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Metabolism, metabolomics, and nutritional support of patients with sepsis

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Abstract

Sepsis is characterized by profound metabolic changes including both systemic and cellular alterations that lead to the disruption of normal metabolic homeostasis. These metabolic changes serve as biomarkers for disease severity. Lactate, a metabolite of anaerobic metabolism, is the most widely used ICU biomarker and its use is incorporated into multiple management algorithms. Technological advances now make broader metabolic profiling possible in sepsis, with early studies identifying several metabolic changes associated with sepsis mortality. Finally, given both the marked changes in metabolism in sepsis and the association of worse short- and long-term prognosis in patients with severe metabolic derangements, we summarize the seminal trials conducted to optimize nutrition in the ICU.

Keywords

Sepsis; metabolism; metabolomics; nutrition; ICU outcomes; biomarker

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 response to a microbial infection. Sepsis is associated with an overall catabolic state leading to the

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breakdown of carbohydrates, lipid, and protein stores.[1] Despite increased nutritional requirements, patients with sepsis are often unwilling (due to anorexia) or unable (due to encephalopathy, respiratory failure requiring mechanical ventilation, etc.) to eat which can lead to a large energy deficit and worse outcomes in critically ill patients.[2] This, in turn, leads to profound skeletal muscle wasting and prolonged recovery.[3]

In this review, we highlight metabolic changes that occur in sepsis, including both the systemic and cellular alterations that lead to the dysregulation of normal human metabolism. We then review the use of metabolic changes as biomarkers for disease severity, with a focus first on lactate, the most widely used 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, we review the seminal trials conducted to optimize nutrition in the ICU.

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] While 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. Most recently, a randomized, multi-center, placebo-controlled trial of hydrocortisone in patients with septic shock did not decrease 28-day mortality regardless of whether an ACTH 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 amongst 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]

Activation of the adrenergic nervous system—Activation of the adrenergic nervous system in septic patients leads to the release of endogenous catecholamines and, in addition, patients with septic shock frequently require the administration of exogenous

catecholamines. 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. It has been appreciated for quite some time that immune cells express adrenergic receptors.[9] The precise effects of adrenergic stimulation on immune cells is incompletely understood but is known to effect cytokine production[12] as well as cell migration.[13] These effects have implications for the patient's ability 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 above. 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 we will focus on the metabolic effects of some of the classic pro-inflammatory 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 prior to its description in the pathogenesis of shock and organ failure.[16] In experimental models, infusion of TNFα was also found to recapitulate the hyperglycemia and insulin resistance found in sepsis.[1]

In addition to its independent effects of metabolic activity, TNFα is also a potent inducer of other cytokines that also play a role in metabolism such as interleukin-1 beta (IL-1β) and interleukin-6 (IL-6). Similar to TNFα, infusion of recombinant IL-1β is also able to induce a hypermetabolic state in preclinical models [17] and IL-6 appears to work synergistically with these other cytokines. Although there are extensive data regarding the key roles of these cytokines in the pathophysiology of sepsis, there have been over 100 clinical trials in sepsis patients targeted at these pathways that have failed to lead to the approval of novel therapies.[18] This is likely multifactorial due to the complex pathogenesis of sepsis, issues with some preclinical models, and substantial heterogeneity among septic patients.[18] It is also possible that an incomplete understanding of how cellular and systemic metabolism is altered in sepsis may be limiting progress in the development of novel therapeutics.

Mechanisms of altered cellular metabolism in sepsis

It is well known that some patients with sepsis develop end organ failure despite appropriate therapy. Organ failure frequently develops in the later phases of sepsis following initial resuscitation and the molecular mechanisms of multi-organ failure remain incompletely understood.[19] Given that sepsis is often accompanied by shock and lactic acidosis, it was initially felt organ failure in sepsis was primarily due to tissue hypoxia from impaired oxygen delivery in the setting of increased microvascular permeability.[20]

