# Metabolic support in sepsis and multiple organ failure: More questions than answers . . .

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**The metabolic support of critically ill patients is a relatively new topic of active research and discussion, and surprisingly little is known about the effects of critical illness on metabolic physiology and activity. The metabolic changes seen in critical illness are highly complex, and how and when to treat them are only just beginning to be determined. Studies have demonstrated that the acute phase and the later phase of critical illness behave differently from a metabolic point of view for many organs, and while many of the alterations in metabolism seen during early critical illness may be appropriate and beneficial responses to cellular stress, whether this is true for all the metabolic alterations in all forms of critical illness is unclear. Currently we face more questions than answers, and further study is needed to elucidate the various components of the metabolic response to acute and chronic critical illness and to develop better techniques to assess and monitor these changes so that we can determine which therapeutic approaches should be used in what combinations and in which patients. (Crit Care Med 2007; 35[Suppl.]:S436–S440)**

**KEY WORDS: metabolic physiology; critical illness; cellular stress**

The metabolic responses to sepsis and multiple organ failure affect every organ and tissue of the body, and yet surprisingly little is known about the mechanisms underlying these responses. During sepsis and other forms of critical illness, the body undergoes a state of stress resulting in hypermetabolism, increased energy expenditure, hyperglycemia, and muscle loss (1, 2). Increasingly it is realized that appropriate metabolic support may improve outcomes in these patients, but considerable controversy remains regarding which therapeutic approaches should be used and in which patients. Here, for simplicity, we will discuss some of the controversies in specific individual areas of metabolic support (Table 1), although clearly these act in concert and the real challenge is how best to combine these aspects in individual patients.

## Nutritional Support

*General Aspects.* Our concepts regarding nutritional support in critically ill patients have evolved over time. In the 1970s, the importance of providing adequate nutritional support to patients began to be realized, and in the 1980s specialized diets began to be introduced that were targeted at specific conditions (e.g., hepatic failure or renal failure), but these specialized "organ-targeted" solutions did not result in better outcomes. Large caloric intakes were considered to be necessary, until it was realized that excessive calories can exacerbate the hypermetabolic state leading to lipogenesis and liver steatosis (3, 4). For a while, it was thought that parenteral feeding would be just as efficacious as enteral. However, it was later realized that although parenteral nutrition enables calories to be supplied quickly and easily, enteral nutrition seems preferable, enabling gut structure and function to be preserved and limiting the infectious complications associated with parenteral feeding. Several recent meta-analyses, however, have suggested that there may be little beneficial effect on outcome of enteral nutrition over parenteral nutrition despite higher complication rates with parenteral nutrition (5, 6), and some have suggested that the nutrition supplied is more important than the route (7). Nevertheless, current guidelines strongly recommend early use of enteral nutrition, with parenteral nutrition being reserved for patients in whom enteral nutrition fails to provide sufficient nutrition (8, 9).

So, how much nutrition should be supplied? Clearly, not all patients are the same, and a one-for-all formula is not appropriate. We have already seen that too many calories can be harmful (3, 4), but too few calories can be equally damaging (10). Various formulas have been suggested to calculate required caloric intake, the most widely used of which is the Harris-Benedict formula (11). However, this formula was derived from data from normal young individuals and may not be applicable to critically ill patients. Even measurements of oxygen uptake are fraught with technical difficulties and may not be very helpful in adapting energy requirements. Important too is the fact that intensive care unit (ICU) patients often fail to receive the full amount of prescribed formula for various reasons, including feeding intolerance and fasting before invasive procedures (12–14).

Adequate protein intake is also difficult to quantify. The hypermetabolic state seen in sepsis is associated with a net protein catabolism in the muscle, with increased nitrogen loss. This loss in muscle protein may result from decreased, normal, or even increased protein synthesis, which is insufficient to compensate for the higher proteolysis. Accelerated protein breakdown is associated with inhibited uptake of amino acids by the muscles, leading to an increased flux of amino acids from the periphery to the liver. At the same time, hepatic uptake of amino acids is stimulated and protein synthesis and gluconeogenesis in

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Table 1. Some controversies in metabolic support

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|---|---|
| Basic nutritional support | How many calories (formulas, indirect calorimetry?) |
| | Route of feeding (parenteral vs. enteral, gastric vs. postpyloric?) |
| | Basic constituents (proteins, lipids, glucose?) |
| Pharmaconutrients—immunonutrition | Glutamine, alanine, cysteine |
| | Antioxidants |
| | Trace elements, vitamins |
| Endocrine support | Sugar control |
| | Cortisol |
| | Vasopressin |
| | Thyroid hormones |
| | Anabolic hormones (growth hormones, oxandrolone) |
| Cellular requirements | β-blocking agents, hibernation? |

