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.

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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-α), 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	↑ =	↓
Cortisol	↑ ↑	↑ (= ↓)
2. HPT Axis		
Pulsatile TSH release	↑ =	↓
T4	↑ =	↓
T3	↓	↓ ↓
rT3	↑	↑ =
3. Somatotropic Axis		
Pulsatile GH release	↑	↓
IGF-1	↓	↓ ↓
ALS	↓	↓ ↓
IGFBP-3	↓	↓ ↓
4. Male Gonadal Axis and Prolactin		
Pulsatile LH release	↑ =	↓
Testosterone	↓	↓ ↓
Pulsatile PRL release	↑	↓

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).