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Hypermetabolism and Nutritional Support in Sepsis

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Abstract

Background: Surgical metabolism has been a founding field of investigation in surgery without which the boundaries of critical care, trauma, and surgical oncology could not have advanced. Traditionally, understanding the shifts in electrolytes, carbohydrates, fats, and amino acids that could explain the rapidly evolving proteolysis after catabolic stress and tumor growth has been a major focus of research that led to our current approach to maintaining homeostasis over the course of major surgical intervention and injury.
Method: Review of the English-language literature.
Results: With the emerging field of inflammation and the discovery of cytokines and chemokines, surgical metabolism has taken a second seat in the surgical research arena. Yet central to all patient management after injury is an understanding of how catabolic stress erodes vital organ function and how current approaches can support metabolism through the most physiologically stressful perturbations known to man, for which there is no evolutionary precedent. Although it is well accepted that unabated proteolysis is not a sustainable physiologic state, in the era of modern medicine, precisely how to manipulate the body nutritionally to drive a recovery-directed immune response remains highly debated. This review incorporates multiple lines of inquiry in surgical metabolism, with a particular focus on sepsis.
Conclusion: The changing landscape of previous paradigms in the field is discussed. Finally, how next-generation technology might spark renewed interest in this field among surgical investigators is considered.

Keywords: metabolism; microbiome; nutrition; sepsis; underfeeding

Nitrogen wasting after surgical injury is an invariable occurrence that is directly proportional to the magnitude and duration of the injury via multiple input signals from both external and internal forces acting on host physiology [1]. In the context of sepsis, an infectious agent, either from an exogenously acquired source or from the patient's own microbiota, can drive the immune response to become pathoadaptive to recovery. Much of the thinking about this concept is founded on the idea that man's adaptation to a catabolic injury did not evolve to accommodate the efforts of modern medical care with respect to immediate resuscitation, life support measures, and the ability to deliver and withstand multiple surgical procedures to address and treat injuries. As a result, modern care has witnessed patients' physiology being pushed into uncharted territories of extreme nitrogen loss, organ dysfunction requiring ventilator support and dialysis, and exposure to virulent and resistant healthcare-acquired pathogens. This newly emerging sepsis paradigm bears witness to the extreme circumstances to which modern medicine can succeed on the one hand and fail on the other [2]. A young liver transplant patient receiving multiple immunosuppressive agents, having undergone an operation necessitating multiple blood transfusions, several takebacks to the operating room, and now exposed to, and colonized by, multi-drug-resistant pathogens represents the new normal in sepsis treatment and metabolism. Leveraging the use of new tools such as mass spectrometry to measure all metabolites and proteins, multi-omics and microbiome sciences, and the computational management of the megadata generated in such a patient is both exciting and daunting [3]. It is no longer useful to measure metabolites, but rather to understand the metabolome at various points of care and its interaction with other body systems. As such, there are no longer units, but only interactive systems whose individual components fade into the background while we zoom out and attempt to understand, in real time, both the trajectory of the illness and the impact of our actions.

A Brief History of Time: Provide Nitrogen, Carbon, and Micronutrients and the Body Will Do the Rest

As early reports by Culbertson et al. began to describe the ebb and flow of metabolism after catabolic injury such as trauma, burns, or sepsis, it became apparent that severe surgical injury induces a process of extreme proteolysis and nitrogen wasting [4]. Multiple attempts to attenuate the process failed, and with the dawn of the provision of exogenous nutritional support, surgeons finally were able to continue to address bleeding, wound issues, and infections. Key discoveries by

