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Citation	Ingels C, Gunst J, (2018), **Endocrine and Metabolic Alterations in Sepsis and Implications for Treatment** Crit Care Clin. 2018 Jan;34(1):81-96
Archived version	Author manuscript: the content is identical to the content of the published paper, but without the final typesetting by the publisher
Published version	http://dx.doi.org/10.1016/j.ccc.2017.08.006
Journal homepage	Critical Care Clinics
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IR	https://lirias2.kuleuven.be/viewobject.html?cid=1&id=1559322

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Endocrine and Metabolic Alterations in Sepsis and Implications for Treatment

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KEYWORDS

- Sepsis • Growth hormone • Thyroid hormone • Cortisol • Hyperglycemia • Insulin
- Nutrition • Endocrine

KEY POINTS

- The neuroendocrine response to sepsis and other critical illnesses follows a biphasic pattern; although acute changes are probably adaptive, they may become maladaptive in a later phase.
- In corticosteroid-naive patients with sepsis, cortisol supplementation should only be considered in patients with fluid-resistant and vasopressor-resistant refractory shock.
- The optimal blood glucose target in patients with sepsis remains unclear and may depend on diabetes status, the available equipment and treatment protocols, and the feeding strategy.
- In the acute phase of sepsis, current evidence supports accepting a low macronutrient intake and does not support the use of early parenteral nutrition.

INTRODUCTION

Sepsis is one of the most stressful conditions encountered by humans and animals.[1] The stereotypical neuroendocrine response to any form of stress, first described in 1878 by Claude Bernard,[2] is a complex constellation of alterations and interactions between the autonomic, endocrine, metabolic, and immune systems. This response is assumed to provide a survival advantage because it works to restore homeostasis.

The central nervous system (CNS) is able to recognize major threats to survival and induces specific physiologic responses, whereas the innate immune system is activated by pathogenic invaders. Crosstalk between both systems is essential to mount an adequate response to sepsis.[1,3] The innate immune system acts as a sensory organ, capable of detecting the presence of pathogens and signaling this invasion to the nervous system.[4] In sepsis, afferent signals to the brain arise from different origins, such as vagus nerve stimulation, the presence of bacterial products, and the production of cytokines and other inflammatory and neurotoxic mediators.[1,5] In this respect, it has been postulated that proinflammatory cytokines such as tumor necrosis factor alpha (TNF-a), interleukin (IL)-1, IL-6, IL-12, and IL-18 are involved in regulation of the acute stress response.[6] As an example, IL-6 is a cytokine that functions as an activator of the hypothalamic-pituitary-adrenal axis. IL-6 is also a potent pyrogen that interacts with hypothalamic centers to induce fever.[3] The generated afferent signals are thus capable of triggering efferent CNS responses that lead to activation of the autonomic nervous system and of the different neurohormonal axes, comprising the hypothalamopituitary-adrenal (HPA) axis, the hypothalamopituitary-thyroid (HPT) axis, the somatotropic axis, and the gonadal axis.

Critical illness is characterized by dysregulation of all hypothalamopituitary axes, and this is associated with an increased risk of morbidity and mortality.[7] As intensive care medicine evolved, more patients have been able to survive acute, life-threatening stress, entering a phase of protracted critical illness. It has become obvious that the neuroendocrine responses to acute and prolonged critical illness differ (Table 1) and may necessitate a different management approach. In the past, endocrine treatments have been advocated based on the erroneous extrapolation of changes

Table 1
Neuroendocrine changes in acute and prolonged critical illness

Hormone	Acute Phase	Protracted Phase
1. HPA Axis		
ACTH	[5	Y
Cortisol	[[	[(5 Y)
2. HPT Axis		
Pulsatile TSH release	[5	Y
T4	[5	Y
T3	Y	Y Y
rT3	[	[5
3. Somatotropic Axis		
Pulsatile GH release	[	Y
IGF-1	Y	Y Y
ALS	Y	Y Y
IGFBP-3	Y	Y Y
4. Male Gonadal Axis and Prolactin		
Pulsatile LH release	[5	Y
Testosterone	Y	Y Y
Pulsatile PRL release	[	Y

Abbreviations: ACTH, adrenocorticotropic hormone; ALS, acid-labile subunit; GH, growth hormone; IGF-I, insulinlike growth factor-I; IGFBP, insulinlike growth factor binding protein; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone (thyrotropin).

occurring in the acute phase of illness to the more protracted phase. This error may explain the unexpected increase in mortality found with some of these treatments.

