogating the proinflammatory cytokine response and improving survival in male as compared to female rats.[62] Furthermore, in these experiments ovariectomy potentiated the antiinflammatory actions of glucocorticoids in females, suggesting antagonism between ovarian hormones and glucocorticoids. It has been suggested that the differential expression of gender-specific coactivators and transcription factors may be responsible for this phenomenon.[63] In addition, estrogen increases expression of protein phosphatase 5, which reduces ligand-induced phosphorylation of the GR, which reduces GR binding to glucocorticoid response elements and gene activation. [64] These data suggest that estrus females may be relatively glucocorticoid resistant.

The human GR contains 20 cysteine residues that span the DNA (DBD) and the ligand binding domains (LBD) of the receptor.[65,66] The ligand-binding activity of the GR is determined by the presence or absence of intramolecular disulfide bridges between pairs of cysteine thiol groups in the LBD. Similarly, cysteine bridges in the DBD are required for recognition and binding to target DNA.[65,66] Oxidation of the sulfhydryls in the GR alters GR function. Antioxidants have been demonstrated to restore GR function and may play a role in reducing glucocorticoid tissue resistance in inflammatory conditions.[67]

"Adrenal Insufficiency" in the Critically Ill

A limited number of patients admitted to the ICU may have "absolute adrenal insufficiency" resulting from acute destruction of the adrenal gland as a consequence of hemorrhage, infarction, or infection (Box 76.3). In addition, a number of drugs are associated with adrenal failure. Probably the most common cause of primary adrenal insufficiency is the preexistent (prolonged) use of corticosteroids with suppression of the HPA axis. Although the diagnosis of "adrenal insufficiency" in the critically ill is fraught with difficulties, at this time this diagnosis is best made by[16]:

- A random (stress) cortisol of less than 10 ug/dL or
- A delta cortisol of less than 9 ug/dL after a 250-ug ACTH stimulation test

BOX 76.3

Causes of Adrenal Insufficiency in Critically Ill Patients

Reversible Dysfunction of the HPA Axis
- Sepsis/septic shock
- Acute lung injury
- Burns
- Pancreatitis
- Liver failure
- Hypothermia
- Drugs
  - Etomidate (primary AI)
  - Corticosteroids (secondary AI)
  - Ketoconazole (primary AI)
  - Megestrol acetate (secondary AI)
  - Rifampin (increased cortisol metabolism)
  - Phenytoin (increased cortisol metabolism)
  - Metyrapone (primary AI)
  - Mitotane (primary AI)

Primary Adrenal Insufficiency (Adrenal Failure)
- Autoimmune adrenalitis
- HIV infection
  - HART therapy
  - HIV virus
  - CMV
- Metastatic carcinoma
  - Lung
  - Breast
  - Kidney
- Systemic fungal infection
  - Histoplasmosis
  - Cryptococcus
  - Blastomycosis
- Tuberculosis
- Adrenal hemorrhage/infarction
  - DIC
  - Meningococcemia
  - Anticoagulation
  - Antiphospholipid syndrome
  - HIT
  - Trauma

AI, Adrenal insufficiency; *CMV,* cytomegalovirus; *DIC,* disseminated intravascular coagulation; *HIT,* heparin induced thrombocytopenia; *HPA,* hypothalamic-pituitary axis.

Critical Illness–Related Corticosteroid Insufficiency

Critical illness is associated with multiple derangement of the HPA axis, including decreased production of CRH, ACTH, and cortisol, decreased expression and dysfunction of the GR, as well as decreased cortisol metabolism. These abnormalities may coexist and change dynamically over time. Because there is currently no test or measure of cellular glucocorticoid activity, the net result of these interacting factors may be almost impossible to determine at the bedside. Standard methods of assessing adrenal activity based on

measuring plasma cortisol concentration have been shown to suffer numerous problems, including lack of reproducibility, large interassay variation, lack of agreement on diagnostic criteria, excessive variation, and poor correlation with outcome.[15,68–71] As a result, it has proven difficult to reliably identify patients with reduced tissue glucocorticoid activity and who may benefit from administration of exogenous corticosteroids. The concept of relative adrenal insufficiency (RAI) has been proposed to resolve this conundrum; however, the pathophysiology and diagnosis of this condition remain elusive.[71,72]

One approach to resolving the question of whether too little glucocorticoid signal ultimately "gets through" is to examine target genes and cellular pathways whose function is primarily regulated by glucocorticoids. Ultimately activation of primary GR target genes will allow quantification of glucocorticoid activity at the tissue and cellular level.[73] However, this approach is currently not widely available. In critically ill patients, particularly those with sepsis, the inhibitory effects of glucocorticoids on NF-κβ signaling pathways may be used as a surrogate marker of activation of GR target genes. Through their inhibitory effects on NF-κβ signaling pathways, glucocorticoids are the most potent antiinflammatory hormones in the body and thereby suppress the production and activity of proinflammatory cytokines during exposure to stress.

Inadequate glucocorticoid-mediated feedback inhibition of the immune response will result in excess circulating levels of inflammatory mediators. This has led to the concept of critical illness–related corticosteroid insufficiency (CIRCI).[3,74] CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness; that is, CIRCI may be due to inadequate levels of circulating cortisol, systemic or local abnormities in cortisol metabolism, corticosteroid tissue resistance, or a combination of these factors. CIRCI manifests with insufficient corticosteroid mediated downregulation of inflammatory transcription factors. Inadequate glucocorticoid-mediated feedback inhibition of the immune response will result in excess levels of proinflammatory mediators and inadequate modulation of the compensatory antiinflammatory response (CARS). Patients with septic shock, severe bacterial pneumonia, acute lung injury (ALI), and burns have immune dysregulation. These patients by definition have CIRCI.