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Randall, Rhodes, and Dudrick demonstrating that essential nutrients could be formulated in their most elemental form and delivered as acellular solutions, both enterally and parenterally, forever changed clinical medicine [5]. Patients could now be resuscitated nutritionally and homeostasis re-established, after which wounds and organs could recover slowly from the initial shock and catabolic stress. Yet a major challenge persisted when the catabolic injury could not be controlled and nitrogen wasting persisted. Key observations by Clowes et al. demonstrated that infection and injury-mediated inflammation amplified and sustained catabolism to the point that lean body mass erosion proceeded in an unabated fashion, driven by yet-to-be-discovered inflammatory mediators [6]. All the exogenous support available was inadequate to suppress the body from converting lean body mass into glucose for energy, even when energy (i.e., fat and glucose) was provided exogenously. Once these ''leukocyte endogenous mediators'' or ''pyrogens'' were identified, the race was on to suppress them selectively in an effort to shut down proteolysis and allow exogenous nutrients to be incorporated into the body so as to drive a recovery-directed inflammatory response [7]. Modern medicine was now entering an era in which the response to injury was viewed as pathoadaptive to recovery, reasoning that evolution has had insufficient time to calibrate the host response to recovery in the face of rapid resuscitation, surgical interventions, and intensive care units (ICUs). Isolation and purification of endotoxin as the ''universal bacterial exoproduct'' responsible for all bacteria-mediated inflammation, and the discovery of tumor necrosis factor alpha (TNF-α) as the responsible host factor driving systemic inflammation and organ failure armed investigators with two reagents and targets to attack pharmacologically [8,9]. Several animal models linked these two agents, and a series of highly controlled and focused studies in both animals and humans suggested that targeted attenuation of inflammation during endotoxin exposure could allow exogenous nutrients to be incorporated into lean body mass, economize nitrogen loss, prevent loss of muscle function, and preserve organ function. Yet, given that neither endotoxin nor TNF-α is solely representative of all possible mediators involved in such a complex process as burn injury, trauma, infection-related sepsis, or severe acute pancreatitis, investigators began exploring a more global approach to attenuating inflammation such as the use of glucocorticoids and beta-blockade [10].

The work of early investigators demonstrated that inflammation follows a neuroendocrine immune loop, whereby local injury activates afferent nerves that travel to the brain, where central processing releases efferent signals via both nerves and hormone-release factors that converge on multiple targets, resulting in the output of hormones, cytokines, chemokines, and many other mediators [11]. That nerve cells abut directly against immune cells speaks to the complex interconnectivity of these systems. Early on, investigators attempted to disrupt this iterative loop with spinal cord transection, then spinal anesthetics, and now vagal nerve pacing [12]. Today, multiple approaches continue in an attempt to interrupt neuroendocrine immune signaling selectively with pacemakers and drugs with the objective of attenuating inflammation while surgeons, intensivists, and healthcare teams provide nutritional support and other means to accelerate recovery in the face of extreme injury, sepsis, and catabolic stress.

However, at this point in the discussion, it is important to understand just how far we have come in our approach to promoting recovery by addressing pain rapidly with epidural and patient-controlled analgesia, surgical techniques that minimize blood loss and tissue trauma, improved anesthesia techniques, resuscitation and supportive care that is more ''physiologic,'' and rapid implementation of oral feeding to enhance gut barrier function. These ''enhanced recovery programs,'' now omnipresent in elective surgery, are termed ''enhanced recovery after surgery'' (i.e., ERAS) programs and can be viewed as an aggregate attempt to interrupt the neuroendocrine immune response to catabolic stress by minimizing pain, preventing tissue trauma, and feeding via the gut as early as possible and giving non-processed foodstuffs [13]. Perhaps this same approach should be developed with the critically ill septic patient, as it facilitates more rapid recovery by interrupting the release of counter-regulatory hormones that are pathoadaptive to recovery.

In this short review, we discuss the strengths and flaws of our current thinking about how to provide nutrition during sepsis, building on the background of the excellent work that has been done to date, as described above. We review key areas of controversy in the approach to providing nutrition when metabolism is accelerated by severe injury, such as occurs after severe acute pancreatitis, trauma, burn injury, and infection-related sepsis. We consider these catabolic states as representative of a common signature of hypermetabolism in terms of how to support the patient nutritionally, recognizing that each may have unique metabolic characteristics that are disease dependent.