Sepsis-related endocrine and inflammatory changes lead to hyperglycemia. This response was traditionally considered to be adaptive, in order to ensure sufficient nutrient availability to immune cells and other cells not relying on insulin for glucose uptake. Concomitantly, patients develop anorexia and/or cannot engage in oral feeding. The ensuing development of a caloric and protein deficit has been associated with the development of muscle weakness and poor outcome.[8] Therefore, experts advocate administration of early nutritional support to septic and other severely ill patients.[9] However, randomized controlled trials (RCTs) have shown that prolonged hyperglycemia and early aggressive nutritional support may induce harm.[10–14] This article highlights the most recent insights in the neuroendocrine and metabolic responses to sepsis, and the potential implications for treatment.

THE NEUROENDOCRINE RESPONSES TO SEPSIS

The Hypothalamic-Pituitary-Adrenal Axis

Activation of the HPA axis is one of the most essential responses to acute stress, and illness in general.[15] Many decades ago, the importance of glucocorticoid production for surviving life-threatening stress was highlighted by Selye.[16] Moreover, earlier work by Addison revealed that the adrenal cortex is essential for survival, because adrenalectomy was inevitably linked to death of the test animals.[15,17]

In normal physiologic conditions, the hypothalamus secretes corticotropin-releasing hormone (CRH) in a pulsatile manner. This hormone induces pulsatile secretion of adrenocorticotropic hormone (ACTH; also known as corticotrophin) by the anterior pituitary gland, which in turn regulates the adrenal production of cortisol and dehydroepiandrosterone (DHEA). Moreover, aldosterone, which is primarily regulated by the renin-angiotensin system, is also influenced by ACTH secretion. Cortisol, and exogenously administered corticosteroids, exert a negative feedback on CRH and ACTH production.[15,18] IL-6 is a major immune stimulator of the HPA axis. Vasopressin produced by the hypothalamus also stimulates ACTH secretion when CRH is present. Cortisol is thought to have an essential role for survival because of its effects, among other things, on gluconeogenesis, inflammation, maintenance of fluid homeostasis, and vascular tone, and via its stimulatory effect on vascular sensitivity to catecholamines.[15,19]

In acute critical illness, the HPA axis is activated by both neuronal circuits and by the massive release of inflammatory cytokines (particularly IL-6, TNF-a, and IL-1), which stimulate CRH and ACTH secretion.[19] Different cytokine receptors have been detected within the neurohumoral organs.[19,20] Vasopressin, endothelin, and atrial-natriuretic factor (ANF) also emerge as stimulators of cortisol secretion. In particular, in septic shock, macrophage-inhibiting factor secretion, triggered by excessive inflammation, modulates the HPA axis. All these additive effects expectedly result in a highly activated HPA axis with increased levels of ACTH and total and free cortisol. However, plasma ACTH concentrations are often low. Besides increased production of cortisol by the adrenal glands, impaired glucocorticoid clearance also contributes to the very high cortisol levels seen in critical illness,[21] that are far in excess of those encountered in many patients with Cushing syndrome. Moreover, corticosteroid binding globulin (CBG) levels are usually suppressed as part of the acute-phase response, especially in patients with impaired hepatic function, and there is enhanced elastase cleavage of CBG,[22] thus contributing to increased free cortisol availability.[15] The biological effects of cortisol may be further amplified by an increase in glucocorticoid

receptor (GR) number and sensitivity,[23] although suppression of the GR has also been observed.[24] In cases of severe sepsis or septic shock, excessive or disproportionate cytokine production may have the ability to reduce the number and binding affinity of GRs.[24] This reduction could lead to the state of glucocorticoid resistance that is sometimes encountered in these conditions, a possibility that requires further investigation. The suppressed cortisol metabolism in the liver and kidney may specifically accentuate cortisol availability in these tissues and contribute to increased plasma levels.[21] The normal diurnal variation of cortisol secretion is lost during critical illness.[7,25] Another feature of enhanced cortisol availability during acute stress is its poor suppressibility by the administration of exogenous steroids.[26]