Over the last 3 decades approximately 40 randomized controlled trials (RCTs) have been conducted evaluating the role of glucocorticoids in patients with pneumonia, sepsis, severe sepsis, septic shock, trauma, head injury, and ARDS. Varying doses (37.5 to 40,000 mg/hydrocortisone eq/day), dosing strategies (single bolus/ repeat boluses/continuous infusion/ dose taper), and duration of therapy (1–32 days) were used in these studies.[75,76] Based on these studies, multiple guidelines and more than 20 meta-analyses evaluating the use of glucocorticoids in critically ill patients have been published. These meta-analyses have provided conflicting outcomes and recommendations. A recent comprehensive meta-analysis, which included a trial sequential analysis, found no "evidence to support or negate the use of steroids in any dose in sepsis patients."[77] Nevertheless, although there are large geographic variations in the prescription of glucocorticoids for sepsis, up to 50% of ICU patients receive such therapy.[78] Furthermore, corticosteroids appear to hasten the resolution of the signs of infection, reduce the need for mechanical ventilation, and reduce ICU stay in patients with pneumonia. [79] Currently, the Australian and New Zealand Intensive Care Society Clinical Trials Group are performing the ADRENAL study, in which 3800 patients with septic shock will be randomized to receive hydrocortisone (200 mg/day as a continuous infusion) versus placebo.[80] The outcome of the ADRENAL study as well as other ongoing studies will hopefully resolve this ongoing therapeutic dilemma. Until definitive data are available, it may be reasonable to treat patients with severe pneumonia, septic shock, and ARDS with a course of low-dose corticosteroids. Hydrocortisone in a dose of 50 mg q6h for 7 days followed by a taper over a few days is suggested.

Chemical modifications to the cortisol molecule have generated derivatives with greater separations of glucocorticoid and mineralocorticoid activity; for a number of synthetic glucocorticoids, the effects on electrolytes are minimal even at the highest doses used. Hydrocortisone, methylprednisolone, and dexamethasone bind to the GR and have similar intracellular receptor mechanisms. However, the synthetic glucocorticoids are metabolized more slowly in the liver, giving them a longer duration of action. The plasma half-lives of glucocorticoids vary, but, because their mechanism of action depend on gene transcription and changes in protein synthesis, their biologic half-lives are long (varying from 8 hours for hydrocortisone to 2 days for dexamethasone). The immunosuppressive and antiinflammatory actions of glucocorticoids are inextricably linked. When they are dosed according to the drug's antiinflammatory properties, there is no evidence to suggest that glucocorticoids have differing effects on immunologic function or have different side effect profiles.

STRESS HYPERGLYCEMIA

The neuroendocrine response to stress is characterized by excessive gluconeogenesis, glycogenolysis, and insulin resistance. However, stress hyperglycemia appears predominantly because of increased hepatic output of glucose (gluconeogenesis) rather than impaired tissue glucose extraction. Cortisol increases blood glucose concentration through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in peripheral tissues such as the skeletal muscles.[81] Epinephrine and norepinephrine stimulate hepatic gluconeogenesis and glycogenolysis; norepinephrine has the added effect of increasing the supply of glycerol to the liver via lipolysis. Stress hyperglycemia and insulin resistance are evolutionarily preserved responses that allow the host to survive during periods of severe stress.[82]

For glucose to reach a cell with reduced blood flow (ischemia, sepsis), it must diffuse down a concentration gradient from the bloodstream, across the interstitial space, and into the cell. Glucose movement depends entirely on this concentration gradient, and for adequate delivery to occur across an increased distance, the concentration at the origin (blood) must be greater. Stress hyperglycemia results in a new glucose balance, allowing a higher blood "glucose diffusion gradient," which maximizes cellular glucose uptake in the face of maldistributed microvascular flow.[83]

Stress hyperglycemia is a component of the stress response, which until 2001 was believed to be beneficial and to enhance the host's chances of survival during stressful situations. In 2001 van den Berghe et al. published the results of the Leuven 1 study, in which they demonstrated that an intensive insulin therapy protocol targeting a blood glucose concentration between 80 and 110 mg/dL reduced the mortality of critically ill surgical patients.[84] This study was supported by retrospective cohort studies in acutely ill patients demonstrating an association between increasing hyperglycemia and poor clinical outcomes. The findings

of the Leuven study were embraced widely and soon became considered the standard of care for ICU patients around the world. In 2006 Van den Berghe et al. repeated their study in medical ICU patients (Leuven II study).[85] Although failing to reproduce the improvement in survival in the entire set of patients, this study demonstrated a reduction in morbidity in the patients randomized to intensive insulin therapy with a reduction in mortality in the subset of patients with an ICU stay of 3 days or more. After the Leuven I study, 14 RCTs in various patient populations, including mixed ICUs, neurosurgical, neurologic, coronary, trauma, and pediatric ICUs, have been performed.[86] All of these studies failed to demonstrate an outcome benefit (any benefit) from tight glycemic control. NICE-SUGAR, the largest trial to date (n = 6022), demonstrated a 2.6% absolute increase in 90-day mortality in patients randomized to intensive insulin therapy ($p = .02$).[87] Until 2010 the discordant findings between the Leuven studies and the "confirmatory studies" were unexplained.[88] However, it became evident that the conflicting findings between the Leuven studies and the "confirmatory studies" were explained by the very large amounts of intravenous glucose provided to the patients in the Leuven studies.[88] In the Leuven studies patients received intravenous glucose on arrival to the ICU at a dosage of 200 to 300 g/day (equivalent of 2 to 3 L of 10% glucose). In addition, parenteral nutrition (intravenous glucose) was provided to almost all patients within 24 hours of ICU admission, even in those patients who could tolerate enteral or oral nutrition.

The rationale to treat hyperglycemia in critically ill patients is to prevent or attenuate acute complications and ultimately to increase survival. No such data exist at any blood glucose threshold. Indeed, the data suggest that attempts at glycemic control in critically ill patients may be harmful, increasing the risk of hypoglycemia, glucose variability, and death. Mild to moderate stress hyperglycemia is likely an adaptive protective mechanism; no data suggest that stress hyperglycemia is harmful. However, attempts at even moderate glycemic control increase the risk of relative and absolute hypoglycemia, which significantly increase the patient's risk of dying.[89] It is not clear at what threshold severe stress hyperglycemia becomes harmful; this is possibly in the range of 220 to 240 mg/dL. This threshold is likely to be higher in patients with poorly controlled diabetes.