While this may be the case early in sepsis, in the later phases (that are characterized by organ failure) tissue oxygen delivery has been shown to be normal in animal models[21] and septic patients.[22,23] This led to the realization that sepsis is characterized by altered cellular metabolism and impaired oxygen utilization despite adequate oxygen delivery. This impairment in cellular respiration, termed cytopathic hypoxia, may be one of the mechanisms responsible for multi-organ failure in the setting of sepsis.[24] The concept of energetic dysfunction in sepsis was first proposed when abnormal swollen mitochrondria were visualized in animal models of sepsis.[25] Since that time it has become clear that sepsis is characterized by impaired oxidative phosphorylation in multiple organs. This defect in the activity of the mitochondrial respiratory chain enzymes leads to a shift toward anaerobic ATP production and is accompanied by increased free radical generation.[26] In one small study, septic patients were found to have decreased tissue ATP and glutathione levels compared to non-septic control subjects.[27] Interestingly decreased tissue ATP levels were associated with worse outcomes in this group of patients.[27] Although it has been long appreciated that cellular metabolism is altered in sepsis, a clear understanding of the exact metabolic derangements has been elusive because previously the technology to simultaneously assess multiple metabolic pathways has not been available.

Macronutrients

The metabolism of all major types of macronutrients (carbohydrate, protein, and lipid) is dysregulated in sepsis. Hyperglycemia is one of the most common metabolic derangements in patients presenting with sepsis and results from altered glycogen metabolism and profound insulin resistance.[1,28] In late stages, sepsis can also be characterized by hypoglycemia due to multi-system organ failure. The molecular events leading to sepsis-induced hyperglycemia are complex and include the effects of inflammatory cytokines and alterations in the regulatory hormones that maintain normal glucose homeostasis, as discussed above.[28,29] Hyperglycemia impairs the function of innate immune system that further impairs the ability of the host to combat infection.[30] Given these effects, it is not surprising that hyperglycemia is an independent predictor of adverse outcomes in critically ill patients.[29,31]

In addition to abnormalities in carbohydrate metabolism, sepsis is also characterized by altered protein and lipid metabolism. Accelerated protein breakdown leads to a net negative nitrogen balance[1] which, in turn, leads to skeletal muscle wasting, deconditioning, and prolonged recovery for critically ill patients. In addition to generalized protein breakdown, sepsis is associated with altered concentrations of circulating amino acids.[32,33] In general, amino acids from the breakdown of peripheral tissues are shunted to the liver to support the synthesis of acute phase reactants.[1] One of the goals of supplemental nutrition in sepsis is to try to mitigate protein catabolism by providing adequate amino acids for protein synthesis, although controversy remains regarding the ideal strategy to prevent protein catabolism.

In addition to accelerated protein breakdown, sepsis is also characterized by increased lipolysis as lipids are the primary source of energy in patients with infections.[1] Patients with sepsis have altered lipid metabolism characterized by increases in serum triglycerides and decreased levels circulating lipoproteins.[34] Furthermore, administration of certain anti-

inflammatory classes of lipid mediators has been showed to improve outcomes in patients with sepsis.[35]

Micronutrients

In addition to changes in the metabolism of macronutrients, sepsis is also associated with changes in various micronutrients including trace minerals and vitamins. Micronutrients play key roles in metabolism and cellular homeostasis and evidence suggests that lower levels of micronutrients in critically ill patients are associated with higher risk of death and multi-system organ failure.[36] Two of the most well-studied micronutrients in sepsis are selenium and zinc. Selenium is a trace mineral with antioxidant and anti-inflammatory properties that is deficient in patients with sepsis.[37] Low selenium levels are associated with poor outcomes in critically ill patients and supplementation with selenium in critically ill patients has been shown to decrease mortality in some studies [38,39]. However, given methodologic concerns with some of these studies, experts suggest additional studies are need before the routine use of selenium can be recommended for septic patients.[40] Similarly, zinc is another essential micronutrient that plays a key roles in cellular homeostasis, immune function, and response to stress.[41] Zinc deficiency increases mortality in pre-clinical models of sepsis[42] and patients with sepsis have lower circulating zinc levels compared to non-septic controls.[43] Although many agree that treatment with micronutrients may be beneficial in sepsis, controversy remains regarding patient selection, choice of specific micronutrients, and optimal dosing.[3,36]

