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Review

Nutritional support for burn injuries

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There are approximately 2,000,000 burns each year in the United States that require medical treatment. Fortunately, most of these can be treated on an outpatient basis; however, 100,000 patients are hospitalized yearly. The mortality rate is higher in patients with large burns or smoke inhalation injury or both, or in patients otherwise compromised by age or concomitant disease. Thermal injury leads to suppression of the immune response, and infectious morbidity is common in all burn patients. In addition, the injury and recovery processes are attended by tremendous catabolism of host tissues, leaving patients debilitated and functionally impaired. Medical nutrition therapy plays a key role in the support of the burn patient, supporting the immune system and blunting the hypermetabolic response. (J. Nutr. Biochem. 10:380–396, 1999)

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Introduction

Thermal injury and smoke inhalation injury lead to prolonged debility, frequent morbidity, and occasionally death. Treatment of the burn patient involves a number of different systems, not the least of which is nutritional support. We will discuss the pathophysiology of the hypermetabolic response associated with thermal injuries, followed by discussions of nutritional assessment; means of support available, including route, timing, and composition of nutritional support; and techniques of assessment of adequacy of support.

Pathophysiology of burn hypermetabolism

Among all acutely injured patients, burn patients have the highest levels of nitrogen loss and oxygen consumption. This hypermetabolism is correlated with the size of the burn, which suggests the mechanisms related to the widespread inflammatory response that is seen after burns.

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Cytokine production

Burn injury is commonly accompanied by intense inflammation, tissue damage, and infection. As anticipated, significantly altered levels of cytokines are found after burn. Tumor necrosis factor (TNF), interleukin 1 (IL-1), and interleukin 6 (IL-6) have been studied most frequently. IL-6 is elevated following burn injury in both animals and humans. For example, sponges from burn wounds in rats have higher IL-6 content than controls,[1] as do enterocytes and gut macrophages from burned guinea pigs.[2] In addition, IL-6 levels in thermally injured humans are elevated in bronchial secretions,[3] donor site exudate,[4] and plasma.[5]

In contrast, TNF and IL-1 show a variable response to burn injury. Although elevation of TNF parallels that of IL-6 in Kupffer cells from burned guinea pigs,[6] TNF levels are frequently unchanged from controls[1,2,7] or even undetectable.[5] Similarly, IL-1 may be elevated following burn,[4–6] or it may show no significant change.[1,2] Studies of burned humans show no significant correlation between plasma IL-1 and burn size.[5]

Many investigators have studied the relationship between inflammatory cytokines and clinical outcomes. IL-6 and TNF plasma levels are higher in infected burn patients than in noninfected patients, and IL-6 levels are higher in infected patients who subsequently die than in those who survive.[5,8,9] The event driving the release of IL-6 may be

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translocation of bacteria and bacterial cell-wall products from the intestinal lumen: Reduction of endotoxemia by intravenous polymyxin B reduces circulating levels of IL-6 in burn patients.[10] Similarly, the frequency of the appearance of TNF correlates with both infection and mortality rate.[11]

Elevated IL-6 levels in burn patients also are associated with all components of the acute phase response such as fever, tachycardia, leukocytosis, decreased albumin, and increased C-reactive protein and α_1-antitrypsin serum levels.[12] IL-6 levels correlate positively with protein turnover (phenylalaninemia) and catabolism (3-methylhistidine/creatinine ratio), and negatively with levels of fibronectin and transthyretin. Although core temperature in burn patients is positively correlated with plasma IL-1,[8] IL-1 does not play a major role in regulating protein metabolism.[13] We can conclude that IL-6 is a major mediator following burn injury, not only of infection and survival from sepsis, but also of hypermetabolism and protein catabolism.

IL-6, along with IL-1 and TNF, is an endogenous pyrogen, capable of causing hyperthermia and thence hypermetabolism by stimulating the hypothalamic thermoregulatory center to release prostaglandin E_2 (PGE_2). The release of PGE_2 in turn up-regulates the hypothalamic set point, and core body temperature is elevated. Blockade of PGE_2 release can be achieved by the administration of cyclooxygenase inhibitors such as ibuprofen. The administration to burn patients of ibuprofen 40 mg/kg/24 hr, for example, reduces the core temperature a mean of 11.4%.[14]

Arachidonic acid (AA) metabolites also feed back on the production of inflammatory cytokines. Thermal injury is associated with a loss of PGE_2-dependent down-regulation of TNF synthesis, which accounts at least in part for increased TNF in experimental animals. In vivo cyclooxygenase blockade partially restores sensitivity to the prostaglandin down-regulated synthesis of TNF.[15] In contrast, the administration of ibuprofen to burn animals leads to a pronounced elevation of TNF production by Kuppfer cells, peritoneal macrophages, and neutrophils compared with vehicle-treated burned animals.[16] This indicates that prostaglandins are critical for down-regulating TNF production. However, caution must accompany the clinical use of cyclooxygenase inhibitors because their role in modulating the immune response in critically ill humans is not well understood.