STRESS HYPERLACTEMIA

It is widely believed that in critically ill patients when oxygen delivery fails to meet oxygen demand, an oxygen debt with global tissue hypoxia ensues.[90,91] This results in anaerobic metabolism and increased lactate production.[90,91] An increased blood lactate concentration therefore is regarded as evidence of anaerobic metabolism and tissue hypoxia.[90] However, this concept is flawed in that in most situations lactate is produced aerobically as part of the stress response—hence the term *stress hyperlactemia*. Furthermore, global oxygen delivery has to fall very low before oxygen consumption becomes supply dependent and lactate production increases; this situation is uncommon in clinical medicine. Ronco et al. determined the critical oxygen delivery threshold for anaerobic metabolism in critically ill humans while life support was being discontinued.[92] In this study the critical oxygen delivery threshold was 3.8 ± 1.5 mL/kg/min (266 mL/min in a 70-kg patient). Shibutani et al. studied the relationship between oxygen consumption (VO_2) and oxygen delivery (DO_2) in 58 patients undergoing cardiopulmonary bypass.[93] The critical value of DO_2 was identified to be 330 mL/min. These values translate into a cardiac output of approximately 2 L/min; it is likely that only preterminal moribund patients with "shock" would have such a low cardiac output. However, lactate may be a marker of anaerobic metabolism in patients who have true organ ischemia as occurs with mesenteric or limb ischemia after arterial occlusion.

Lactate as a Marker of Illness Severity

An elevated blood lactate concentration (hyperlactatemia) is a typical finding during exercise and in critical illness, most notably sepsis, cardiogenic shock, cardiac surgery, and liver failure. In essentially all situations of severe disease-related physiologic stress, an elevated blood lactate concentration has been demonstrated reproducibly and consistently to be an independent predictor of mortality.[94–98] More than 50 years ago Dr Weil's group demonstrated an exponential increase in the mortality of critically ill patients with increasing blood lactate concentrations.[99,100] More recent studies suggest that the mortality increases linearly above a lactate concentration of 1.4 mmol/L and that this association is independent of organ dysfunction or the presence of shock.[94,101–103] Stress hyperlactemia, similar to stress hyperglycemia, is a marker of illness severity and a beneficial adaptive evolutionary response.

Several studies performed more than four decades ago provide strong evidence that hyperlactacidemia noted during shock states was unlikely to be caused by tissue hypoxia.[104,105] These studies showed that hyperlactacidemia accompanying hemorrhage could be prevented by pretreatment with combined α- and β-adrenergic receptor blockade.[106] Subsequent experimental studies confirmed that elevated arterial lactate in shock was due not to lack of oxygen but to increased lactate production that could be mimicked by epinephrine infusion and blocked by adrenergic receptor blockade.[107–111] It now has been well established that epinephrine released as part of the stress response in patients with shock stimulates Na+ K+-ATPase activity. Increased activity of Na+ K+ ATPase leads to increased lactate production under well-oxygenated conditions in various cells, including erythrocytes, vascular smooth muscle, neurons, glia, and skeletal muscle.[112,113] Lactate production in skeletal muscle, the liver, and other organs occurs at a rate that exceeds its ability to be oxidized, resulting in an accumulation of lactate. In this setting the increased lactate concentration likely serves as an important source of energy for vital organs (heart and brain).

Lactate produced in the cytosol is transported across lipid bilayer membranes by a family of monocarboxylate transport proteins (MCTs).[114,115] Lactate then can be converted to pyruvate within mitochondria rather than the cytosol by mitochondrial LDH and then oxidized. In a normal heart at rest, approximately 60% to 90% of ATP generated comes from β-oxidation of fatty acids, and 10% to 40% comes from pyruvate formed by glycolysis and the conversion of lactate.[116] The proportion of lactate uptake by the myocardium and its use as metabolic fuel increases during exercise, β-adrenergic stimulation, elevated afterload, fast pacing, and during shock.[117–120] Lactate may account for up to 60% of cardiac oxidative substrate and could exceed glucose as a source of pyruvate in the presence of elevated lactate levels.[117,118,121] Accelerated lactate clearance has been demonstrated to compromise cardiac performance during shock.[111,122] Similarly, during exercise and shock states there

is an increase in cerebral lactate uptake and oxidation. These data suggest that hyperlactemia in the setting of acute stress may have a protective effect on the heart and brain.

Hypothalamic-Pituitary-Thyroid Axis Dysfunction

Thyrotrophin (TSH) is released from the anterior pituitary gland and stimulates the thyroid gland. Thyroxine (T4) is released into the circulation predominantly by the thyroid gland. Approximately 80% of the circulating triiodothyronine (T3) is produced in peripheral tissues by 5′-deiodination of free T4, whereas the remainder is secreted by the thyroid. Type 1 iodothyronine 5′-deiodinase (D1) is responsible for the deiodination of T4 and rT3 at the 5′ position of the phenolic ring. Type 3, 5-deiodinase (D3) removes iodide from the 5′-position of the tyrosyl ring, leading to inactivation of T4 and generation of rT3. T3 is the active hormone, whereas free T4 is considered the prohormone. The function of T3 is to maintain metabolic stability; this hormone affects the function of every organ system. rT3 is thought to be hormonally inactive and possibly inhibitory on T3 activity at the cellular level and on D1.