METABOLIC CHANGES AS BIOMARKERS IN SEPSIS

Lactate: the prototypical biomarker for sepsis diagnosis and prognosis

Human cells use ATP for energy. In the resting state, most glucose is metabolized through the aerobic pathway, with mitochondria processing pyruvate into CO_2, H_2O and 38 ATP via the citric acid cycle. In times of stress, such as exercise or sepsis, however, high cellular ATP requirements coupled with mitochondrial dysfunction can outstrip the capacity of the cell for aerobic glycolysis, and the cell switches to less efficient anaerobic metabolism, in which pyruvate is processed into 2 lactic acid and 2 ATP. This rise in lactate locally is a major reason for elevated plasma lactate levels, though additional mechanisms including impaired lactate clearance in sepsis may contribute.[44,45]

Lactic acid level is the most widely used biomarker used by clinicians caring for patients with severe sepsis today. The importance of lactic acid elevation has long been recognized.[46] Elevated lactate levels can occur due to impaired organ perfusion (Type A lactic acidosis) or in the absence of tissue hypoperfusion (Type B) due to malignancy, liver disease, or mitochondrial disorders. Despite this lack of specificity, an elevated lactate level has been validated in both sepsis diagnosis and prognosis, and failure to normalize lactate during resuscitation is similarly associated with a poor prognosis. This evidence is discussed in further detail below.

Lactate as a biomarker in the diagnosis of sepsis—As discussed elsewhere in this collection, severe sepsis is part of the inflammatory cascade that occurs in the setting of

infection, from SIRS to sepsis, sepsis with organ hypoperfusion, and finally septic shock. Elevated lactate (most commonly ≥ 4 mmol/L, though upper limits of normal may vary for a given lab) is a marker of sepsis-induced hypoperfusion, even in the absence of frank septic shock. [47] This cut-off was used for entry into pivotal human sepsis trials including the Early Goal-Directed Treatment (EGDT) protocol by Rivers *et al*[48], whose entry criteria included suspected infection with at least 2 SIRS criteria and either systolic blood pressure ≤90 mm Hg or lactate ≥ 4 mmol/L. The same threshold was incorporated into the Surviving Sepsis Campaign guidelines for early identification of sepsis in 2008 with Grade 1C evidence,[26] and used as an entry criteria for the follow-up early goal directed therapy ProCESS trial.[49]

Lactate as a prognostic biomarker in sepsis—Not only does lactate serve as an important biomarker for the diagnosis of sepsis, but it is also very clearly associated with increased risk for mortality in patients with sepsis, in both the ICU and ED setting.[50,51] Even a moderate elevation of lactate (range 2.1 ≤ 4 mmol/L) has been associated with increased risk of death in normotensive patients who present with sepsis.[52,53]

In addition to the importance of baseline lactate levels, the clearance of lactate during the first 6 hours of sepsis treatment is highly associated with mortality. For example, patients who fail to decrease their lactate level by at least 10% are twice as likely to die as those who reach that threshold.[54] Two randomized controlled clinical trials (RCTs) have evaluated targeting lactate clearance as an endpoint in early sepsis resuscitation. The EMShockNet trial showed a 17% mortality rate in subjects randomized to lactate clearance-guided resuscitation vs. 23% in those randomized to $ScVO_2$-guided resuscitation, with the conclusion that this resuscitation goal was non-inferior and led to very similar early fluid resuscitation.[55] Another RCT randomized patients to routine EGDT or to lactate measurement every 2 hours for the first 8 hours; while lactate clearance was not appreciably different between the 2 groups, the lactate group did receive more fluids, inotropes, and had a lower hospital mortality after adjustment for severity of illness.[56] Measurement of 6-hour lactate clearance was included in the 2012 surviving sepsis guidelines with grade 2C evidence.[47]

Broader metabolic profiling in sepsis

While lactate is a highly useful biomarker for sepsis diagnosis and prognosis, it is highly non-specific and often elevated in patients without sepsis (Type B lactic acidosis). Given the myriad metabolic changes induced by sepsis, it makes sense that changes in many other metabolites in addition to lactate would occur.

