Metabolism, Metabolomics, and Nutritional Support of Patients with Sepsis

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KEYWORDS

• Sepsis • Metabolism • Metabolomics • Nutrition • ICU outcomes • Biomarker

KEY POINTS

- Sepsis is characterized by profound metabolic derangements.
- Metabolic changes can serve as diagnostic and prognostic biomarkers for patients with sepsis. Lactate is already in widespread clinical use, but technological advances make broader metabolic profiling possible.
- Many large-scale clinical trials have been conducted to optimize nutrition in septic patients. Most failed to show a benefit to early full feeding or supplementation with specific nutrients or metabolites in patients with normal nutritional status at presentation.

INTRODUCTION

Metabolism, derived from the Greek word "to change," refers to all chemical reactions required by cells. In the healthy state, human metabolism is characterized by synchronized catabolic and anabolic processes that not only allow cells to maintain homeostasis but also respond to their microenvironment. The main source of cellular energy is ATP from aerobic metabolism and nutritional needs are largely met through nutrient intake, not catabolism of endogenous lipid and protein stores.

This state of metabolic homeostasis is massively disrupted in sepsis. Sepsis is a syndrome characterized by a dysregulated inflammatory response leading to organ damage in following a microbial infection. Sepsis is associated with an overall catabolic state leading to the breakdown of carbohydrates, lipid, and protein stores.[1] Despite increased nutritional requirements, patients with sepsis are often unwilling (because of anorexia) or unable (because of encephalopathy, respiratory failure requiring mechanical ventilation, and so forth) to eat, which can lead to a large energy deficit and worse outcomes in critically ill patients.[2] This deficit, in turn, leads to profound skeletal muscle wasting and prolonged recovery.[3]

In this review, the authors highlight metabolic changes that occur in sepsis, including both the systemic and cellular alterations that lead to the dysregulation of normal human metabolism. The authors then review the use of metabolic changes as biomarkers for disease severity, with a focus first on lactate, the most widely used intensive care unit (ICU) biomarker, and then a broader discussion of metabolomics in general. Finally, given the marked changes in metabolism in sepsis and the association of worse short- and long-term prognosis in patients with severe metabolic derangements, the authors review the seminal trials conducted to optimize nutrition in the ICU.

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METABOLIC CHANGES IN SEPSIS

Mediators of Altered Metabolism in Sepsis

The metabolic changes associated with sepsis are complex, with many of the key features highlighted in **Table 1**. Many of these metabolic derangements are mediated by changes in the endocrine and autonomic nervous systems. The activation of these two systems occurs simultaneously and, in general, increases energy consumption. Of note, neuroendocrine activation in sepsis is dynamic and can change frequently throughout a patient's course.

Altered endocrine physiology

Acute illness, including sepsis, typically leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol release.[4] Increased circulating corticosteroid levels act to preserve vascular tone and reactivity in order to maintain perfusion of vital organs.[5] Although the normal response to stress is to increase adrenal corticosteroid secretion, there are many different factors that can lead to the impairment of adrenal function in septic patients. High levels of circulating cytokines can directly impair adrenal corticosteroid production,[6] and the use of medications that can impair adrenal function is common in septic patients.[5]

Although absolute adrenal insufficiency is rare in patients with sepsis, there has been substantial controversy surrounding the use of adjunctive corticosteroids to treat relative adrenal insufficiency in patients with septic shock. A randomized, multicenter, placebo-controlled trial of hydrocortisone in patients with septic shock did not decrease 28-day mortality regardless of whether an adrenocorticotropin hormone stimulation test was positive.[7] Patients treated with hydrocortisone did have a more rapid resolution of shock but also had an increased incidence of new infection.[7] In light of these results, debate persists among experts regarding the use of corticosteroids in sepsis and septic shock. In addition to the changes in the HPA axis with sepsis, altered function of other endocrine organs, such as the thyroid, can also lead to hormonal changes that alter metabolism.[8]

Table 1
Summary of major metabolic changes in sepsis

Physiologic Change in Sepsis	Metabolic Impact
↑ Gluconeogenesis, glycolysis	Hyperglycemia
↑ Protein catabolism	Altered circulating amino acids
↑ Lipolysis	↑ Triglycerides, ↓ lipoproteins
↓ Micronutrients	↑ Oxidative stress
↑ Neuroendocrine activation	↑ Catecholamines, ↑ counter-regulatory hormones
↑ Cortisol	Hyperglycemia
↑ Catecholamine release	↑ Gluconeogenesis, ↑ glycolysis
↑ Cytokine release	Hyperglycemia, insulin resistance
Impaired oxygen utilization	↑ Reactive oxygen species

Activation of the adrenergic nervous system

Activation of the adrenergic nervous system in septic patients leads to the release of endogenous catecholamines; in addition, patients with septic shock frequently require the administration of exogenous catecholamines for blood pressure support. The release or administration of epinephrine, norepinephrine, and dopamine can have profound effects on metabolism that increase catabolism of most macronutrients.[9] One of the main effects of catecholamine release is to increase the production of glucose by increasing hepatic glycogenolysis and gluconeogenesis.[10] Furthermore, the insulin resistance that occurs in sepsis is mediated, at least in part, by activation of the adrenergic system.[11] In addition to the effects of catecholamines on metabolic regulation, they also can affect immune function. Immune cells express adrenergic receptors[9] and catecholamines are known to affect cytokine production[12] and cell migration.[13] These effects have implications for the ability of patients to clear the inciting infection and return to a state of metabolic homeostasis.

Metabolic effects of cytokine release

The inflammatory cytokines that mediate that pathogenesis of sepsis play a key role in the activation of the neuroendocrine system described earlier. In addition, these cytokines can also directly alter metabolism in septic patients. The role of cytokines in the pathogenesis of sepsis has been reviewed in detail by others.[14,15] Here the authors focus on the metabolic effects of some of the classic proinflammatory cytokines. Many years after its initial discovery, tumor necrosis factor alpha (TNFα) was reported to be the same substance as the hormone cachectin. Cachectin was initially described for its role in increasing catabolism by upregulating lipolysis in the setting of malignancy and chronic infection