Serum thyroid hormone levels undergo predictable changes in systemic nonthyroidal illness. The initial change in the hypothalamic-pituitary-thyroid (HPT) axis during a mild illness is a decrease in T3 production caused by inhibition of the conversion of T4 to T3, with a reciprocal increase in rT3, the so-called "low T3 syndrome," "non-thyroidal illness syndrome" (NTIS), or "sick euthyroid syndrome" (SES).[123–126] This decrease can occur very rapidly, and the decrease in serum T3 and the rise in rT3 have been reported to correlate with severity of illness. The SES is a strong predictor of poor outcome in critically ill patients.[127–129] Thyroxine-binding globulin (TBG) levels usually are decreased as is the total T4; however, free T4 is usually normal as are the TSH levels. With severe disease and in patients with chronic illness the free T4 (T4 syndrome) and TSH may decrease. The cause of the SES is poorly understood; however, cytokines, most notably IL-1 and IL-6, may play a role by decreasing hepatic 5'-deiodinase type 1 expression.[124,130,131] Derangement in hypothalamic and pituitary function also may contribute to the pathogenesis of SES. These changes in thyroid function are considered adaptive, an attempt to decrease catabolism and energy expenditure at a time of need. Whether the SES becomes maladaptive during critical illness in unclear. SES is observed in about 70% of hospitalized patients with diseases of various causes[132] and is almost universal in critically ill patients. In a cohort of patients undergoing mechanical ventilation, the incidence of the SES was reported to be 79%, with patients with SES having a higher SAPS II score, duration of mechanical ventilation, and mortality.[133] Leon-Sanz et al. studied the HPT axis in 27 patients with septic shock. All patients had SES.[134] However, survivors were characterized by a greater TSH response to TRH, and only survivors demonstrated an increase in T3 over time (by day 5).[134] SES is common after myocardial infarction and stroke, with rT3 levels being an independent predictor of mortality.[135,136]

The role of thyroid hormone replacement in patients with SES is controversial. Brent et al. randomized MICU patients with severe SES (low free T4) to receive T4 (1.5 ug/kg) daily for 2 weeks or placebo.[137] In the treatment group total T4 and free T4 concentrations increased significantly by day 3 and were normalized by day 5. A significant rise in the T3 occurred in the control group on day 7 but was delayed until day 10 in the treatment group. Mortality was equivalent in the two groups (75% control vs. 73% treatment). In a study of severely burned patents given 200 ug T3 daily, there was no evidence of benefit from thyroid replacement.[138] In a randomized controlled study of patients with acute renal failure treatment with thyroxine (150 ug four times daily over 2 days) was associated with an increase in mortality compared with the control group (43% vs. 13%).[139] These data suggest that in critically ill patients with the SES treatment with T4 or T3 alone may not be beneficial. The administration of TSH secretagogues seems to have a more "physiologic" effect[140]; however, additional studies are required before this therapy can be recommended.

A low T3 syndrome has been reported to occur after cardiac surgery.[141] In small studies of patients undergoing cardiac surgery, treatment with T3 appeared beneficial. However, large trials show no benefit of treatment with T3.[142–144] Similarly, retrospective cohort studies suggested a benefit of T3 in improving the function of impaired hearts before transplant. [145–147] "Hormonal resuscitation" consisting of thyroid hormone together with methylprednisone and vasopressin was recommended in brain-dead organ donors, particularly those with a cardiac ejection fraction less than 45%. However, a meta-analysis that included four placebo-controlled RCTs was unable to confirm the benefit of thyroid hormone in this setting.[148] T3 replacement therapy has been shown to improve the neuroendocrine profile and ventricular performance in patients with a dilated cardiomyopathy.[149,150] However, the clinical benefits of treating patients with heart failure and the T3 syndrome have yet to be determined.[150]

Hypothalamic-Pituitary-Growth Hormone Dysfunction

Growth hormone (GH) is a polypeptide hormone with anabolic, immunomodulatory, and lipolytic properties. Its action is mediated partly via insulin growth factor -1 (IGF-1), which is synthesized in the liver as well as the kidneys and pituitary gland. GH secretion is stimulated by growth hormone–releasing hormone (GHRH) and inhibited by somatostatin. The pulsatile secretion of GH seems to be particularly important for its action. During the first hours or days after an acute insult, such as surgery, trauma, or infection, circulating GH levels become elevated and the normal GH profile, consisting of peaks alternating with virtually undetectable troughs, is altered; peak GH and interpulse concentrations are high, and the GH pulse frequency is elevated.[151] However, serum concentration of IGF-1 and the GH-dependent binding protein, IGF-binding protein-3 (IGFBP3) decrease. This reflects reduced GH-receptor expression in peripheral tissues and results in acquired peripheral resistance to GH. It has been suggested that the proinflammatory mediators reduce GH-receptor expression, which, in turn, through negative feedback inhibition, induces the abundant release of GH, exerting direct lipolytic, insulin antagonizing, and immune-stimulating actions, while the indirect IGF-1–mediated effects of GH are attenuated.[152] In prolonged critical illness lowered GH levels and a reduced pulsatile fraction have been found. As a result of this low pulsatility, levels of IGF-1 and IGF binding protein 3 are low. Low levels of IGF-1 are associated with muscle wasting.

To investigate the effect of administration of (high doses) GH in critically ill patients, Takala et al. carried out two parallel RCTs.[153] A total of 532 patients who had been in the ICU for 5 to 7 days and who were expected to require intensive care for at least 10 days were enrolled. The in-hospital mortality rate was significantly higher in patients

who received GH in both studies. Among the survivors, length of ICU stay was prolonged in the GH group. The study has been criticized for the very high dose of GH used, which may have been associated with insulin resistance and hyperglycemia, aggravated concealed hypoadrenalism and hypothyroidism, and promoted apoptosis in compromised tissue. Furthermore, it does not appear logical to treat patients with prolonged critical illness, who have normal to moderately decreased GH, with high doses of GH. Attempts to restore GH pulsatility with GH secretagogues may be more physiologic.

CONCLUSION

The hypothalamic-anterior-pituitary peripheral-hormone axes are uniformly dysregulated in critical illness. The dysregulation of these axes is related to the severity of illness and is a dynamic process. The endocrine and metabolic alterations observed in acute illness include increased serum cortisol and GH levels, blunted GH pulsatility, low ACTH levels, low T3 levels, insulin resistance, stress hyperglycemia, and stress hyperlactemia. These changes are likely an adaptive beneficial response during acute short-lived stress but may become maladaptive during chronic critical illness. The management of these deregulated hormonal axes is controversial with limited data supporting an improvement in outcome with hormonal replacement therapy.