Metabolomics, the study of chemical products (metabolites) used and produced by cellular metabolism, measures small molecules including lipids, nucleotides, amino acids, carbohydrates, and even drug metabolites. Metabolomics is a rapidly growing field of study in genomics, in part because it represents the end of the genomic cascade, from single nucleotide polymorphism and methylation changes (many of which are present at birth), through gene expression, protein translation, and finally to metabolic changes. These latter genomic markers (gene expression, protein translation, and metabolites) are dynamic, and can change in response to environmental perturbations, making them particularly compelling

potential biomarkers in sepsis. The human plasma metabolome includes >4000 metabolites identified to date; however, because the human metabolome is not complete, this is likely an underestimate.[57] Metabolic profiling was previously extremely technically difficult, limiting exploration of the metabolic changes in sepsis beyond single-metabolite studies in small numbers of individuals. However, recent technological advances in liquid and gas chromatography and mass spectroscopy now allow high-resolution screening of the human metabolome.[58]

A full discussion of technical aspects of metabolic profiling is beyond the scope of this review and can be found elsewhere.[59,60] Briefly, metabolic profiling is usually performed in a two-step fashion: 1) a combination of gas and/or lipid chromatography is used to separate metabolites followed by 2) mass spectroscopy or nuclear magnetic resonance (NMR) mass spectroscopy for quantification. Untargeted metabolic profiling is designed to measure all metabolites in a given sample, while targeted profiling is designed to identify a fixed subset of metabolites of interest. Both methods have their strengths. The major advantage of untargeted profiling is the lack of bias and broader ability to discover novel, unanticipated metabolites, but limitations include the substantial time and cost required to definitively characterize newly identified metabolites and the lack of absolute quantification of metabolites. Even in untargeted profiling, resolution of metabolites based on hydrophilicity and size may vary depending on strategy used, with greatest resolution across a part of the metabolite spectrum. Conversely, targeted metabolomic profiling identifies only a subset of metabolites (often on the order of 100–500), but use of internal calibration standards allows both absolute quantification and high confidence in the individual metabolites attained.

To date, several groups including our own have performed broader metabolic profiling in sepsis to test whether incorporation of multiple metabolites, could serve as prognostic indicators in sepsis. Plasma metabolomic changes associated with sepsis mortality published to date are summarized in Table 2. The studies vary dramatically in 1) sample size 2) metabolites measured 3) modeling method used to differentiate survivors vs. non-survivors. Given these varying methodologies in study design, coupled with high correlation among many metabolites, it is perhaps not surprising that the metabolites identified vary greatly across studies. While settling on one particular metabolic network is thus premature at this time, it is worth noting that all studies reveal profound metabolic derangements in sepsis, most (but by no means all) metabolites are upregulated, and these changes extend far beyond the anaerobic metabolism/lactate cycle. Identifying the optimal network of metabolites, establishing importance of these networks across varied populations with sepsis, and addressing whether incorporation of these networks into critical illness severity models improves their performance in prospective cohorts is all needed to determine the clinical utility of metabolomics in sepsis.

The field of metabolomic profiling in sepsis is still in its infancy, and its diagnostic promise is not yet clear. Even such basic issues as type of body fluid to sample are still evolving. While the studies summarized in Table 2 have all focused on serum and plasma, Stringer et al. recently suggested that whole blood sampling may be a better target, as it also reflects endothelial cell metabolism and free hemoglobin level.[61] Additional options include

studying samples that reflect a particular organ function in sepsis, for example urine in acute kidney injury, or bronchoalveolar lavage fluid in septic patients with ARDS.

NUTRITION IN THE SEPSIS PATIENT

As noted throughout this review, patients with severe sepsis and septic shock have profoundly altered metabolism, with a catabolic state leading to breakdown of both protein and lipids coupled with decreased production of new muscle mass. Critically ill patients have been shown to have a profound loss of muscle mass, a mean of 17% loss of femoral mass by day 10, worse among patients with increased severity of illness.[62] Patients who develop critical illness neuropathy are known to have both increased ICU length of stay and increased ICU mortality.[63]

Given these substantial metabolic changes in sepsis, the potential to reduce these effects through nutritional therapy has been studied extensively. Major topics include timing, route, and rate of nutrition, as well as the nutrient composition to optimize sepsis survival. We highlight the strongest evidence for each of these issues below and in Table 3. While many of these studies are not restricted to only sepsis patients, most of them include critically ill patients that have sepsis as their primary or secondary ICU risk factor. For further reading on this evidence, several excellent reviews of ICU nutrition have been written previously.[64,65]

Timing of nutrition—The majority of critically ill patients are unable to take in adequate oral nutrition, particularly early in the course of critical illness. While several meta-analyses have suggested a mortality benefit to early feeding within the first 48 hours in critically ill patients,[66] methodologic concerns about high potential for bias in the small trials included in these meta-analyses limit their usefulness.