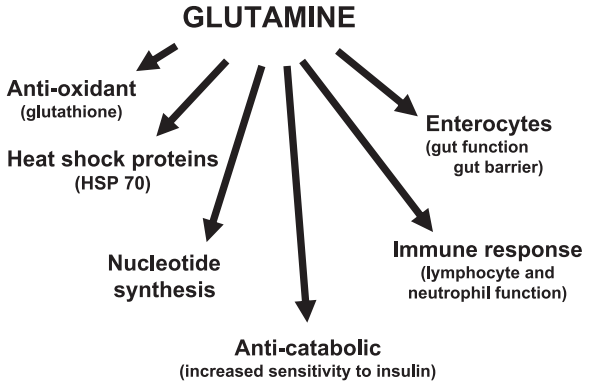


Figure 1. Potentially beneficial effects of glutamine. *HSP*, heat shock protein.

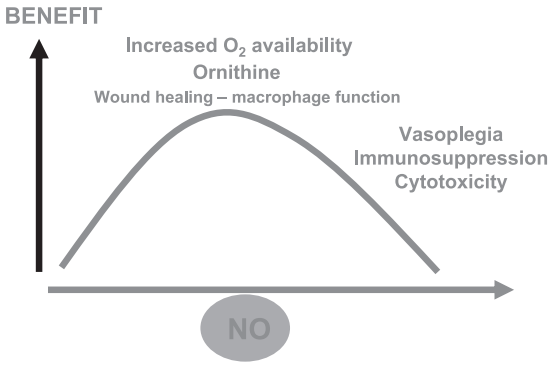


Figure 2. The beneficial and harmful effects of arginine supplementation. *NO*, nitric oxide.

the liver are enhanced (15). In general, therefore, protein needs are increased in patients with sepsis, and protein should be provided in sufficient amounts to provide a positive nitrogen balance. The branched chain amino acids, leucine, isoleucine, and valine, seem to be more efficient in promoting nitrogen retention and hepatic protein synthesis (15, 16), and clinical studies have suggested that branched chain amino acid-rich formulas may be associated with better outcomes (17).

*Immunonutrition—Specialized Diets.* Although the possibilities of immunonutrition caused some excitement when initially proposed, the evidence in support of this approach is still relatively weak, except maybe for glutamine supplementation (Fig. 1). One of the difficulties in this field has been that studies have used different formulas with varying additional, supposedly immune-enhancing nutrients, and it is therefore difficult to compare results or even to determine which formulas or specific supplements may be of benefit.

There is some evidence that formulas enriched with arginine, nucleotides, and omega-3 fatty acids may be beneficial in patients who have undergone elective upper gastrointestinal surgery, in those with mild sepsis (18), and in trauma patients, but in patients with severe sepsis data suggest that such formulas may be harmful (19) and they are not recommended. Arginine in particular may be detrimental in critically ill patients with an ongoing inflammatory response, by increasing nitric oxide formation, although this suggestion is also controversial (20) (Fig. 2). A formula enriched with omega-3 fatty acids, γ-linoleic acid, and antioxidants has been shown to reduce ventilator requirements, length of ICU stay, and the incidence of organ failure in patients with acute lung injury or acute respiratory distress syndrome (21, 22) and, more recently, to reduce mortality rates in mechanically ventilated patients with severe sepsis and septic shock (23). Supplementation of feeds with glutamine has also been suggested to be beneficial in patients with burns or trauma (24); however, in heterogeneous groups of critically ill patients, glutamine-enriched formulas had no effect on infectious complications, length of stay, or mortality rates (9).

The addition of antioxidants as nutrients may be beneficial. It has recently been suggested that selenium supplementation may improve outcomes in patients with severe sepsis or septic shock (25). Clearly, selenium is a cheap option, but it could potentially have unwanted effects as well, and at least one multicenter study is underway to define its place in the metabolic support of the critically ill.

There is clearly no perfect nutritional formula for all patients, and we need to develop methods to better determine and monitor specific patient needs. With the range of potential nutrients available, determining which may be of benefit for which patients will require considerable further study; however, with the high costs of these specialized solutions limiting their widespread use, clinical research is difficult as companies do not want to invest the large amounts of funding necessary to perform high-quality studies in view of the likely limited marketplace for their products.