A substantial proportion of patients survive the acute threat of sepsis or critical illness, providing an adequate and immediate HPA axis response. However, when patients enter the chronic, protracted phase of critical illness, this exposes them to other threats. During this chronic phase, circulating cortisol levels remain increased, but this seems not to be induced by corticotrophin-mediated increases in cortisol production,[7] because high cortisol levels are dissociated from low ACTH levels.[27] Putative factors that drive cortisol secretion apart from CRH include cytokines, ANF, endothelin, and substance P.[27] However, the cortisol production rate is only moderately increased beyond the very acute phase in septic patients treated in the intensive care unit (ICU), whereas the role of suppressed cortisol breakdown becomes more prominent.[21] Whatever the exact mechanism underlying the increase in plasma cortisol, persisting hypercortisolism observed in protracted critical illness may confer certain advantages by providing energy from gluconeogenesis, minimizing excessive inflammation, and preserving vascular tone. It may also mediate some harmful complications such as hyperglycemia, myopathy, and increased susceptibility to infection.[15]

The degree of the increase in circulating cortisol reflects the severity of illness.[28] However, several events may hamper an adequately increased cortisol availability, such as the direct damage to the hypothalamus or the pituitary gland with head injuries, adrenal hemorrhage, inflammatory mediators, and the use of certain pharmacologic agents (etomidate, azoles, phenytoin, and opioids).[27,29] Moreover, there is an important interindividual variation in cortisol levels after a stressful event, as well as variation related to age. An important unresolved issue is how to assess whether the cortisol availability in a given patient is sufficient or insufficient. The clinical term relative or functional adrenal insufficiency, also referred to as critical illness-related corticosteroid insufficiency, has been proposed to denote those patients with septic shock for whom corticosteroid treatment brings about improvement of hemodynamic status. Although sepsis holds a risk of absolute adrenal failure, for several reasons, there is still much controversy regarding the definition of relative adrenal insufficiency, its diagnosis, and its treatment.[27,30]

At present, experts still advise to use the cosyntropin stimulation test to detect relative adrenal insufficiency in critically ill patients. After injection of 250 mg of cosyntropin, a synthetic ACTH analogue, plasma cortisol is measured repeatedly over 1 hour. However, because 250 mg of cosyntropin induces supraphysiologic ACTH activity, some experts therefore advise to use a lower dose (1 mg) instead.[31] There is no consensus at present as to which cosyntropin dose should be used, what plasma level should assess the cortisol response to cosyntropin (cortisol peak level or incremental cortisol response), or which cutoff reference should be used to diagnose this condition. Hence, there is even more uncertainty on which patients may potentially benefit from corticosteroid treatment of such presumed relative adrenal insufficiency. A further rationale for using corticosteroids in such patients, mostly those with sepsis or septic shock, is based on their potent antiinflammatory properties and their effect

on the vasopressor response and thus on blood pressure. It is postulated that corticosteroids are capable of preventing sepsis-induced catecholamine receptor desensitization.[15] Corticosteroid treatment of patients with sepsis or septic shock has evolved from the use of very high doses to lower daily doses (200 mg), although the latter are still the equivalent of 6-fold to 10-fold greater than the normal daily cortisol production rate.[21] More than 15 years ago, following several smaller studies that showed earlier shock reversal with hydrocortisone treatment, a multicenter RCT showed that 200 mg daily of intravenous (IV) hydrocortisone plus 50 mg of fludrocortisone administered enterally for 7 days reduced mortality in those patients with septic shock who showed an incremental cortisol response of less than 9 mg/dL to 250 mg of cosyntropin.[32] However, this RCT has been criticized for the high mortality in the control group and the use of an inappropriate statistical test to assess a mortality difference.[33,34] Moreover, a subsequent RCT could not confirm these results in patients with septic shock who received 200 mg of IV hydrocortisone per day for 5 days.[35] It has been suggested that the absence of a benefit in the latter RCT was explained by the omission of fludrocortisone. However, an RCT randomizing patients with septic shock to administration of hydrocortisone or hydrocortisone plus fludrocortisone found no difference between the two strategies.[36] A more recent trial could also not detect a benefit from hydrocortisone when administered to patients with severe sepsis.[37] Current Surviving Sepsis guidelines recommend administration of 200 mg of hydrocortisone per day only to patients with fluid-resistant and vasopressor-resistant septic shock (weak recommendation).[38] The guidelines also advise dose tapering as quickly as clinically tolerated.