Several recent large, high-quality RCTs are highly relevant. The EDEN trial focused on patients with the acute respiratory distress syndrome (ARDS); the vast majority of these patients had underlying sepsis (>70% with either sepsis or pneumonia as their ARDS risk factor). Subjects were randomized within 48 hours of mechanical ventilation to either trophic or full enteral feeds for the first 6 days. Despite a marked difference in calories (400 vs. 1300), there was no difference in duration of mechanical ventilation, infectious complications, or 60-day mortality in the two groups. Patients followed for up to 1 year after discharge also demonstrated no difference in physical or cognitive function based on nutrition strategy.[67] These data suggest that delay of full nutrition up to 6 days is likely safe in patients without baseline malnutrition (who were excluded from these trials).[68]

Enteral vs. parenteral nutrition—Enteral feeding is the accepted first choice for nutrition in critically ill patients who can tolerate it, given consistent evidence of improved outcomes including fewer infections and improved gut integrity.[65] However, a large proportion of critically ill patients have relative contraindications to enteral feeding and fail to meet their caloric needs in the early days of ICU care. Thus, several large RCTs have been conducted to address the timing of initiation of parental nutrition in high-risk ICU patients.

The EPaNIC trial randomized 4,640 critically ill subjects at high nutritional risk for malnutrition to receive either early parental nutrition (PN, glucose x 48 hours then full caloric parental nutrition) or a late-initiation group that did not receive parenteral nutrition until day 8. The late initiation strategy was associated with faster recovery (6% increased likelihood of discharge alive from ICU and hospital), and fewer ICU infections.[69] The Early PN Trial randomized 1,372 with short-term contraindications to enteral feeding to receive either early PN vs. pragmatic standard care (of the latter group, 29% commended enteral nutrition, 27% parenteral and 40% unfed). The early PN strategy led to no difference in 60-day mortality, but fewer days of mechanical ventilation.[70] Finally, the SPN trial randomized 305 critically ill patients who were reaching <60% of nutrition targets by day 3 to receive either PN or enteral nutrition. They found substantially lower rates of infection in the PN group (the primary outcome).[71] Cumulatively, these trials suggest that PN and full nutrition can be delayed for at least 7 days in most critically ill patients with normal nutritional status at presentation, and that any advantages to early PN initiation are likely modest.

Role of macro and micronutrient replacement

Sepsis is characterized by marked systemic inflammation, with increased production of reactive oxygen species and a depletion of antioxidant nutrients associated with increased mortality, as discussed above.[27] Not surprisingly, numerous trials of therapeutic administration of macronutrients and anti-oxidants have been performed in an attempt to improve sepsis mortality. While many small RCTs and subsequent meta-analyses have shown encouraging trends toward improved sepsis mortality[39], this has not borne out in larger RCTs to date which are summarized in Table 3.

Low glutamine levels are associated with worse prognosis in critical illness, and it has thus been the subject of several large RCTs. The REDOXS trial randomized 1,223 critically ill patients to receive glutamine, antioxidants (including selenium, zinc, vitamins C, E, and β carotene), both, or placebo. The groups that received glutamine had higher in-hospital and 6 month mortality, while antioxidants had no effect.[72] The SIGNET trial randomized 500 subjects to a lower dose of glutamine (~1/3 the dose in REDOXS), and identified no difference in mortality or new infections in all patients randomized.[73]

The ARDSnet Omega trial randomized 272 patients with ARDS (75% with sepsis or pneumonia as their ARDS risk factor) to receive omega-3 fatty acids, which favor production of less active prostaglandins and leukotrienes. The trial was stopped early for futility, with subjects receiving supplements with fewer ventilator-free and ICU free days, and a trend toward higher 60-day hospital mortality.[74] Although multiple studies have identified deficiencies of specific nutrients/metabolites in septic patients, there are currently no data to support the use of replacement therapy in sepsis.