## Endocrine Support

*Glucose Control.* The exciting results of the study by Van den Berghe et al. (26) in surgical ICU patients showing that careful control of blood glucose levels was associated with improved outcomes

have not been as straightforward as they initially appeared. First, the same study performed in medical patients again resulted in improved outcomes but only in patients who stayed ≥3 days in the ICU (and this was the primary hypothesis), failing to improve outcome in all patients by an intention-to-treat analysis (27). Second, the multicenter Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study in patients with severe sepsis/septic shock in Germany showed no reduction in mortality rates and a higher incidence of hypoglycemic episodes in the tight glucose control group (28), and a large European study, Glucontrol, was stopped after enrollment of 1,109 patients (for a planned study of 3,500 patients) for safety reasons, because there was no reduction in mortality rate (16.7 vs. 15.2%, $p$ not significant) and increased mortality rates in patients with hypoglycemia (18.8 vs. 10.8%, $p < .0001$) (results presented at the 2007 ISICEM, Brussels). Nevertheless, the rationale for this approach is strong and probably more complex than initially thought. Indeed, administration of insulin initially was considered to be the beneficial component because of its anti-inflammatory and anabolic properties, but avoidance of hyperglycemia *per se* may bring benefit.

*Cortisol.* After studies failed to show a benefit of one or two big bolus doses of methylprednisolone (29), the concept of relative adrenal insufficiency emerged. Annane et al. (30) reported that moderate doses of steroids (hydrocortisone 50-mg intravenous bolus every 6 hrs and fludrocortisone 50-μg tablet once daily for 7 days) were beneficial in a subgroup of patients with an abnormal response to an adrenocorticotropic hormone test, although this was only statistically significant after statistical adjustment. The recent multicenter CORTICUS study, in which patients with septic shock were given 50 mg of hydrocortisone (no fludrocortisone) every 6 hrs for 5 days or placebo, showed no differences in mortality rates between groups regardless of response to an adrenocorticotropic hormone test. In the subgroup of patients with an abnormal response to the adrenocorticotropic hormone test, there was a more rapid reversal of shock, but treated patients also had higher rates of infectious complications and hyperglycemia than placebo patients. The reasons behind these differences are unclear, although the patients in the CORTICUS study may have been less severely ill than those in the Annane study, because the overall mortality rates were considerably lower in CORTICUS; there may also have been differences due to the lack of fludrocortisone in CORTICUS. These data suggest that corticosteroids should be restricted to patients with severe septic shock, similar to the population studied by Annane et al. (30) and not extended to patients with less severe forms of sepsis.

*Vasopressin.* Vasopressin is synthesized in the hypothalamus and stored in the posterior lobe of the pituitary gland. It is involved in maintaining blood osmolality and volume and controlling blood pressure. It is also involved in insulin and corticotropin release. Despite its effects on vascular smooth muscle, vasopressin should be considered as a hormone rather than as another vasopressor (31). In patients with septic shock, the expected increase in vasopressin levels is blunted (32, 33), with a relative vasopressin deficiency (a bit like the relative adrenal insufficiency concept). Infusion of low doses of vasopressin has been shown to increase blood pressure and reduce vasopressor requirements (33–40). In the recently completed multicenter randomized VASST study comparing low-dose vasopressin with norepinephrine in patients with septic shock, vasopressin administration was shown to be beneficial in less severe cases (data presented at the Society of Critical Care Medicine meeting, Orlando, FL, 2007).

*Thyroid.* In acute critical illness, serum levels of triiodothyronine, thyroxine, and thyroid-stimulating hormone decrease (41). Certain therapeutic interventions, such as dopamine, dobutamine, and corticosteroids, can also influence thyroid-stimulating hormone levels. Subsequently, circulating thyroid-stimulating hormone and thyroxine levels often return to "normal," whereas triiodothyronine levels remain low. The changes in thyroid hormones have been found to reflect the severity of illness and to predict mortality (42, 43). The mechanisms underlying the development of the so-called sick euthyroid syndrome are not clearly defined but likely include the influence of various cytokines, including tumor necrosis factor-α, interleukin-1, and interleukin-6 (44). There are no clinical data showing a consistent beneficial effect on outcome with thyroid hormone treatment in critically ill patients, and in the absence of clinical signs of thyroid disease, abnormal thyroid function tests should not prompt thyroid treatment in the critically ill patient (41). Thyroid function generally returns to normal as the acute illness resolves.