Key Points

1. Corticotropin-releasing hormone (CRH) plays a pivotal role in integrating the stress response.
2. Critical illness–related corticosteroid insufficiency (CIRCI) is common in critically ill patients, particularly those with severe sepsis. A course of "low-dose" corticosteroids may be beneficial in patients with severe pneumonia, septic shock, and acute lung injury.
3. Stress hyperglycemia and stress hyperlactemia are exceedingly common in critically ill patients, are a reflection of disease severity, and likely represent a beneficial adaptive host response.
4. Critical illness causes a decrease in T3 with an increase in rT3 with a normal TSH, resulting in the "low T3" or "sick euthyroid syndrome." There is no evidence that treatment with thyroid hormone is beneficial in this situation.
5. Critical illness is characterized by elevated levels of GH together with resistance to growth hormone. Treatment with GH in this setting is likely harmful.

Key References

13. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med*. 2013; 368:1477.
16. Annane D, Maxime V, Ibrahim F, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2006;174:1319.
74. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36:1937.
87. Intensive versus conventional glucose control in critically ill patietns. The NICE-Sugar Study Investigators. *N Engl J Med*. 2009;360:1283.
126. van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid*. 2014;24:1456.

A complete reference list can be found online at ExpertConsult.com.

References

1. Selye H. A syndrome produced by diverse nocuous agents. *Nature*. 1936;136:32.
2. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA*. 1992;267:1244.
3. Marik PE. Critical illness related corticoseroid insufficiency. *Chest*. 2009;135:181.
4. Lehoux JG, Fleury A, Ducharme L. The acute and chronic effects of adrenocorticotropin on the levels of messenger ribonucleic acid and protein of steroidogenic enzymes in rat adrenal in vivo. *Endocrinology*. 1998;139:3913.
5. Yaguchi H, Tsutsumi K, Shimono K, et al. Involvement of high density lipoprotein as substrate cholestrol for steroidogenesis by bovine adrenal fasciculo-reticularis cells. *Life Sci*. 1998;62:1387.
6. Rogerson FM, Fuller PJ. Interdomain interactions in the mineralocorticoid receptor. *Mol Cell Endocrinol*. 2003;200:45.
7. Edwards CR, Stewart PM, Burt D, et al. Localisation of 11 beta-hydroxysteroid dehydrogenase–tissue specific protector of the mineralocorticoid receptor. *Lancet*. 1988;2:986.
8. Funder JW, Pearce PT, Smith R, et al. Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. *Science*. 1988;242:583.
9. Oakley RH, Jewell CM, Yudt MR, et al. The dominant negative activity of the human glucocorticoid receptor beta isoform. Specificity and mechanisms of action. *J Biol Chem*. 1999;274:27857.
10. Lu NZ, Collins JB, Grissom SF, et al. Selective regulation of bone cell apoptosis by translational isoforms of the glucocorticoid receptor. *Mol Cell Biol*. 2007;27:7143.
11. Duma D, Jewell CM, Cidlowski JA. Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modification. *J Steroid Biochem Mol Biol*. 2006;102:11.
12. Galon J, Franchimont D, Hiroi N, et al. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *FASEB J*. 2002;16:61.
13. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med*. 2013;368:1477.
14. Boonen E, Meersseman P, Vervenne H, et al. Reduced nocturnal ACTH-driven cortisol secretion during critical illness. *Am J Physiol Endocrinol Metab*. 2014;306:E883-E892.
15. Venkatesh B, Mortimer RH, Couchman B, et al. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. *Anaesth Intensive Care*. 2005; 33:201.
16. Annane D, Maxime V, Ibrahim F, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2006;174:1319.
17. Vermes I, Beishuizen A, Hampsink RM, et al. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab*. 1995;80:1238.
18. Vassiliadi DA, Dimopoulou I, Tzanela M, et al. Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcomes. *J Clin Endocrinol Metab*. 2014;99:4471.
19. Boonen E, van den Berghe G. New concepts to furhter unravel adrenal insufficiency during critical illness. *Eur J Endocrinol*. 2016.
20. Boonen E, van den Berghe G. Understanding the HPA response to critical illness: novel insights with clinical implications. *Intensive Care Med*. 2015;41:131.
21. Boonen E, van den Berghe G. Cortisol metabolism in critical illness: implications for clinical care. *Curr Opin Endocrinol Diabetes Obes*. 2014;21:185.
22. Boonen E, Langouche L, Janssens T, et al. Impact of duration of critical illness on the adrenal glands of human intensive care patients. *J Clin Endocrinol Metab*. 2014;99:4212.
23. Peeters B, Boonen L, Langouche G, et al. The HPA axis response to critical illness: New study results with diagnostic and therapeutic implications. *Mol Cell Endocrinol*. 2015;408:235.
24. Gaillard RC, Turnill D, Sappino P, et al. Tumor necrosis factor alpha inhibits the hormonal response of the pituitary gland to hypothalamic releasing factors. *Endocrinology*. 1990; 127:101.
25. Deutschman CS, Raj NR, McGuire EO, et al. Orexinergic activity modulates altered vital signs and pituitary hormone secretion in experimental sepsis. *Crit Care Med*. 2013;41:e368-e375.
26. Festti J, Grion CM, Festti L, et al. Adrenocorticotropic hormone but not high-density lipoprotein cholesterol or salivary cortisol was a predictor of adrenal insufficiency in patients with septic shock. *Shock*. 2014;42:16.
27. Kwon YS, Suh GY, Jeon K, et al. Cytokine levels and dysfunction in the hypothalamus-pituitary-adrenal axis in critically-ill patients. *Intensive Care Med*. 2010;36:1845.
28. Jaattela M, Ilvesmaki V, Voutilainen R, et al. Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. *Endocrinology*. 1991;128:623.
29. Natarajan R, Ploszay S, Horton R, et al. Tumor necrosis factor and interleukin-1 are potent inhibitors of angiotenisin II induced aldosterone synthesis. *Endocrinology*. 1989;125:3084.
30. Jaattela M, Carpen O, Stenman UH, et al. Regulation of ACTH-induced steroidogenesis in human fetal adrenals by rTNF-alpha. *Mol Cell Endocrinol*. 1990;68:R31.
31. Murch O, Collin M, Hinds CJ, et al. Lipoproteins in inflammation and sepsis. I. Basic science. *Intensive Care Med*. 2007;33:13.
32. Rye KA, Clay MA, Barter PJ. Remodelling of high density lipoproteins by plasma factors. *Atherosclerosis*. 1999;145:227.
33. Chien JY, Jerng JS, Yu CJ, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Crit Care Med*. 2005;33:1688.
34. van Leeuwen HJ, Heezius EC, Dallinga GM, et al. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med*. 2003;31:1359.
35. Gordon BR, Parker TS, Levine DM, et al. Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients. *Crit Care Med*. 2001;29:1563.
36. Bonville DA, Parker TS, Levine DM, et al. The relationships of hypocholesterolemia to cytokine concentrations and mortality in critically ill patients with systemic inflammatory response syndrome. *Surg Infect (Larchmt)*. 2004;5:39.
37. Ly H, Francone OL, Fielding CJ, et al. Endotoxin and TNF lead to reduced plasma LCAT activity and decreased hepatic LCAT mRNA levels in Syrian hamsters. *J Lipid Res*. 1995;36:1254.
38. Ettinger WH, Varma VK, Sorci-Thomas M, et al. Cytokines decrease apolipoprotein accumulation in medium from Hep G2 cells. *Arterioscler Thromb*. 1994;14:8.
39. Delgado-Rodriguez M, Medina-Cuadros M, Gomez-Ortega A, et al. Cholesterol and serum albumin levels as predictors of cross infection, death, and length of hospital stay. *Arch Surg*. 2002;137:805.
40. Barlage S, Gnewuch C, Liebisch G, et al. Changes in HDL-associated apolipoproteins relate to mortality in human sepsis and correlate to monocyte and platelet activation. *Intensive Care Med*. 2009;35:1877.
41. Acton S, Rigotti A, Landschultz KT, et al. Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science*. 1996;271:518.
42. Calco D, Gomez-Coronado D, Lasuncion MA, et al. CLA-I is an 85-kD plasma membrane glycoprotein that acts as a high affinity receptor for both native (HDL,LDL, and VLDL) and modified (OxLDL and AcLDL) lipoproteins. *Arterioscler Thromb Vasc Biol*. 1997;17:2341.
43. de la Llera-Moya M, Connelly MA, Drazul D, et al. Scavenger receptor class B type 1 affects cholestrol homeostasis by magnifying cholestrol flux between cells and HDL. *J Lipid Res*. 2001;42:1969.
44. Liu J, Heikkila P, Meng QH, et al. Expression of low and high density lipoprotein receptor genes in human adrenals. *Eur J Endocrinol*. 2000;142:677.
45. Cai L, Ji A, de Beer FC, et al. SR-B1 protects against endotoxemia in mice through its roles in glucocorticoid production and hepatic clearance. *J Clin Invest*. 2008;118:364.