CONCLUSION

In summary, sepsis is characterized by profound metabolic changes. Some of these metabolic changes contribute to sepsis pathophysiology, and others (*e.g.* high lactate, hyperglycemia, low selenium and zinc) are recognized markers of ICU outcomes. Given these profound metabolic changes, numerous large-scale trials have been designed to

optimize nutrition in the ICU, though most have failed to show that nutrition strategies improve outcomes for septic patients, at least early in the ICU course of patients with adequate baseline nutrition.

Finally, technical advances in metabolomic profiling have enabled cheaper, high resolution testing than was previously available. The option to simultaneously examine multiple metabolic pathways in large populations is now more feasible, and will likely allow a more nuanced picture of the metabolic changes that occur in sepsis. As these data emerge in the coming years, developing a more individualized approach to metabolism and nutrition in septic patients may become possible.

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Key points

1. Sepsis is characterized by profound metabolic derangements.
2. Metabolic changes can serve as diagnostic and prognostic biomarkers for sepsis patients. Lactate is already in widespread clinical use, but technological advances make broader metabolic profiling possible.
3. 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.

Table 1

Summary of major metabolic changes in sepsis

Physiologic change in sepsis	**Metabolic impact**
↑Gluconeogenesis, glycolysis	Hyperglycemia
↑l1;Protein catabolism	Altered circulating amino acids
↑Lipolysis	↑Triglycerides, ↓lipoproteins
↓Micronutrients	↑Oxidative stress
↑Neuroendocrine activation	↑Catecholamines, ↑counterregulatory hormones
↑Cortisol	Hyperglycemia
↑Catecholamine release	↑Gluconeogenesis, ↑glycolysis
↑Cytokine release	Hyperglycemia, insulin resistance
Impaired oxygen utilization	↑Reactive oxygen species

Table 2

Published metabolomic studies in sepsis

Reference	# Cases/ controls[1]	Control population	Metabolites profiled	Analytic strategy	Final metabolites
Mickiewicz et al.[75]	10/10	Pediatric septic shock survivors	58	PCA & PLS[2]	11 metabolites (not identified)
Langley et al[76]	31/119 33/67 25/65	Surviving subjects with SIRS or sepsis	>300	Support Vector Machine	Cis-4-decenoylcarnitine, 2-methylbutyroylcarnitine, butyroylcarnitine, hexanoylcarnitine, lactate, age, and hematocrit
Rogers et al.[77]	30/60 115/34	Surviving subjects with SIRS or sepsis	167	Bayesian Network	γ-glutamylphenyl-alanine, -γ-glutamyl-tyrosine, 1-arachidonoyl-GPC(20:4), taurochenodeoxycholate, 3-(4-hydroxyphenyl) lactate, sucrose, kynurenine
Mickiewicz et al [78]	4/4	ICU survivors with sepsis	60	PLS	Network of 20 (not identified)

[1] When multiple case/control populations are shown, these represent the N for testing and replication populations in that work

[2] Principal components analysis and partial least squares techniques

[3] Langley et al. and Rogers et al. analyses use highly overlapping datasets.

Table 3

Highlighted papers in ICU nutrition

Trial (Ref)	Treatment groups	Population (% sepsis)	Primary outcome
EDEN[68]	Trophic vs full feeds in first 6 days	ARDS (>70%)	No Δ in vent time, infections, 60 day mortality, 1yr physical function
Early PN[70]	Early PN vs standard care	ICU patients with short term contraindication to enteral nutrition (6%)	No difference in mortality, early PN had fewer vent days
EPNaIC[69]	Early PN vs delayed to day 8	ICU patients at nutritional risk (22%)	Late PN: 6% more likely to d/c alive from ICU & hospital, fewer infections
SPN[71]	PN or EN if not meeting caloric need by day 3	ICU patients not meeting nutritional needs by day 3 (~45%)	No Δ in ICU stay or 60 day mortality, but ↓ vent days
REDOXS[72]	Glutamine or antioxidants	ICU patients with 2 or more organ failures (~30%)	↑ in-hospital & 6 month mortality in glutamine group. No effect with antioxidants
SIGNET[73]	Glutamine or selenium	ICU needing at least 50% of calories via PN (~60%)	No Δ in mortality or infection rate in all patients
OMEGA[74]	Omega 3 fatty acids	ARDS (75% sepsis or pneumonia)	↓Vent-free and ICU days, trend toward ↑ 60 day mortality