The direct release of large quantities of PGE from skin cells after thermal injury also is well documented.[17] PGE is involved in the generation of many burn injury-related vascular and tissue viability problems.[18] PGE suppression of mixed lymphocyte cultures can be blocked by either delipidation of serum fractions or by the addition of monospecific anti-PGE antibodies to the cultures. The data also suggest the existence of a serum protein with a molecular weight of approximately 5,000 daltons, which appears to be necessary for the expression of the immunosuppressive properties of PGE contained in patient sera.[19]

Stress hormones

Thermal injury also leads to the activation of a number of endocrine and metabolic systems. It changes the concentration of several hormones, especially cortisol, glucagon, and catecholamines. For example, burn patients have increased free plasma cortisol and decreased plasma corticosteroid binding globulin, resulting in a relatively high percentage of unbound cortisol.[20] The urinary corticosteroid excretion is also higher in burn patients.[21] There is a direct correlation between the levels of total plasma cortisol and the severity of the thermal injury.[21] In addition, some studies indicate increases in serum growth hormone,[22] plasma corticotrophin,[23] and plasma somatomedin.[24]

Glucagon levels also are increased immediately after burn. The initial glucagon level (327 ± 42 pg/mL) on admission is significantly higher than the control fasting level (75 ± 4 pg/mL).[25] A correlation between negative nitrogen balance and glucagon levels occurs during the early catabolic period starting on the second and third postburn days.[26] After the closure of the burn wound and the approach of convalescence, glucagon levels return to normal.[25] The results of the study by Jahoor and coworkers[27] support the role of glucagon as the principal mediator of the increase in basal glucose production, because the lowering of glucagon concentration in all of their experimental groups was associated with a decrease in glucose production. There is insufficient evidence that glucagon causes protein breakdown; however, the high rate of glucose production is directly related to the high rate of protein breakdown.

Burn patients show a marked elevation of catecholamine output resulting in urinary epinephrine and norepinephrine levels 8 to 12 times normal.[28] There is a significant correlation between the increase in the excretion of these catecholamines and the corresponding increase in metabolic rate.[29] The infusion of epinephrine in normal humans results in increased metabolic rate when compared with the basal period.[30,31] This hypermetabolism is accompanied by an increase in respiratory rate and minute ventilation, and these alterations in metabolic and respiratory functions return to normal when epinephrine infusion is discontinued. Blood glucose, free fatty acids, and glucagon increase, whereas growth hormone falls, and insulin and glucocorticoids remain unchanged.[30] During catecholamine infusions in fasting subjects, nitrogen loss also increases.[30] In contrast, short-term epinephrine infusion in healthy human volunteers, especially when hypoaminoacidemia is prevented, inhibits endogenous leucine flux, which does not support the concept that epinephrine is a catabolic hormone.[32]

Bessey and associates[31] investigated the role of stress hormones as mediators of the metabolic response to injury. Nine normal male volunteers received a continuous 74-hour infusion of cortisol, glucagon, and epinephrine, which increased their hormone concentrations similar to those seen following mild to moderate injury. Body temperature, systolic blood pressure, and pulse all were elevated during the infusion, and metabolic rate increased 6.2 $Kcal/m^2/hr$. Skeletal muscle catabolism and glucose production also increased, thus mimicking many of the physiologic alterations characteristic of critical illness. However, the degree of skeletal muscle breakdown was not as accelerated as that observed in injured patients, suggesting that the increase in stress hormone concentration, although clearly associated with increases in metabolism and protein catabolism, is not

in itself sufficient to induce the clinical features observed in trauma and burn patients.

Heat loss

In addition to release of these inflammatory mediators, burn injury leads to hypermetabolism because of increased heat loss. The loss of skin removes the most important thermoregulatory organ, leading to increases in radiative, conductive, convective, and evaporative heat losses. Conduction, convection, and radiation, the routes of dry heat loss, account for only 5 to 10% of total heat loss.[33,34] Of these three, radiative heat loss, which is defined as the loss due to the difference between the surface temperature and the temperature of the surrounding environment, is the primary cause of dry heat loss. This heat loss can be greatly influenced by ambient temperature. The bulk of heat loss is from evaporation, which is normally controlled by the stratum corneum, a condensed fibrous membrane that is only 30 to 60 μ thick. Loss of the stratum corneum, a complex of lipids, sterols, and keratin elaborated by the epidermis, results in a 50-fold increase in evaporative water loss.[35]

Evaporation of water is an energy consuming process. It requires an extra heat production of approximately 576 cal/L of water at normal temperature.[36] Lieberman and Lansche[37] found that heat loss through vaporization of water represents 24% of the total heat produced under normal conditions in rats. After large burns, the heat loss by vaporization increases to 40 to 60% of all the heat produced. After the separation of the eschar and the conversion of the injury to an open wound, the insensible loss of water increases further, reaching 100 to 150% above preburn levels. Coverage of these experimental burns by skin grafts restores the insensible water loss and rate of oxygen consumption to normal.[37] The key point is that dead, burned skin (eschar), although hard, dry, and leathery, is much more water permeable than living skin, transmitting water vapor 70 times faster.[38]

Because the major portion of heat loss following burn is due to increases in evaporative and radiative losses, dressings for insulation and ambient temperature control can reduce part of the hypermetabolic response in burn patients.[39] Caldwell et al.[40] have shown that bulky occlusive dressings are effective in reducing heat loss to the environment. For example, metabolic studies performed on 23 burned children with and without dressings showed that heat production, evaporative heat loss, and radiative heat loss are higher in the exposed group than in the bandaged group. Removal of dressings in the study group was associated with an increase in metabolic rate, which was higher at ambient temperatures of 22°C and 28°C than at thermoneutrality (32°C). Furthermore, burn patients who are subjectively cold have higher metabolic rates than those in environmental conditions within the zone of thermal preference.[41]

Kelemen and associates[42] studied hypermetabolism in 44 burn patients with burn sizes ranging from 20 to 97% total body surface area (TBSA) treated by the open method of wound care with dressings covering only recently grafted areas. Patients were studied in metabolic chambers with a relative humidity of 50%, and the ambient temperature was increased stepwise from 22°C to 28°C and 32°C to 35°C. These authors found that metabolic rate is independent of burn size at thermoneutrality (32°C and 35°C), but was positively correlated with burn size at the lower temperatures where nonshivering thermogenesis occurred. Caldwell and associates[40,43] also observed that increased heat production in both burned rats and humans is correlated with evaporative heat loss and burn size. At thermoneutrality the metabolic rate is approximately 1.5 times the basal rate regardless of burn size, reflecting the centrally mediated component of hypermetabolism mediated by cytokines and stress hormones. The temperature-sensitive component of burn hypermetabolism described by Kelemen et al.[42] results from the increase in metabolic efforts necessary to maintain stable body temperature in a cool environment.