Does hypermetabolism mandate the provision of calories and nitrogen that keep up with losses? The use of the term ''hypermetabolism'' to describe the metabolic response to injury implies that calorie expenditure and nitrogen utilization are accelerated and hence on a course counterproductive to recovery unless supply keeps up with demand. However, the surge in counter-regulatory hormones such as epinephrine, glucocorticoids, and others drive much of the response into fast forward, causing excess nitrogen loss as a result of proteolysis from gluconeogenesis, which provides energy at the expense of lean body mass. Adaptation to severe injury runs a course of rapid muscle breakdown and an attendant loss of function that supplies key amino acids in order to drive reverse glycolysis to generate glucose and adenosine triphosphate. As long as the counter-regulatory response is sustained by injury and infection, exogenous nitrogen and glucose are supportive but cannot alone suppress the hypermetabolic response [14].

Over the years, there has been much controversy with respect to the optimal amount of calories and nitrogen needed to support the patient undergoing catabolism. Many of these studies have become outdated as immediate resuscitation efforts, early implementation of antibiotics, rapid availability of trauma service, etc. have changed the course of recovery. Use of beta-blockade in burn injury, early enteral nutrition, and even permissive underfeeding have proved to be useful in attenuating the catabolism, indicating, perhaps, that the nitrogen loss, and hence the nitrogen requirement during injury and sepsis, needs rethinking and reformulation. It seems, after multiple clinical studies, many involving trial and error approaches of various formulations, nutrients, dosing, and routes of administration, that we have arrived at conclusions that have turned tradition on its head. Here, I address three emerging concepts in this regard toward nutritional support

of the septic patient: (1) Delaying the provision of nutrients to the septic patient is beneficial; (2) there is no difference between enteral and parenteral nutrition in terms of outcome from sepsis; and (3) feeding less nitrogen and calories than those that are being lost during the sepsis response improves outcomes.

Delaying nutritional support for as long as seven days during sepsis is beneficial

The standard argument to justify delaying exogenous nutritional support to patients who are critically ill or septic is that supplying calories in the form of glucose or lipids at a time when sepsis physiology can neither be suppressed nor calories combusted and utilized may be ill-advised, potentially even harmful. Both hyperglycemia and hyperlipidemia can ensue when calories are provided during acute sepsis and cause a significant risk to the outcome [15]. Multiple studies seem to confirm that stabilizing the patient first, obtaining source control, and then addressing nutritional concerns is more in line with how the adaptive response to injury is best supported by modern medicine, in particular nutritional support [16,17]. The concept that key nutrients ought to be supplied as early as, and equal to, the time and rate at which they are being burned is not in line with the evolved response of humans to injury and infection, which is anorexia and inanition.

The counterargument has been that human physiology has not adapted to the life support provided by modern ICUs and care and therefore that supportive nutrition is required to establish and maintain a recovery-directed response. Yet the uncertainties in the approach have much to do with our inability to measure and track the metabolome over the course of injury and infection to inform therapy. With the advent of mass spectrometry and bioinformatics analysis, a more comprehensive and holistic understanding of precisely when and how to begin feeding the critically ill septic patient can emerge [18]. At the present time, however, a short delay in feeding until the patient is considered to be stable enough to be nutritionally supported is in line with the best outcome and supported by reliable and reproducible evidence.

Enteral and parenteral nutrition are equally beneficial in terms of outcome from sepsis: the gut barrier hypothesis demystified