46. Polito A, de la Grandmaison GL, Mansart A, et al. Human and experimental septic shock are characterized by depletion of lipid droplets in the adrenals. *Intensive Care Med*. 2010;36:1852.
47. van der Voort PH, Gerritsen RT, Bakker AJ, et al. HDL-cholestrol level and cortisol response to synacthen in critically ill patients. *Intensive Care Med*. 2003;29:2199.
48. Marik PE, Gayowski T, Starzl TE, et al. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med*. 2005;33:1254.
49. Atogo-Asse FE, Vincent RP, Hughes SA, et al. High density lipoprotein in patients with liver failure; relation to sepsis, adrenal function and outcome of illness. *Liver Int*. 2012;32:128.
50. Matthews JG, Ito K, Barnes PJ, et al. Defective glucocorticoid receptor nuclear translocation and altered histone acetylation patterns in glucocorticoid-resistant patients. *J Allergy Clin Immunol*. 2004;113:1100.
51. Hew M, Bhavsar P, Torrego A, et al. Relative corticosteroid insensitivity of peripheral blood mononuclear cells in severe asthma. *Am J Respir Crit Care Med*. 2006;174:134.
52. Goleva E, Li LB, Eves PT, et al. Increased glucocorticoid receptor Beta alters steroid response in glucocorticoid-insensitive asthma. *Am J Respir Crit Care Med*. 2006;173:607.
53. Wikstrom AC. Glucocorticoid action and novel mechanisms of steroid resistance: role of glucocorticoid receptor-interacting proteins for glucocorticoid responsiveness. *J Endocrinol*. 2003;178:331.
54. Pariante CM, Pearce BD, Pisell TL, et al. The proinflammatory cytokine, interleukin-1alpha, reduces glucocorticoid receptor translocation and function. *Endocrinology*. 1999;140:4359.
55. Webster JC, Oakley RH, Jewell CM, et al. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci USA*. 2001;98:6865.
56. Guerrero J, Gatica HA, Rodriguez M, et al. Septic serum induces glucocorticoid resistance and modifies the expression of glucocorticoid isoform receptors: a prospective cohort study and in vitro experimental assay. *Crit Care*. 2013;17:R107.
57. Bergquist M, Nurkkala M, Rylander C, et al. Expression of the glucocorticoid receptor is decreased in experimental Staphylococcus aureus sepsis. *J Infect*. 2013;67:574.
58. Bergquist M, Jirholt P, Nurkkala M, et al. Glucocorticoid receptor function is decreased in neutrophils during endotoxic shock. *J Infect*. 2015;69:113.
59. van den Akker EL, Koper JW, Joosten K, et al. Glucocorticoid receptor mRNA levels are slelectively decreased in neutrophils of children with sepsis. *Intensive Care Med*. 2013;35:1247.
60. Indyk JA, Candido-Vitto C, Wolf M, et al. Reduced glucocorticoid receptor protein expression in children with critical illness. *Horm Res Paediatr*. 2013;79:169.
61. Meduri GU, Muthiah MP, Carratu P, et al. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation*. 2005;12:321.
62. Duma D, Collins JB, Chou JW, et al. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Sci Signal*. 2010;3:ra74.
63. Quinn M, Ramamoorthy S, Cidlowski JA. Sexually dimorphic actions of glucocorticoids: beyond chromosomes and sex hormones. *Ann N Y Acad Sci*. 2014;1317:1.
64. Zhang Y, Leung DY, Nordeen SK, et al. Estrogen inhibits glucocorticoid action via protein phosphatase 5 (PP5)-mediated glucocorticoid receptor dephosphorylation. *J Biol Chem*. 2009;284:24542.
65. Simons SS, Pratt WB. Glucocorticoid receptor thiols and steroid-binding activity. *Methods Enzymol*. 1995;251:406.
66. Evans RM. The steroid and thyroid hormone receptor superfamily. *Science*. 1988;240:889.
67. Okamoto K. Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 (L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-yl hydrogen phosphate] potassium salt), via a redox-dependent mechanism. *Biochem Pharmacol*. 1998;56:79.
68. Cohen J, Venkatesh B. Assessment of tissue cortisol activity. *Crit Care Resusc*. 2009;11:287.
69. Cohen J, Ward G, Prins J, et al. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. *Intensive Care Med*. 2006;32:1901.
70. Cohen J, Smith ML, Deans RV, et al. Serial changes in plasma total cortisol, plasma free cortisol and tissue cortisol activity in patients with septic shock: an observational study. *Shock*. 2012;37:28.
71. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348:727.
72. Venkatesh B, Cohen J, Cooper M. Ten false beliefs about cortisol in critically ill patients. *Intensive Care Med*. 2015.
73. Wang JC, Derynck MK, Nonaka D, et al. Chromatin immunoprecipitation (ChIP) scanning identifies primary glucocorticoid receptor target genes. *Proc Natl Acad Sci USA*. 2004;101:15603.
74. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36:1937.
75. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *Br Med J*. 2004;329:480.
76. Minneci PC, Deans KJ, Banks SM, et al. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med*. 2004;141:47.
77. Volbeda M, Wetterslev J, Gluud C, et al. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015;41:1220.
78. Beale R, Janes JM, Brunkhorst FM, et al. Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry. *Crit Care*. 2010;14:R102.
79. Siemieniuk RA, Meade MP, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia. A systematic review and meta-analysis. *Ann Intern Med*. 2015.
80. Venkatesh B, Myburgh J, Finfer S, et al. The ADRENAL study protocol: adjunctive corticosteroid treatment in critically ill patients with septic shock. *Crit Care Resusc*. 2013;15:83.
81. Dungan K, Braithwaite SS, Preiser JC. Stress hyperglycemia. *Lancet*. 2009;373:1798.
82. Soeters MR, Soeters PB. The evolutionary benefit of insulin resistance. *Clin Nutr*. 2012;31:1002.
83. Losser MR, Damoisel C, Payen D. Bench-to-bedside review: Glucose and stress conditions in the intensive care unit. *Crit Care*. 2010;14:231.
84. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359.
85. van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449.
86. Marik PE. Tight glycemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med*. 2016; [ePub].
87. Intensive versus conventional glucose control in critically ill patietns. The NICE-Sugar Study Investigators. *N Engl J Med*. 2009;360:1283.
88. Marik PE, Preiser JC. Towards understanding tight glycemic control in the ICU: a systemic review and meta-analysis. *Chest*. 2010;137:544.
89. Krinsley JS, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is independently associated with increased mortality in the critically ill. *Crit Care*. 2011;15:R173.
90. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32:1637.
91. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guielines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580.
92. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA*. 1993;270:1724.