Assessment of nutritional needs

The purpose of the nutritional assessment is to characterize the patient's nutritional status and recognize preexisting malnutrition. This is essential for developing an appropriate nutritional regimen to treat specific nutritional disorders (e.g., thiamin replacement for alcoholic patients), to provide optimal repletion during the metabolic insult of the burn and multiple surgeries, to reduce morbidity and mortality, and to minimize loss of muscle strength. Nutritional status is assessed in most patients by a variety of methods, such as anthropometric measurement, biochemical data, clinical signs, and diet history.[44] The traditional parameters of anthropometric, biochemical, and clinical data will not be accurate in burn patients because their results are distorted by fluid resuscitation, surgeries, and systemic inflammatory responses.[45] For example, body weight, mid-arm circumference, blood count, and visceral protein status are affected by fluid resuscitation and transfusion, and nitrogen balance is affected by burn exudate and immobility. Therefore, diet history becomes more important to nutritional assessments than usual.

To assess patient nutritional status, a detailed history, including medical, surgical, social, and nutritional data, is essential. Burn patients may not be able to provide a history because of heavy sedation, obtundation, or endotracheal intubation, family members or caregivers need to be approached to obtain this information. Any factors that impair adequate selection, ingestion, digestion, absorption, and excretion of nutrients should be identified. These include:

- ability to chew, swallow, and self-feed
- comprehensive review of usual eating pattern, appetite, number of meals consumed daily, alcohol intake, food preferences, food allergies or intolerances, use of nutritional supplements, and drug history (nutrient-drug interactions)
- problems with nausea, vomiting, diarrhea, constipation, and steatorrhea
- weight history, including preburn weight and weight changes over the last 6 months
- chronic diseases affecting appetite and nutrient utilization, such as renal disease, liver disease, diabetes mellitus, pancreatitis, and malabsorption

- surgical resection of the gut or accessory organs of digestion
- history of depression

Review of diagnosis, medical treatment, and evaluation of laboratory data is also necessary. It includes percentage of body surface area (BSA) burned, percentage of full-thickness (third-degree) burns, presence and severity of inhalation injury, presence of other traumatic injuries, whether the patient is sedated or intubated, anticipated number of surgeries, and extent of donor sites. Laboratory data include blood urea nitrogen (BUN), serum creatinine, electrolyte levels, blood glucose level, serum albumin (or other serum protein levels as available), urine output, and ongoing evaluation of renal and liver function. All patients should be weighed.

In addition to weight, pediatric patients should be measured for length and head circumference on admission. The child's head circumference, weight for age, height for age, and weight for height should be plotted on the National Center for Health Statistics Growth Charts. Fat reserves can be assessed by visual examination. This information will help with early identification of failure to thrive or preexisting malnutrition. This is especially necessary for victims of child abuse by burning.

All burn patients should be assessed for the timing and route of nutritional support. Nutritional support is often necessary for the critically ill burned patient (e.g., an adult who has second- or third-degree burns greater than 20% TBSA, or a child who has second- and third-degree burns over 15% TBSA). Some elderly patients with minor burns may require nutritional support. Preburn dietary habits often limit postburn voluntary caloric intake; that is, patients are unlikely to change their eating habits after burn. Therefore, a registered dietitian trained in clinical nutrition science is required to provide this consultation to identify the high nutritional risk patient.

Estimation of energy requirements

Energy expenditure for burn patients is a composite of the basal metabolic rate (BMR), thermic effect of food, catabolism secondary to the degree of injury, level of physical activity, and the number and severity of infections. Long[46] noted nearly two decades ago that observed caloric expenditure measured with indirect calorimetry was up to 220% of the basal energy expenditure (BEE) estimated by the Harris-Benedict equations; that is, these patients were burning twice as many calories as they would without the thermal trauma. Although burn injury still results in significant increases in metabolism, recent advances in the care of these patients (i.e., earlier excision of the burns and closure of the wounds, improved support of the lungs following smoke inhalation injury, and prompt attention to nutritional needs) has been associated with reduction in energy consumption. For example, Saffle and associates[47] found that in their patients with burns covering between 40 and 60% TBSA, the mean elevation of resting energy expenditure was only 1.67 times the BEE.

Many equations have been used to determine the energy needs of burn patients. According to a recent survey of burn units,[48,49] the two most commonly used equations for adults are the modified Harris-Benedict equations (*Table 1*) and the Curreri formula. The Curreri formula is 25 Kcal × weight (kg) + 40 Kcal × % BSA burned, and was determined from observations of nine adult burn patients studied 20 days after burn.[46,50] It is important to note that this study was done prior to the introduction of early excision and grafting, and all of these patients had open wounds. Curreri and his associates calculated a regression line based on the percentage of weight lost and the average daily caloric intake to describe the ideal levels of daily caloric intake necessary to maintain weight. The most recent studies done on patients with early wound closure suggest that the Curreri formula overestimates energy expenditure in burn patients.[47,51]

Table 1 Use of the modified Harris-Benedict equations[46,48] to estimate resting energy expenditure
Men: BEE = (66.47 + 13.75W + 5.0H − 6.76A) × (Activity Factor) × (Injury and/or Burn Factor)
Women: BEE = (655.10 + 9.56W + 1.85H − 4.68A) × (Activity Factor) × (Injury and/or Burn Factor) where: W = weight in kg; H = height in cm; A = age in years.