The Hypothalamic-Pituitary-Thyroid Axis

Thyroid hormone is essential for regulation of energy metabolism in virtually all tissues and plays an essential role in many physiologic processes of cell differentiation, growth, and metabolism.[39] In health, the production and release of thyrotropin (thyroid-stimulating hormone [TSH]) by the pituitary is controlled by hypothalamic thyrotropin-releasing hormone (TRH). TSH, released in bursts that are superimposed on basal, nonpulsatile secretion, activates the thyroid gland to produce T4. T4 is peripherally converted into the active hormone T3 and the metabolic inactive rT3 by deiodinases. T4 and T3 both exert negative feedback on TRH and TSH.

During critical illness, profound alterations occur within the HPT axis. After a stressful event, such as the onset of sepsis, circulating levels of T3 immediately decrease and rT3 levels increase. The degree of these changes reflects the severity of illness. These alterations are predominantly brought about by altered peripheral conversion of T4. Thyrotropin and T4 levels increase briefly and return to normal, although occasionally, in very severe acute disease, T4 levels can decrease. Although TSH levels quickly decrease within the normal range, the normal nocturnal TSH surge is absent. Because low T3 levels persist despite normalization of TSH, this condition has been referred to as the low T3 syndrome, sick euthyroid syndrome, or more recently nonthyroidal illness (NTI). From an evolutionary point of view, NTI can be interpreted as an attempt to protect the organism by reducing energy consumption and catabolism, and may thus be beneficial in the acute setting. The changes encountered in NTI resemble those induced by starvation, with decreased peripheral activation and increased inactivation of thyroid hormone. In addition, reduced concentrations of thyroid hormone binding proteins, inhibition of hormone binding, and changes in hormone transport are further hallmarks of the low T3 syndrome of critical illness.[6,40]

In the acute phase of critical illness, such peripheral changes in thyroid hormone action and metabolism dominate. In contrast, the chronic phase of critical illness is

characterized by a combination of peripheral and central adaptations. After several days of critical illness, levels of T3 further decline and T4 levels are also reduced. Moreover, pulsatile TSH secretion is suppressed and this correlates with suppressed hypothalamic TRH gene expression.[6] The combination of low peripheral thyroid hormone levels together with low TSH and TRH levels suggests a major change in the central regulation of the HPT axis. Several findings support such a resetting of the hypothalamic set point for feedback inhibition, including increasing TSH levels as a marker of recovery onset, and the ability of an infusion of TRH (particularly in combination with growth hormone [GH] secretagogues) to restore normal levels of TSH, T4, and T3.[6,40,41] The triggers of these changes in the HPT axis during protracted illness remain unclear, but possible players are cytokines, sustained hypercortisolism, neuropeptide Y, and alterations in hypothalamic deiodinase activity and thyroid hormone transporter expression. In addition, iatrogenic factors such as treatment with dopamine and corticosteroids could play a role.[6,40,42]