After it became well established that total parenteral nutrition (TPN) was safe and life-saving for critically ill patients who could not receive nutrients via the enteral route, in the late 1980s investigators began to examine the immune response of animals fed TPN versus the identical nutrients via the enteral route [19,20]. Not only were immune parameters enhanced by the enteral presentation of nutrients, but the host response to stress, in the form of endotoxin administration of direct bacterial inoculation, was superior with enteral nutrition. Several clinical trials provided compelling evidence that enteral nutrition was superior to parenteral nutrition after burn injury or trauma and among critically ill adult patients [21]. In fact, mortality differences were observed among enterally fed patients compared with matched parenterally fed patients. A flurry of animal studies suggested that the enteral presentation of nutrients maintained gut barrier function, enhanced liver protein synthesis, and improved immune responsiveness to a traumatic stress (i.e., femur fracture, burn injury) and infection [22,23]. This difference seemed to be most apparent in prolonged and profound catabolic stress such as occurs during severe acute pancreatitis in critically ill patients. Given that infected pancreatic necrosis consequent to severe acute pancreatitis is the most feared and lethal complication of the disease, enteral nutrition seemed logical to prevent bacterial translocation and contamination of the infected pancreatic tissue [24]. Animal studies began to unravel potential mechanisms of enteral nutrition enhancement of the immune system, including greater secretory immunoglobulin (Ig) A synthesis, preservation of the mucus layer, maintenance of the epithelial tight-junction permselectivity, and activation of immune cells such as macrophages and neutrophils [25,26]. Yet as advances in the treatment of disease such as severe acute pancreatitis shifted from open surgery with multiple take-backs to the operating room to percutaneous drainage, selective antibiotic decontamination of the gut microbiota, probiotic administration, and minimally invasive surgery when indicated, the advantage of enteral nutrition was less apparent. An analogous situation with all critically ill patients could be imagined with more physiologic mechanical ventilation, immediate source control, improved imaging, rapid deployment of antibiotics on presentation, goal-directed fluid therapy, etc., and the effect size of enteral over parenteral nutrition has diminished [27]. More attention to early extubation and resumption of a normal diet has reduced the previously observed effect size between enteral and parenteral nutrition. Also, the availability of broader-range antibiotics with an ever-better safety profile also may be playing a role. In point in fact, several recent trials have failed to observe differences in either infection-related morbidity or the overall mortality rate among critically ill patients fed enterally versus parenterally [28]. It is possible that the progress achieved to date in treating the critically ill lessened the effect size between enteral and parenteral nutrition, as observed previously. The mechanistic basis for this is beyond the scope of this discussion but likely involves greater attention to minimizing stress, providing more physiologic therapies, treating infection at the earliest point of care, providing analgesia, rapidly achieving source control, etc. Precisely how the microbiome is involved in this response remains to be determined; however, there is now compelling evidence that gut microbes can obtain nutrients from parenteral nutrition via transfer of serum nutrients across the gut barrier [29]. Therefore, the previous notion of ''feed the gut'' may be less of an issue, as there now is credible evidence that the gut and its microbiota seem to have figured out how to feed themselves when nutrients are delivered exclusively via the parenteral route.

Less is more: The beneficial role of underfeeding for the hypermetabolic septic patient

Although seemingly counterintuitive, purposive underfeeding during sepsis may benefit hypermetabolic patients, perhaps by avoiding hyperglycemia and hyperlipidemia, although the mechanisms are yet to be discovered [30]. This important trial has been reviewed recently and its conclusions validated [31]. A major flaw in the approach to the hypermetabolic patient in terms of nutritional support has been our poor understanding of the response to injury and infection at the systems biology level and at the level of personalized

medicine. For example, an obese insulin-dependent diabetic patient who has life-threatening pneumonia after major surgery may actually suffer from unrecognized protein–calorie malnutrition and frailty at the time of the index operation. When faced with such a patient, overzealous provision of nutrients and calories may not necessarily be restorative to lean body mass and organ function if the exogenous nutrients cannot be incorporated intracellularly. Chemically defined enteral nutrients in this patient, now on broad-spectrum antibiotics, may fail to be either absorbed or metabolized, given that the normal microbiome is eliminated. Indeed, the most common cause of diarrhea in ICU patients is exposure to broad-spectrum antibiotics, which further exacerbates the malabsorption. Finally, the assumption that currently available diets meet the metabolic needs of the critically ill patient, absent analysis with next-generation technology, remains unconfirmed. As a result, overfeeding, which itself remains to be defined, may be harmful, in contrast to underfeeding, which at the very least may lessen harm while the body's nitrogen sources seek to economize and distribute themselves in response to modern medicine's attempt to establish source control and support organ function.