Stressors	Stress factors
Activity factor	
Confined to bed	1.2
Out of bed	1.3
Injury factor	
Minor operation	1.2
Skeletal trauma	1.3
Major surgery	1.4
Sepsis	1.6
Burn factor	
<20% TBSA	1.2
20–25% TBSA	1.6
25–30% TBSA	1.7
30–35% TBSA	1.8
35–40% TBSA	1.9
>40% TBSA	2.0

BEE–basal energy expenditure. TBSA–total body surface area.

The estimation of caloric needs in burned children is even more challenging than in adults. The most commonly used formulas for pediatric burn patients' energy needs are outlined in *Table 2*.[48,49] Hildreth and associates[52] found that the actual intake required for weight maintenance in a group of pediatric burn patients is significantly lower than the requirements suggested by both the Curreri Junior and the Galveston formulas for burned children. The equation 2,100 Kcal/m^2 BSA/day + 100 Kcal/m^2 burned/day has been recommended by Hildreth et al.[53] for pediatric burn patients under 1 year of age. The caloric needs of older children are appropriately described by any of the equations in *Table 2*.

There is an assumption that energy expenditure will be reduced as burn wounds are covered and burn size is reduced. However, it is not always true because infections, sepsis, and multiorgan system failure (MOSF) will still increase the energy requirements. Measured energy expenditure (MEE) by indirect calorimetry is the best method for determining caloric requirements because of individual variations, daily fluctuations, operative procedures, and different stages of rehabilitation.[47,51] Within-individual variations can be minimized by measuring at a time of rest

Table 2 Formulas for estimating energy needs in pediatric patients

- Galveston formula: (1,800 kcal/m^2 body surface area + 2,200 kcal/m^2 burn surface area)[181]
- Solomon's formula: (RDA for age + 30 kcal/% TBSA burn)[48,49]
- 60 kcal/kg + 35 kcal/% TBSA burn[48]
- Curreri junior formulas[179,180]:
  Birth to 1 year: basal kcal from RDA + (15 kcal/% burn)
  1 to 3 years: basal kcal from RDA + (25 kcal/% burn)
  4 to 15 years: basal kcal from RDA + (40 kcal/% burn)

Age	RDA (kcal/kg)[180]	Basal calories
Birth to 6 months	108	320
6 to 12 months	98	500
1 to 3 years	102	740
4 to 6 years	90	950
7 to 10 years	70	1,130
Males 11 to 14 years	55	1,440
Males 15 to 18 years	45	1,760
Females 11 to 14 years	47	1,310
Females 15 to 18 years	40	1,370

Resting energy expenditure × 1.2[182] or predicted basal energy expenditure according to Harris-Benedict equation × 2.[183]
RDA–Recommended Daily Allowance. TBSA–total body surface area.

such as early morning. A factor of 20 to 30% above the MEE is recommended to account for activity and physical stress of wound care and other nursing treatments.

There are no definitive answers to how many calories each individual burn patient needs. Variation occurs from person to person and from day to day. For example, D.J. was a 46-year-old male who sustained 46% TBSA burn in a motor vehicle accident. During his hospitalization, he had a total of eight surgeries for debridement of wounds and skin grafting, and one for gastrojejunostomy tube placement. He had several episodes of sepsis and MOSF and was on respiratory support and hemodialysis for weeks. His resting energy expenditure (REE) was measured by indirect calorimetry twice a week, and for the first 5 weeks was 3,103, 2,647, 3,417, 4,779, 4,344, 4,309, 4,433, 4,912, 3,708, and 5,153 cal. His highest REE was approximately double the lowest REE, and occurred when he had sepsis and MOSF.

Estimation of protein requirements

Protein requirements are also increased in burn patients because of increased catabolism of skeletal muscle, leading to average losses of 260 mg protein/kg/hr (*Figure 1*). The rate of protein breakdown into amino acids and the reincorporation of these amino acids is important for collagen synthesis in wound healing as well as for maintenance of visceral proteins for optimal organ function, especially the immune system. Maintenance of diaphragm and intercostal muscle mass is also important for survival to avoid reduction of vital capacity and respiratory efficiency. In addition to the urinary losses from degradation of muscle mass, nitrogen is lost from wound exudate, excision of burns, and