Because low levels of thyroid hormone and low T3/rT3 ratios have been associated with risk of death, the question arises whether these low levels should be treated. Are these low levels merely a reflection of the severity of illness, and could they be adaptive and protective against hypercatabolism, or do they represent a maladaptive response that should be treated? Because the acute changes that occur uniformly immediately after the onset of critical illness are comparable with, and coincide with, a fasting response, it is likely that these represent a neuroendocrine beneficial evolutionary conserved adaptation; an attempt to reduce energy consumption and protein catabolism.[43] Therefore, it seems common sense to not treat this acute NTI. However, the central and peripheral changes that occur in the prolonged phase of critical illness, when patients are usually fully fed, are different and may be maladaptive. The protracted phase of illness with ongoing dependency on intensive care represents an unnatural condition to which evolutionary adaptation has not been possible. Whether the low circulating and tissue thyroid hormone levels in the chronic phase of illness should be treated is still a matter of debate. Studies on this topic have used either substitution doses or high doses of the peripheral hormones T4 or T3 and did not reveal any benefit. However, during critical illness, substitution doses of T4 and T3 are unable to increase the circulating plasma levels of thyroid hormones, and supraphysiologic doses lead to a risk of overtreatment with further TSH suppression as a consequence. Because the chronic phase of illness is characterized by hypothalamic suppression, a more logical approach would be to infuse TRH, because this also respects normal feedback mechanisms and hence prevents overtreatment. Infusion of the combination of TRH (together with a GH secretagogue) restored the pulsatile secretion of TSH and reestablished normal physiologic levels of peripheral hormones in prolonged critical illness.[44] Although this intervention, when continued for 5 days, also elicited an anabolic/anticatabolic response, no RCTs exist that have investigated the impact on patient-centered, clinically relevant outcomes.[43]

The Somatotropic Axis

GH, secreted by the somatotropic cells, is the most abundant pituitary hormone.[45] Besides its well-known essential role in linear growth in childhood, GH also supports many important functions throughout the lifespan.[45] In adults, GH deficiency is associated with a distinct clinical syndrome comprising physical and psychological defects, such as altered body composition with increased fat and decreased lean body mass, relative hypercortisolism (caused by increased conversion of cortisone to cortisol), increased loss of water and sodium, loss of skeletal muscle mass, impairment of cardiovascular function, and reduced exercise capacity.[45] Under normal

conditions, the synthesis and secretion of GH is regulated by hypothalamic GH-releasing hormone (GHRH), the gut hormone ghrelin, and the inhibitory somatostatin.[7,45] GH is secreted in a typical pulsatile pattern, which seems to be essential for its metabolic effects[7] and responds to physiologic stimuli like stress, food intake, and circadian rhythms.[45] Moreover, synthetic releasing peptides and nonpeptide GH-secretagogues interact with the ghrelin receptor and, in synergy with GHRH, stimulate pulsatile GH secretion.[7,45] GH has direct and indirect effects that are mediated by insulinlike growth factor-I (IGF-I) and insulinlike growth factor binding proteins (IGFBPs).[7]

In response to acute stress, the typical pattern of GH secretion is altered, with higher pulse frequency, amplitude, and interpulse levels, in the presence of peripheral GH resistance in tissues such as the liver; this is reflected by decreased serum concentrations of IGF-I, IGFBP-3, and the acid-labile subunit (ALS).[46] Enhanced GH secretion may contribute to lipolysis and insulin antagonism, thereby providing valuable fatty acids and glucose, whereas the indirect anabolic effects that are brought about by IGF-I, which at that time are not essential for survival, are suppressed.[7] Particularly in patients with sepsis and severe sepsis, low IGF-I and IGFBP-3 levels have been reported, further decreasing in septic shock. Moreover, IGF-I levels were related to IGFBP-3, T3, and T4, and were inversely related to cortisol, the severity of sepsis, CRP, and IL-6.[47] Normalization of the altered somatotropic axis components precedes clinical recovery, whereas failure to do so was associated with worse clinical outcomes from sepsis-induced multiorgan dysfunction syndrome.[48] However, in the prolonged phase of critical illnesses, a dramatic reduction in GH pulsatile secretion and further reduction of IGF-I and IGFBP-3 levels are present, which may contribute to hypercatabolism, an inability to rebuild tissues, and to the so-called wasting syndrome.[48,49]