A major flaw in the thinking regarding nutritional support of the critically ill is the traditional view that the intestinal tract is a mere conduit for the absorption of nutrients. Although this concept led to the current formulation of life-saving TPN, the fact that these products contain only single amino acids, lipids, and glucose with the addition of micronutrients should make us pause. Advances in microbiome sciences and metabolomics are indicating that there are thousands of micro-organism-derived metabolites that enter the circulation that are absent when animals are raised germ free or receive antibiotics. Given this sobering information, it is naïve to think that forcing more single amino acids, glucose, and fats directly into the circulation is necessarily restorative or will drive a recovery-directed host response during injury and infection. Although some nutrition in its current form clearly is good, more is not necessarily better. What is becoming increasingly clear is that in terms of clinical outcome of critical illness, including infection-related morbidity and the overall mortality rate, permissive underfeeding is non-inferior to currently recommended calorie and nitrogen dosing. This simple observation should force a rethinking of our current approach to feeding the hypermetabolic septic patient.

Future Directions for Nutritional Support of the Hypermetabolic Septic Patient

Multiomic approaches that incorporate longitudinal assessment of the interactome of transcriptomic, proteomic, metabolomic, and microbiome sciences offer the promise of applying precision medicine to the septic patient. Most important will be the use of point-of-care diagnostics that can allow physicians to calibrate, in real time, the use of antibiotics, nutritional support regimens, probiotics, and other methods of resuscitation to best feed the septic patient. It is important to recognize that a critically ill septic patient's metabolic status can be very unstable, changing from one moment to the next. In addition, it is critical that we begin to examine the metabolites that originate from both the host and its colonizing micro-organisms [32,33]. Being able to understand how they interact, synergize, and antagonize each other during the metabolic response to injury or when a patient is critically ill along a sepsis continuum will be highly informative to the prescription of nutritional support. Although essential amino acids, glucose, and lipids in their current form are highly effective in supporting the critically ill septic patient, many shortcomings have been identified, such as hyperglycemia, hyperlipidemia, the inability to promote anabolism, and variability in their effect on a recovery-directed immune response. The degree to which short-chain fatty acids, which are supplied only by the metabolism of anaerobes in the gut, and which are eliminated by antibiotics, needs to be reconciled. Another problem that might be solved using a multiomic approach is to understand the degree to which dysbiosis, invariables seen in critically ill patients, contributes to sepsis hypermetabolism [34]. For example, the recent finding that indigenous bacteria from the gut regulate host serotonin biosynthesis is both intriguing and potentially important to sepsis hypermetabolism [35,36]. Both bacteria-derived tryptophan and serotonin were shown recently to play a major role in brain activity, and the extent to which they contribute to the delirium and cognitive deficits seen during critical illness remains unknown but likely is significant [37]. The use of serial metabolomics across multiple body fluids (blood, urine, cerebrospinal fluid) among septic patients can now be applied to address these important and frequently occurring co-morbidities that have devastating consequences. Finally, when to stop antibiotics and repopulate the gut microbiome using probiotics or a fecal transplant could have a major restorative impact on the hypermetabolism observed during sepsis and its disabling consequences.

Conclusion

Nutritional support for the hypermetabolic septic patient remains a challenge. Both enteral and parenteral nutrition have advantages and disadvantages, but at the present time, one cannot be considered superior to the other, assuming hyperglycemia and overfeeding are avoided. As such, delaying nutritional support until the patient achieves initial source control and hemodynamic stability seems rational. Finally, permissive underfeeding may be a viable strategy to ''do no harm'' when prescribing nutritional support for the septic patient as a means of preventing hyperglycemia and other sequelae of overfeeding.

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