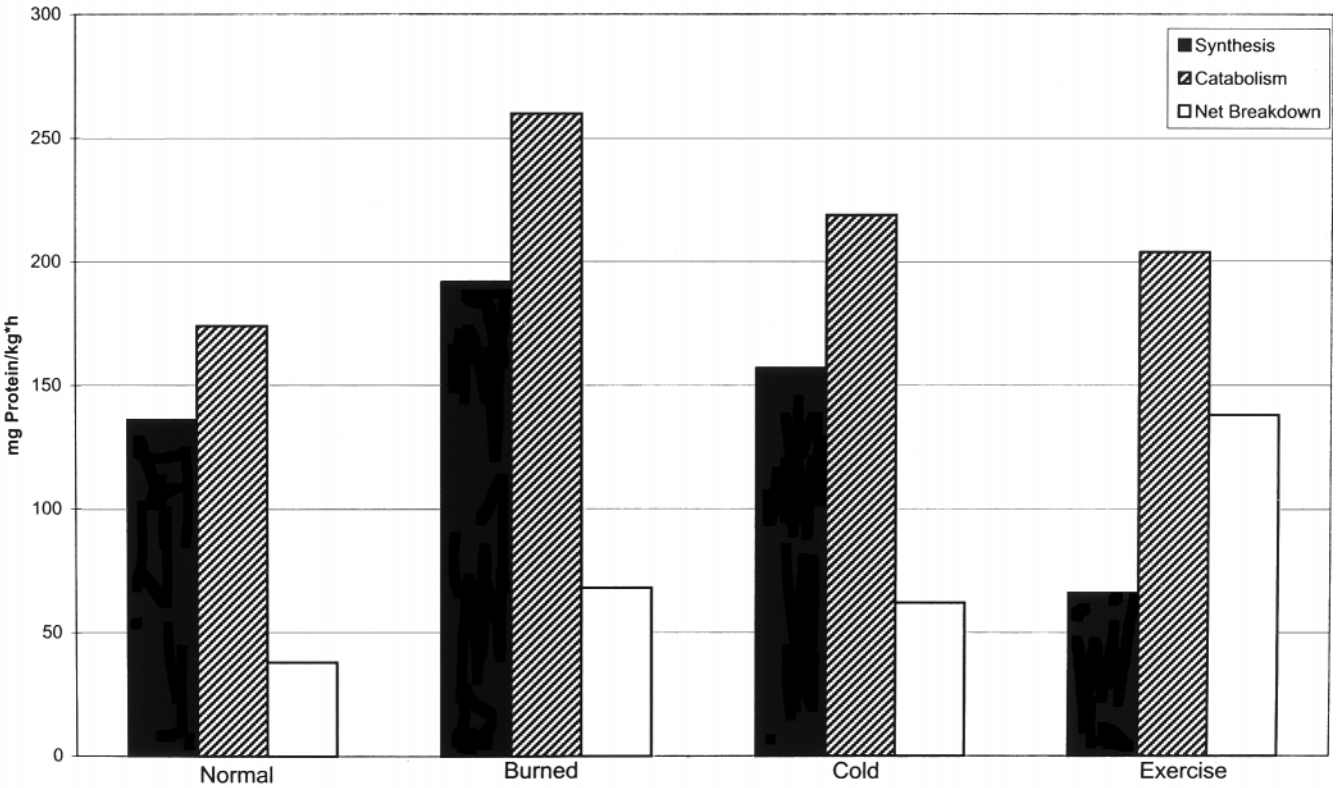

Figure 1 Protein turnover in burn injury, cold, and exercise. Wolfe and associates[55] have shown that the rate of whole-body protein catabolism, calculated from leucine kinetics, is markedly increased in burn patients, not only as compared with resting volunteers, but also as compared with volunteers whose metabolic expenditure is increased by either cold exposure or exercise. Thus, the increase in protein catabolism in burn patients is out of proportion to the increased energy expenditure. (Based on data from Wolfe et al.[55])

blood loss during surgery, leading to extraordinarily negative nitrogen balance.

The goal of nutritional therapy is to prevent rather than treat already established malnutrition, but protein degradation in burn patients proceeds despite adequate protein supplementation. A trauma patient may lose 20 to 25 g of lean body nitrogen daily, but anabolism is usually limited to approximately 3 to 8 g of nitrogen gain; for this reason, tissue loss is not easily regained.[54] Wolfe and associates[55] studied protein metabolism in six adults with an average of 70% TBSA burns in a crossover experimental design with two levels of protein support: 1.4 and 2.2 g protein/kg/d. All diets were isocaloric and provided 25% more calories than the MEE. Rates of whole-body protein synthesis and catabolism were calculated from measurements of ^{13}C-leucine flux and oxidation, disposition of $^{15}N_2$, and excretion of urea nitrogen. Regardless of the level of protein intake, the alterations in protein metabolism that accompany burn injury were unchanged, although increasing protein intake could stimulate both catabolism and anabolism. Only with the nitrogen excretion data was a beneficial increase in net nitrogen synthesis detected with the infusion of higher protein levels. These studies are consistent with the findings of Shizgal and Forse[56] in surgical patients in whom increasing the protein intake from 1.3 to 2.3 g/kg/d had no discernible beneficial effect on body composition that could not be accounted for by the increased calories provided by the greater protein intake. Similarly, a study of the effect of dietary protein intake on urea and protein metabolism in burn patients showed that high protein diets significantly increase skin protein synthesis and may enhance wound healing, but have little benefit on whole body protein breakdown and muscle protein synthesis rates.[57]

Nonetheless, clinical outcomes in burned children are improved by higher protein diets. The study of Alexander and coworkers[58] showed that severely burned children with high protein diet (calorie to nitrogen ratio 110:1; 4.9 g/kg/d) had better immune function, higher survival rate, fewer bacteremic days, and fewer days on systemic antibiotics than the control group (calorie to nitrogen ratio 150:1; 3.8 g/kg/d). The urinary sodium was lower and urinary potassium higher in the high protein group, suggesting that they also have better renal tubular function. In addition, the low protein group needed a higher volume of red cell transfusions to maintain hematocrit. Thus, the addition of supernormal amounts of protein to the diet of severely burned patients improves outcome through effects on the immune, renal, and hematologic systems, which may be independent of its effect on protein metabolism.