Recent research has highlighted the role of ghrelin in sepsis. This enteric hormone is produced by the stomach and, when adequately acetylated, acts on the brain to stimulate the somatotropic axis. Ghrelin is a strong stimulator of GH secretion as well as a potent vasodilatory peptide.[50,51] Moreover, ghrelin has been reported to downregulate inflammatory cytokines[50] and to attenuate age-related immunosuppression in septic rats.[52] Acetylated ghrelin levels were significantly decreased in an animal model of endotoxemia,[53] suggesting that ghrelin or ghrelin receptor agonists could provide therapeutic benefit in sepsis. Previous attempts to restore GH action with the use of recombinant GH gave conflicting results. A large multicenter RCT by Takala and colleagues[54] showed that treatment with GH, given in high doses with the intention of overcoming GH resistance, resulted in a striking increase in mortality, in longer ICU stays, and in longer durations of mechanical ventilation. In contrast, earlier studies had indicated that GH has the ability to reduce catabolism and improve nitrogen balance in selected patient populations.[48,55,56] The high doses used in the Takala and colleagues[54] study may have been relevant in mediating the harm. Infusion of releasing factors, such as GHRH and the GH-releasing peptide-2 (GHRP-2), produces a more physiologic reactivation of endogenous pulsatile GH secretion; respecting normal feedback loops, overtreatment was also prevented.[7] Furthermore, coinfusion of GHRP-2 with TRH for 5 days was effective in restoring pulsatile secretion of GH and TSH, with increases of IGF-I and thyroid hormone levels within the low-normal ranges, suppressing breakdown of muscle and increasing bone anabolism.[41] Experimental, animal, and in vitro studies have supported a role for ghrelin in improving hemodynamics, reducing catabolism, attenuating immunosuppression, and enhancing autophagic repair mechanisms in sepsis models.[48,53,57,58] However, there are currently no large RCTs that have investigated the potential clinical relevance and safety of these experimental findings.

The Male Gonadal Axis and Prolactin

The gonadal axis is hallmarked by pulsatile secretion of the hypothalamic gonadotropin releasing hormone (GnRH), in response to which luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are secreted by the pituitary. In men, LH mediates production of androgens and, in concert with FSH, stimulates spermatogenesis. In women, LH causes ovarian androgen production and FSH aromatizes androgens to estrogens.[7] Sex steroids exert a negative feedback inhibition on gonadotropins and GnRH. Prolactin (PRL) is secreted in a pulsatile manner by a distinct cell type in the anterior pituitary, under a tight negative control by dopamine. PRL is a stress hormone with immune-enhancing properties.[7]

In the acute phase of critical illness in men, plasma testosterone concentrations are immediately suppressed in the presence of increased or maintained LH levels. In the prolonged phase of critical illness, suppressed LH secretion further contributes to the low circulating levels of testosterone in men. In addition, increased aromatization of testosterone to estrogen occurs.[59,60] Because testosterone is a powerful anabolic hormone, low testosterone levels during critical illness may contribute to the catabolic wasting syndrome. Also, PRL levels increase rapidly after onset of critical illness; this may be interpreted as an attempt to activate the immune system. However, in the prolonged phase, PRL secretion is blunted, possibly adding to immune suppression in prolonged illness.[7,59]

In protracted critical illness, pulsatile GnRH treatment can increase pulsatile LH secretion. However, when only LH is reactivated, only a transient increase in circulating testosterone level followed. In contrast, pulsatile administration of GnRH combined with infusion of GHRP-2 and TRH induced an increase in testosterone and a clear anabolic response in target tissues.[61] The clinical relevance of these findings has not yet been investigated in large RCTs.

Summary of the Neuroendocrine Responses to Sepsis

The acute neuroendocrine response to sepsis and other critical illnesses consists primarily of an activated hypothalamopituitary function with inactivated peripheral (anabolic) pathways. This response is thought to be adaptive, because it temporarily shuts down anabolic processes to provide metabolic substrates for essential survival functions. As patients survive this acute phase and enter a more protracted critical illness, another pattern of changes can be discerned. Here, a uniformly reduced pulsatile secretion of ACTH, TSH, GH, PRL, and LH is observed, which may be related to a reduced availability of hypothalamic and peripheral releasing hormones. The pulsatile secretion of TSH, GH, and LH can be reestablished by relevant combinations of releasing factors. This process offers an important safety aspect because active feedback inhibition mechanisms prevent the target organs and cells from being overstimulated. Administration of a combination of GHRP-2, TRH, and GnRH can positively affect metabolism.[61] Further research is needed to address the therapeutic potential in large RCTs.

METABOLIC RESPONSES TO SEPSIS

The neuroendocrine and inflammatory alterations in response to a life-threatening insult also induce metabolic changes.