93. Shibutani K, Komatsu T, Kubal K, et al. Critical level of oxygen delivery in anesthetized man. *Crit Care Med*. 1983;11:640.
94. Regnier MA, Raux M, Le MY, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology*. 2012;117:1276.
95. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med*. 2005;45:524.
96. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med*. 2007;33:970.
97. Varpula M, Tallgren M, Saukkonen K, et al. Hemodynamic variables related to outcome in septic shock. *Intensive Care Med*. 2005;31:1066.
98. Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg*. 1996;171:221.
99. Broder G, Weil MH. Excess lactate: an index of reversibility of shock in human patients. *Science*. 1964;143:1457.
100. Cady LD Jr, Weil MH, Afifi AA, et al. Quantitation of severity of critical illness with special reference to blood lactate. *Crit Care Med*. 1973;1:75.
101. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*. 2009;37:1670.
102. Nichol AD, Egi M, Pettila V, et al. Relative hyperlactatemia and hospital mortialty in critically ill patients: a retrospective multi-centre study. *Crit Care*. 2012;14:R25.
103. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new cliical criteria for septic shock. For the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:775.
104. Irving MH. The sympatho-adrenal factor in haemorrhagic shock. *Ann R Coll Surg Engl*. 1968;42:367.
105. Daniel AM, Shizgal HM, MacLean LD. The anatomic and metabolic source of lactate in shock. *Surg Gynecol Obstet*. 1978;147:697.
106. Halmagyi DF, Kennedy M, Varga D. Combined adrenergic receptor blockade and circulating catecholamines in hemorrhagic shock. *Eur Surg Res*. 1971;3:378.
107. Liddell MJ, Daniel AM, MacLean LD, et al. The role of stress hormones in the catabolic metabolism of shock. *Surg Gynecol Obstet*. 1979;149:822.
108. McCarter FD, James JH, Luchette FA, et al. Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. *J Surg Res*. 2001;99:235.
109. Halmagyi DF, Irving MH, Gillett DJ, et al. Effect of adrenergic blockade on consequences of sustained epinephrine infusion. *J Appl Physiol*. 1967;23:171.
110. Wutrich Y, Barraud D, Conrad M, et al. Early increase in arterial lactate concentration under epinephrine infusion is associated with a better prognosis during shock. *Shock*. 2010;34:4.
111. Levy B, Mansart A, Montemont C, et al. Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock. *Intensive Care Med*. 2007;33:495.
112. James JH, Luchette FA, McCarter FD, et al. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;354:505.
113. James JH, Fang CH, Schrantz SJ, et al. Linkage of aerobic glycolysis to sodium-potassium transport in rat skeletal muscle. Implications for increased muscle lactate production in sepsis. *J Clin Invest*. 1996;98:2388.
114. Hashimoto T, Hussien R, Brooks GA. Colocalization of MCT1, CD147, and LDH in mitochondrial inner membrane of L6 muscle cells: evidence of a mitochondrial lactate oxidation complex. *Am J Physiol Endocrinol Metab*. 2006;290: E1237-E1244.
115. Hashimoto T, Brooks GA. Mitochondrial lactate oxidation complex and an adaptive role for lactate production. *Med Sci Sports Exerc*. 2008;40:486.
116. Beadle RM, Frenneaux M. Modification of myocardial substrate utilisation: a new therapeutic paradigm in cardiovascular disease. *Heart*. 2010;96:824.
117. Stanley WC. Myocardial lactate metabolism during exercise. *Med Sci Sports Exerc*. 1991;23:920.
118. Lopaschuk GD, Ussher JR, Folmes CD, et al. Myocardial fatty acid metabolism in health and disease. *Physiol Rev*. 2010;90:207.
119. Bergman BC, Tsvetkova T, Lowes B, et al. Myocardial glucose and lactate metabolism during rest and atrial pacing in humans. *J Physiol (Lond)*. 2009;587:2087.
120. Kline JA, Thornton LR, Lopaschuk GD, et al. Lactate improves cardiac efficiency after hemorrhagic shock. *Shock*. 2000;14: 215.
121. Ide K, Schmalbruch IK, Quistorff B, et al. Lactate, glucose and O2 uptake in human brain during recovery from maximal exercise. *J Physiol*. 2000;522(Pt 1):159.
122. Barbee RW, Kline JA, Watts JA. Depletion of lactate by dichloroacetate reduces cardiac efficiency after hemorrhagic shock. *Shock*. 2000;14:208.
123. Docter R, Krenning EP, de Jong M, et al. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol (Oxf)*. 1993;39:499.
124. Peeters RP, Wouters PJ, Kaptein E, et al. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab*. 2003;88:3202.
125. Burman KD, Wartofsky L. Thyroid function in the intensive care unit setting. *Crit Care Clin*. 2001;17:43.
126. van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid*. 2014;24:1456.
127. Plikat K, Langgartner J, Buettner R, et al. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. *Metabolism*. 2007;56:239.
128. Gangemi EN, Garino F, Berchialla P, et al. Low triiodothyronine serum levels as a predictor of poor prognosis in burn patients. *Burns*. 2008;34:817.
129. Liu J, Wu X, Lu F, et al. Low T3 syndrome is a strong predictor of poor outcomes in patients with community-acquired pneumonia. *Sci Rep*. 2016;6:22271.
130. Boelen A, Maas MA, Lowik CW, et al. Induced illness in interleukin-6 (IL-6) knock-out mice: a causal role of IL-6 in the development of the low 3,5,3′-triiodothyronine syndrome. *Endocrinology*. 1996;137:5250.
131. van der Poll T, Romijn JA, Wiersinga WM, et al. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. *J Clin Endocrinol Metab*. 1990;71:1567.
132. Bello G, Paliani G, Annetta MG, et al. Treating nonthyroidal illness syndrome in the critically ill patient: still a matter of controversy. *Curr Drug Targets*. 2009;10:778.
133. Bello G, Pennisi MA, Montini L, et al. Nonthyroidal illness syndrome and prolonged mechanical ventilation in patients admitted to the ICU. *Chest*. 2009;135:1448.
134. Leon-Sanz M, Lorente JA, Larrodera L, et al. Pituitary-thyroid function in patients with septic shock and its relation with outcome. *Eur J Med Res*. 1997;2:477.
135. Friberg L, Drvota V, Bjelak AH, et al. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med*. 2001;111:699.
136. Alevizaki M, Synetou M, Xynos K, et al. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. *Eur J Clin Invest*. 2007;37:651.
137. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *J Clin Endocrinol Metab*. 1986;63:1.
138. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. *Crit Care Med*. 1982;10:870.
139. Acker CG, Singh AR, Flick RP, et al. A trial of thyroxine in acute renal failure. *Kidney Int*. 2000;57:293.
140. van den Berghe G, de Zegher F, Baxter RC, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab*. 1998;83:309.
141. Sabatino L, Cerillo AG, Ripoli A, et al. Is the low tri-iodothyronine state a crucial factor in determining the outcome of coronary artery bypass patients? Evidence from a clinical pilot study. *J Endocrinol*. 2002;175:577.