Changes have occurred in the care of the burned patient since the study by Alexander and associates[58] in the late 1970s. Similar to the drop in energy requirements noted since Wilmore's seminal studies at the United States Army Institute of Surgical Research in the early 1970s,[30] there has been a reduction in the amount of protein needed to adequately replete the burn patient now that wounds are excised and grafted earlier. In a retrospective study, Prelack and coworkers[59] observed that in 27 burned children with burns over 40% TBSA, energy intakes approximating the predicated BMR $\times$ 1.2 with a minimum of 3 g protein/kg/d support adequate wound healing (i.e., healing of all but 20% TBSA within 4 weeks of injury). Current recommendations range from 1.5 to 3.0 g protein/kg body weight, or 20 to 25% of total kilocalories as protein, depending on the size of burn.[60–63] The calorie to nitrogen ratio of 150:1 may not provide adequate nitrogen to achieve equilibrium in patients with greater than 10% TBSA burn,[64] and a calorie to nitrogen ratio of 100:1 may be required to achieve nitrogen balance.[65] However, using the calorie to nitrogen ratio alone to calculate needs is not sufficient to determine an optimal nutrition picture. For example, one patient receiving 2,500 cal with 120 g protein is given the same calorie to nitrogen ratio as a patient given 250 cal and 12 g; however, the latter is obviously energy malnourished. It is important to determine optimal calorie goals prior to those of other nutrients.

Means of support

The route of feeding, timing of initiation of nutritional support, and composition of the formula should be tailored to the estimated needs of each patient. How we support patients with supernormal nutritional requirements after burn injury is essential to their survival.

Route of feeding

The route of feeding can make a clear difference in outcome because of the preservation of mucosal immunity and the prevention of bacterial translocation. In addition, major differences among oral, enteral, and parenteral routes of nutrition are related to nutritional composition.

Food (defined as raw and cooked whole nutrients masticated and swallowed by the patient) has more therapeutic effect than tube feeding formulas and parenteral solutions. In addition to micronutrients and macronutrients, hundreds of phytochemicals are present in food and may expand its role in the prevention and treatment of disease. For example, allyl sulfides, which are found in onions and garlic, enhance immune function, increase the production of enzymes that help to excrete the carcinogens, decrease the proliferation of tumor cells, and reduce serum cholesterol levels.[66] Indoles, isothiocyanates, and sulforaphane, which are found in vegetables such as broccoli, trigger enzyme systems that block or suppress cellular DNA damage in animal studies.[66] Flavonoids act as antioxidants by extending the activity of vitamin C, protect low density lipoprotein cholesterol from oxidation, inhibit blood clot formation, and have other anti-inflammatory and antitumor properties.[67] Tube feeding formulas and total parenteral nutrition (TPN) solutions do not contain the above mentioned ingredients, and the oral diet is still the only way for patients to obtain different varieties of nutrients and phytochemicals presumed, although not yet proven, to improve the quality and speed of wound healing, recovery of the immune system and overall health of the patient.

There are also many differences between enteral and parenteral, not the least of which is the difference in infectious complications.[68,69] Notably, Herndon and associates[70] observed a higher mortality rate in severely burned patients fed parenterally, probably because of an increase in severe infections related to central lines and the absence of gut nutrition. Alverdy and associates[71] found that secretory

immunoglobulin A (IgA) levels in rats fed enterally is significantly higher than those fed parenterally, suggesting that an important defense barrier is compromised during parenteral hyperalimentation. Fong and Marano[72] and Myer et al.[73] studied healthy human volunteers and found that subsequent peak levels of glucagon, epinephrine, and arterial and hepatic venous TNF, the efflux of lactate and amino acids from peripheral muscle, and the impairment of polymorphonuclear (PMN) cell function were all higher in the TPN group. The authors concluded that antecedent TPN may influence the metabolic alterations seen in infection and sepsis via both an exaggerated counterregulatory hormone response as well as an enhanced systemic and splanchnic production of cytokines.

There is still merit to the adage, "If the gut works, use it." The preferred route of feeding for burn patients is oral feeding. If a patient cannot eat at least 80% of estimated caloric or protein needs or both, enteral feeding is indicated. For some patients, nocturnal feeding (enteral feeding at nighttime only) is appropriate to stimulate appetite and oral intake during the day. TPN is usually contraindicated because of the high risk of infectious complications, unless there are specific contraindications to enteral feeding, such as acute pancreatitis, recent bowel resection, high output enterocutaneous fistula or ileostomy, or paralytic ileus. Peripheral parenteral nutrition is occasionally used if the patient is unable to meet his or her nutritional goals enterally due to intolerance or other reasons.

Oral intake sufficient to meet estimated needs can often be achieved with burns of less than 20% TBSA if attention is given to patient food preferences. Burn patients need diets high in protein and calorie but moderate in fat content. High protein foods such as lean meat, fish, milk and milk products, dried peas, and beans (especially legumes) are encouraged. A regular diet with double portions and high protein snacks is recommended. Food can be fortified or enriched with hidden nutrients, such as powdered milk or protein modules with milk shakes, cream soups, or cottage cheese with fruit. Commercially made nutritional supplements also are recommended for patients to drink if nutritional goals are not met. "Empty calorie" drinks such as soft drinks, coffee, tea, and alcohol are discouraged for burn patients; in addition, caffeine leads to an unnecessary diuresis.

Timing of feeding

Early administration of enteral nutrition ("early feeding") is beneficial for a number of reasons. Early feeding decreases infections and the incidence of sepsis in humans,[69,74] improves wound healing,[75] and diminishes gut bacterial translocation in animals.[76] Most studies show that early feeding attenuates the hypermetabolic response to illness,[76] decreases protein catabolism, and improves nitrogen balance,[74] as well as reducing weight loss and duration of hospitalization.[77] In contrast, Wood and associates[78] observed that the timing of feeding had no demonstrable effect on the postburn increment in heat loss and the secondary increment in heat production following thermal injury in rats. Eyer and associates[79] also demonstrated that early enteral feeding after blunt trauma neither attenuated the stress response nor altered patient outcome. Nonetheless, the majority of studies, in both animal models and at the bedside, support the beneficial effect of early feeding.