Stress Hyperglycemia

The development of hyperglycemia is a universal metabolic response to severe physical stress, including sepsis. Hyperglycemia is induced by stress hormones (cortisol,

GH, glucagon, and catecholamines) and proinflammatory cytokines, leading to gluconeogenesis and peripheral insulin resistance. Drugs such as catecholamines and corticosteroids that increase insulin resistance, as well (parenteral) nutrition, may further aggravate the degree of hyperglycemia.[62] The hyperglycemic response to severe stress, first described by Selye,[16] used to be interpreted as a desirable, adaptive process, hypothesized to provide a survival advantage by providing sufficient nutrients to cells that do not rely on insulin for glucose uptake, including neurons and leukocytes.[62] However, several studies have associated the degree of hyperglycemia with an increased mortality risk.[63,64] Whether hyperglycemia merely reflects severity of illness or causally relates to outcome has been a matter of ongoing debate.

Three RCTs from Leuven[10–12] have shown that strictly normalizing blood glucose concentrations to the healthy fasting range with insulin therapy (80–110 mg/dL for adults, 70–100 mg/dL for children older than 1 year, and 50–80 mg/dL for infants) reduced morbidity and mortality of critically ill patients compared with tolerating hyperglycemia up to 215 mg/dL, with the clinical benefit maintained up to 4 years after randomization.[10–12,65,66] All studied patient subgroups benefited from tight blood glucose control (TGC), with the potential exception of patients with preadmission diabetes mellitus, in whom there was only a nonsignificant trend toward benefit.[67] Mechanistic animal studies identified the avoidance of glucose toxicity to cells with insulin-independent glucose uptake as a mediator of organ protection, rather than the insulin treatment.[68–72] These beneficial effects of reducing glucose level included a beneficial impact on immune function.[68–70] Post hoc observational studies suggested a dose-dependent effect of glucose reduction on mortality risk, with the greatest mortality reduction achieved by targeting strict normoglycemia.[67]

Although several implementation studies and smaller RCTs subsequently confirmed a clinical benefit from implementing TGC, in part by preventing infections, multicenter RCTs did not confirm this, with the largest multicenter RCT even finding an excess mortality with TGC.[36,73–80] The investigators of that trial subsequently attributed the increased mortality risk to an increased incidence of hypoglycaemia.[81] However, in the Leuven studies, hypoglycaemia also occurred more frequently with TGC and, in this context, a nested case-control study could not detect a harmful impact (including long term) of a short-lasting episode of iatrogenic hypoglycemia.[66,82] Several methodological differences may explain the opposite effects of TGC on outcomes in these trials. First, the multicenter RCTs targeted a lower glucose target in the control group than the Leuven trials, in general less than 180 mg/dL, which decreases any potential benefit of such an intervention.[67] Second, in contrast with Leuven, the largest multicenter RCT did not focus on standardization, because it was designed as a pragmatic study in order to maximize external validity.[80] As a consequence, glucometers and capillary glucose measurements were allowed, which were shown to be too inaccurate to target a narrow glycemic range.[83] This inaccuracy may have led to an increased incidence of prolonged and undetected hypoglycaemia, which may have increased the mortality risk. The feeding protocol was also not standardized in these pragmatic multicenter studies, in contrast with the Leuven studies, in which early parenteral nutrition was administered as a standard of care to all patients. However, because this feeding strategy was afterward shown to be harmful in 2 multicenter RCTs, it remains unknown whether TGC remains beneficial in the absence of early parenteral nutrition.

Hence, the optimal blood glucose target remains unclear. This target may depend on the patient population, the equipment and protocols used, and the feeding regimen. Until new evidence becomes available, it seems prudent to avoid severe hyperglycemia in all critically ill patients, including patients with sepsis.