*Anabolic Hormones.* The use of anabolic hormones to enhance anabolic activity in critically ill patients would seem logical, but no consistent benefits have been shown in clinical studies. In acutely critically ill patients, growth hormone secretion is generally increased but there appears to be peripheral growth hormone resistance, with reduced levels of its main effector molecule, insulin-like growth factor-1, as well as insulin-like growth factor-binding and growth hormone-binding proteins (45, 46). In more prolonged critical illness, growth hormone levels are decreased, and growth hormone resistance is no longer present. Growth hormone replacement may, therefore, appear beneficial, but despite some promising results in small studies, two parallel randomized controlled trials showed increased mortality rates in patients receiving growth hormone (47). One of the reasons behind this may have been related to the harmful effects of hyperglycemia induced by the relatively high doses of growth hormone used (48), but clearly further insight is needed into the complex relationships involved. Testosterone is another potent anabolic steroid, levels of which are reduced in prolonged critical illness (49). Testosterone and oxandrolone, a testosterone analogue, have been shown to have beneficial effects on muscle catabolism in patients with severe burns (50, 51). However, in trauma patients, oxandrolone had no effect on nutritional or clinical outcomes (52), and in ventilator-dependent surgical patients, oxandrolone was associated with a more prolonged course of mechanical ventilation (53). Insulin is another important anabolic hormone, and maintaining normoglycemia with insulin infusion has been associated with improved outcomes and is widely recommended, although the mechanisms underlying the benefits are unclear and may be related more to the glycemic control than to the insulin dose given (54). Nevertheless, insulin has additional anti-inflammatory and metabolic effects that need to be further elucidated.

## Cellular Support

The mitochondria are key organelles in cellular energy production, and mitochondrial dysfunction is believed to play a key role in the development of multiple organ failure in critical illness. The initial hypermetabolic state seen in critical ill-

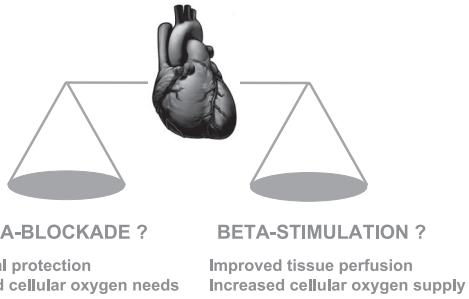


Figure 3. The dilemma of β-blockade vs. β-stimulation in the acutely ill patient (including the perioperative period).

ness is fueled by an increase in mitochondrial respiration (55). However, later stages of illness are associated with mitochondrial dysfunction and damage. Interestingly, as cell death is not a key feature of sepsis and other critical illness, it is suggested that mitochondria enter a hibernation-like state with biochemical/physiologic shutdown manifest clinically as multiple organ dysfunction/failure (55). Once the acute disease process has diminished, mitochondria can come out of their hibernation and recovery processes can begin, with additional production of new mitochondria to produce sufficient energy for restorative metabolic processes and patient survival.

The mitochondria have, therefore, become an exciting target for cellular support. Several therapeutic approaches recently associated with improved outcomes in critically ill patients, including protective ventilation strategies and tight glucose control, may reduce mitochondrial dysfunction (56, 57). β-adrenergic blockade may have beneficial cellular effects particularly on the myocardium, but β-stimulation can also be beneficial by increasing cellular oxygen supply; ensuring the correct adrenergic balance is thus important to maximize cellular function (Fig. 3). Other more specific approaches are also being studied, but the complexity of the mechanisms controlling mitochondrial function needs to be elucidated in greater detail before effective therapeutic agents can be developed.

## CONCLUSION

The metabolic support of critically ill patients is a relatively new topic of active research and discussion, yet with the obvious importance of cellular metabolism as one of the key building blocks of life, it is somewhat surprising that so little is known about the effects of critical illness on metabolic physiology and activity. It is now clear that the acute phase and the later phase of critical illness behave differently from a metabolic point of view for many organs. Many of the alterations in metabolism seen during early critical illness may be appropriate beneficial responses to cellular stress, but whether this is true for all the metabolic alterations in all forms of critical illness is unclear. In addition, even if early changes are beneficial, at what stage do they become harmful such that they may benefit from therapeutic intervention?

The metabolic changes seen in critical illness are highly complex and interact at various levels to create an often confusing picture. Currently we seem to be faced with more questions than answers in this vast and complex field of metabolic support. Further study is needed to elucidate the different components of the metabolic response to critical illness, both acute and prolonged, and to develop better techniques to assess and monitor these changes so that we can determine which approaches should be used in what combinations and in which patients.

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