There are several theories why early feeding reduces septic complications. The mechanisms include its effects on gut mucosal thickness and permeability and the immunologic barrier, and indirect effects on metabolism. For example, Mochizuki and coworkers[80] demonstrated improvement in postburn hypermetabolism and catabolism by early feeding in guinea pigs. They also demonstrated improved mucosal thickness and noted a negative correlation between plasma cortisol level and jejunal mucosal weight. This led the authors to postulate that early feeding attenuates postburn hypermetabolism by maintaining the gut mucosa. Because mucosal mass has a strong negative correlation with glucagon, cortisol, and catecholamines, they theorized that maintenance of mucosal integrity prevents activation of the inflammatory cascades, decreasing the catabolic response. Further work by this group suggests that the reduction in bacterial translocation plays a key role in modulating the response to the burn injury.[76,81]

Early feeding not only provides calories and protein to minimize the weight and functional loss of vital organs, but also increases mucosal blood flow, maintaining gut integrity and immune function.[82] Because the sepsis syndrome and MOSF may be the result of gut rather than systemic responses to translocation,[81] prevention of gut bacterial translocation may prevent sepsis and MOSF. Although bacterial translocation has been documented in animal models, its relationship to disease or injury has never been well documented in humans. If bacterial translocation does not occur in humans, it is possible that other complexes, such as endotoxin, complement, or cytokines may be responsible for infection after disruption of the gut barrier.[83]

Enteral feeding should be initiated as soon as it is determined that the patient will be unable to replete orally within an acceptable period of time. Nasogastric (NGT) or nasoenteric (NET) tubes should be used if the anticipated duration of tube feeding is less than 30 days. NGT is preferred if the stomach is functioning because of its simplicity and also the cytoprotective effect of formula on gastric mucosa. (The incidence of Curlings ulcers, which are gastroduodenal erosions that appear after burn injury, has fallen to practically nil since the routine use of enteral feedings.) NGT feeding is contraindicated in gastric ileus, diabetic gastroparesis, or gastric outlet obstruction. The medications occasionally given to burn patients, such as theophylline, anticholinergics, calcium channel blockers, beta-agonists, and alpha-antagonists, cause reduction in lower esophageal sphincter pressure, increasing the risk of aspiration.[84]

On the other hand, NET feedings in which the tip of the feeding tube is placed beyond the second part of duodenum should be used when NGT feedings are not tolerated or for patients with a high risk of aspiration. Patients with large burned surface areas usually develop gastric ileus, which limits the tolerance of the gastrointestinal tract to gastric feedings. Even though NET feedings may be better tolerated than NGT feedings, it is unclear whether the risk of aspiration pneumonia is significantly different.[84]

NGT placement is the easiest and least expensive mode

of access. NET placement requires fluoroscopic and endoscopic techniques, although blind placement is also possible by experienced personnel. Percutaneous endoscopic gastrostomy (PEG), percutaneous endoscopic jejunostomy (PEJ), and percutaneous endoscopic gastrojejunostomy (PEG-J) tubes are reasonable options for patients with long-term (greater than 30 days) need for nutritional supplementation.

In most cases, full strength formula with an initial flow rate of 20 to 30 mL/hr is appropriate. The infusion rate should be increased by 20 to 30 mL every 6 to 8 hours until goal rate is reached. The tube should be flushed with appropriate amounts of free water every 4 to 6 hours to prevent constipation and tube occlusion. The infusion rate may be lower in certain circumstances such as patients who have delayed feeding for 2 days or more. For malnourished infants and graduates from the neonatal intensive care unit, the rate may be limited to 1 or 2 cc/hr and progress slowly until goal reached. Feeding should proceed with extreme caution in patients who have not been adequately fluid resuscitated or who have had hemodynamic instability. Not only is aspiration pneumonia a constant concern, but we have occasionally seen extensive small bowel necrosis, not unlike necrotizing enterocolitis in newborns, in critically ill burn patients on aggressive enteral support.

Composition of formula

Diet therapy for burn patients plays a decisive role in clinical outcome. Choosing the right formula containing appropriate nutrients to meet their needs can significantly reduce complications and hospital cost, and may improve the odds of survival. Appropriate selection of an enteral product becomes more complicated because the formula market is rapidly growing. The proper fit between formula composition and a patient's individual needs depends on nutritional completeness, lactose content, osmolarity, viscosity, caloric density, molecular form of the substrates, and presence of fiber or immune modules.

Protein. Urinary nitrogen losses increase with the severity of burn injury and illness (*Figure 1*). For example, burn patients excrete a mean of approximately 26 g nitrogen/d (nitrogen loss for a normal person ranges from 7 to 10 g/d).[46] Consequently, protein requirements are increased to 1.2 to 2.5 times normal after burn injury. Protein catabolism can be estimated by combining 24-hour urinary nitrogen loss, 2 to 4 g of nitrogen for fecal loss, and 4 to 5 g/d for anabolism. Converting each gram of nitrogen to 6.25 g of protein leads to an estimate of dietary protein needs. Measurement of urinary nitrogen excretion can be misleading in burn patients, underestimating protein catabolism because there are no easy methods for quantifying protein losses from the open wounds. Waxman and associates[85] have estimated daily protein losses in grams from burn wounds during the first postburn week as $1.2 \times m^2$ BSA $\times$ %burn; on subsequent weeks protein loss is approximately half this rate. Thus, both fecal and skin losses are approximated quantities; only urinary nitrogen can be measured accurately. (Experienced clinicians will also recognize the frustrating challenge of collecting reliable 24-hour urine specimens!)