142. Bennett-Guerero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. *JAMA*. 1996;275:687.
143. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. *N Engl J Med*. 1995;333:1522.
144. Vohra HA, Bapu D, Bahrami ZT, et al. Does perioperative administration of thyroid hormones improve outcome following coronary artery bypass grafting? *J Card Surg*. 2008;23:92.
145. Rosendale JD, Kauffman HM, McBride M, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation*. 2003;75:1336.
146. Novitzky D, Mi Z, Sun Q, et al. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation*. 2014;98:1119.
147. Nath DS, Liu MH, Moazami N, et al. Increased recovery of thoracic organs after hormonal resuscitation therapy. *J Heart Lung Transplant*. 2010;29:594.
148. Macdonald PS, Aneman A, Bhonagiri D, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med*. 2012;40:1635.
149. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2008;93:1351.
150. Arcopinto M, Salzano A, Isgaard J, et al. Hormone replacement therapy in heart failure. *Curr Opin Cardiol*. 2015;30:277.
151. Ross R, Miell J, Freeman E, et al. Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. *Clin Endocrinol (Oxf)*. 1991;35:47.
152. Timmins AC, Cotterill AM, Hughes SC, et al. Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and induction of an insulin-like growth factor binding protein 3 protease. *Crit Care Med*. 1996;24:1460.
153. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341:785.