Anorexia accompanies any form of acute physical stress. In response to an infection, it is at least partially mediated via both central neural and peripheral effects of proinflammatory cytokines.[84] In addition, a poor general condition often precludes any volitional intake. From an evolutionary point of view, anorexia may have conferred some survival benefit, helping the host to recover from illness or to combat an infection.[85] However, prolonged underfeeding is associated with ongoing catabolism, an increased risk of infections, and mortality.[8,86] Therefore, clinical practice guidelines have recommended early, full enteral nutrition, eventually supplemented by parenteral nutrition, although the recommended timing to add parenteral nutrition has differed.[9,87] Because of the lack of sufficiently powered RCTs, these recommendations were mainly based on expert opinion. However, several large RCTs have recently challenged these guidelines. Early, full nutritional support did not deliver the hypothesized benefit and may harm critically ill patients, including patients with sepsis.[88] Two large multicenter RCTs found no benefit from normocaloric enteral feeding compared with so-called trophic hypocaloric feeding during the first weeks of ICU stay.[89,90] One of these RCTs also restricted protein calories in the hypocaloric feeding arm,[90] whereas the other administered isonitrogenous feeding to both groups, thereby only restricting nonprotein calories in the hypocaloric group.[89] Both studies found a neutral impact on clinical outcome and did not identify any subgroup in which the effect of the intervention was different. The results from these 2 RCTs were recently corroborated by 2 meta-analyses, which investigated the impact of normocaloric versus hypocaloric enteral feeding in critically ill patients.[91,92] Neither of these meta-analyses, with slightly different inclusion criteria, detected a benefit from normocaloric enteral feeding. One meta-analysis even suggested potential harm, with increased rates of bloodstream infections and renal replacement therapy.[91]

Likewise, recent RCTs have not confirmed the hypothesized benefit from early supplementation of insufficient enteral nutrition with parenteral nutrition; the 2 largest multicenter RCTs even found significant harm.[13,14,93] Compared with withholding supplemental parenteral nutrition for 1 week, early supplemental parenteral nutrition increased the ICU dependency of both critically ill adults and children, with a prolonged need for vital organ support and an increased incidence of new infections. Importantly, in these 2 multicenter studies, both randomization groups received sufficient micronutrients and vitamins in the acute phase, to prevent refeeding syndrome.[13,14] The harmful effect of early parenteral nutrition was present in all studied subgroups, including patients with sepsis on admission and patients with the highest nutritional risk scores. In the adult population, in contrast with expectations, early parenteral nutrition also increased the incidence of muscle weakness and hampered recovery.[94] Mechanistic research attributed the harmful impact of early parenteral nutrition to nutrient-induced suppression of autophagy, a crucial cellular repair process that removes damaged organelles, toxic protein aggregates, and intracellular or macrophage-engulfed microorganisms.[94,95] However, restricting macronutrient intake may come at a price, and may only be tolerated for a limited period of time. The optimal timing when parenteral nutrition can be initiated safely and effectively remains unclear.

Small studies have suggested that certain specialized nutritional formulae may have immune-modulating properties that could improve outcomes. These formulations contain mixtures enriched in glutamine, omega-3 fatty acids, and/or pharmacologic amounts of micronutrients and vitamins such as vitamin C, vitamin E, beta-carotene, selenium, and zinc. However, large, multicenter RCTs have not confirmed

the hypothesized benefit of administering these formulations, with several RCTs even suggesting harm, especially for glutamine supplementation.[96–99] Hence, the authors do not recommend the use of these so-called immunonutrients.

SUMMARY AND FUTURE DIRECTIONS

In conclusion, the neuroendocrine response to any form of stress, including sepsis, follows a distinct biphasic pattern. The acute neuroendocrine changes are probably adaptive and directed toward restoring homeostasis and limiting unnecessary energy consumption. These changes may become maladaptive in the prolonged phase of critical illness, in which a there is a central suppression of the neuroendocrine axes. Further research is needed to establish whether hypothalamic release factors improve the outcomes of these patients.[61] In the acute phase, hydrocortisone treatment can be considered in patients with fluid-resistant and vasopressor-resistant refractory septic shock, although this recommendation is based on a low level of evidence.

The optimal blood glucose target in patients with sepsis remains to be studied and may depend on diabetic status, available equipment, and the blood glucose control algorithm and feeding regimen being used. Strict blood glucose control requires accurate monitoring tools and a validated (computerized) insulin infusion protocol, which minimizes the risk of hypoglycemia.[100] Until new evidence from RCTs becomes available, preventing severe hyperglycemia is recommended for all critically ill patients. In the acute phase of sepsis, current evidence supports tolerating low macronutrient intake and does not support the use of early parenteral nutrition.

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