The amount of protein in enteral formulas ranges from 4 to 32% of total calories (en%). Formulas are classified as low protein ($<$10 en%), standard protein (11 en%–15 en%), intermediate protein (16 en%–20 en%), and high protein ($>$20 en%). Burn patients, especially growing children or patients with large burns, usually need intermediate to high protein formulas because of protein hypercatabolism. Patients undergoing surgery frequently are more likely to miss their feedings due to preoperative NPO status or postoperative ileus, and therefore, should be given high protein diets to compensate for missed protein calories. High protein formulas may lead to uremia, especially in children; this can be obviated in some patients by increasing the free water given with the tube feedings.

There are three forms of protein in commercial formulas: intact or whole protein, protein hydrolysates or peptides, and crystalline amino acids. The form of protein influences absorption in critically ill patients. Peptide-based enteral diets are associated with better hepatic protein response and less diarrhea compared with intact protein diets.[86] The lower incidence of diarrhea is probably due to better absorption, as is the beneficial effect on visceral protein synthesis. Absorption of dipeptides and tripeptides from protein hydrolysates is more efficient than that of free amino acids because of active transport carriers.[87] In fact, there are no data that support the use of amino acid-based enteral products over intact protein or peptide formulas.

Because of their lower cost, whole protein formulas can be used for patients who have normal gastrointestinal function and small burns (e.g., an elderly patient with inadequate oral intake because of Alzheimer's disease). For all other patients, formulas with protein hydrolysates should be used because of the improved absorption of small peptides. Our experience has shown that these peptide-based formulas are associated with better protein utilization and less diarrhea than intact protein formulas because the digestive and absorptive functions of patients with large burns are abnormal due to fluid resuscitation-induced hypoproteinemia, increased capillary permeability of the gastrointestinal tract, and paralytic ileus secondary to narcotics or sepsis.

Lipids. Lipid stores are critical for long-term fuel provision after major thermal injury. Fat oxidation is higher in hypermetabolic patients than in normal subjects,[88] and burn patients usually have increased fat mobilization and elevated serum levels of free fatty acids and glycerol. Dependence on lipid storage fuels begins soon after injury once hepatic and skeletal glycogen stores are depleted. Under conditions of carbohydrate shortage and free fatty acid utilization, ketones (acetoacetate, hydroxybutyrate, and acetone) are preferentially produced in the liver for oxidation by the brain, heart, and muscle.[89]

Lipids may be the body's preferred fuel substrate after injury or during sepsis.[90] For example, exogenous lipids can be effectively utilized as a fuel source during sepsis.[91] Nanni and associates[92] found that septic patients receiving glucose-only fuel had 3.75 mg/kg/min of glucose utilization, whereas the same patients receiving a glucose plus

lipid fuel mixture had 4.34 mg/kg/min of glucose utilization. These data suggest that the use of lipids increases the net oxidation of glucose in sepsis, and thereby enhances the use of both fuels (lipids and carbohydrates) for energy generation.

Caution should be exercised, however, in the use of dietary lipids in burn patients. Gottschlich and associates[93] found that, although the cause of diarrhea in burn patients is multifactorial, one of the nutritional variables clearly correlated with the incidence of diarrhea is fat intake. Diarrhea tends to be associated with high-fat diets, and dietary lipids exceeding 30 en% should be avoided. A number of enteral products contain medium-chain triglycerides (MCT) to enhance absorption and tolerance. MCT do not provide essential fatty acids and are ketogenic. Most commercial enteral products address these concerns by combining MCT with polyunsaturated fatty acids (PUFA).

In addition, stress states and exogenous PUFA generate lipid peroxides and can lead to significant cellular damage in the absence of adequate lipid-soluble free radical scavengers such as vitamin E.[94,95] Excess dietary lipids also may contribute to complications such as prolonged bleeding times, impaired phagocytosis, and depressed function of the reticuloendothelial system.[96]

Nonetheless, there are advantages to including lipids in the nutritional support of all burn patients. First, compared with carbohydrates and protein, lipids are more concentrated forms of energy and are useful when a large quantity of calories must be consumed. Second, lipid emulsions based on vegetable oils provide essential fatty acids and fat-soluble vitamins (absorption of the fat-soluble vitamins A, D, E, and K is also dependent on the presence of dietary lipids when the vitamins are provided in the form of enteral supplements). Third, lipids have especially potent and complex effects on the body's response to infection or stress. These effects are related to the diverse functions of lipids, especially as metabolic intermediates and components of cell membranes (which are phospholipid bilayers). They influence the structural integrity and membrane fluidity of membranes, receptor activity and signal transduction, and cell surface enzyme activity.

Essential fatty acids are stored in cell membranes, usually in the Sn-2 position within the inner leaf of the phospholipid bilayer where they are metabolized to eicosanoids when mobilized by phospholipases in the inflammatory response. ω-6 PUFA such as linoleic acid (18:2 ω-6) are elongated and desaturated to AA (20:4 ω-6), which is the precursor of potent immunomodulating eicosanoids such as PGE_2 and leukotriene B_4 (LTB_4). In contrast, the ω-3 fatty acids from some fish and vegetable oils are metabolized to eicosapentaenoic acid (EPA; 20:5 ω-3) and docosahexaenoic acid (DHA; 22:6 ω-3). EPA directly suppresses cyclooxygenase activity, inhibiting metabolism of AA, and provides substrates for production of less biologically potent eicosanoids such as PGE_3 and LTB_5.[97]

Excessive activation of the AA pathway occurs in burn patients[98] and contributes to the prolonged immunosuppression noted in these patients. Because of their effects on eicosanoid production, ω-3 PUFA may play a role in the treatment of stressed patients such as those recovering from burn injury. Clinical trials have been conducted in other groups of surgical patients with products constructed with ω-3 PUFA, and the results from these trials suggest improvement in infection rates and length of stay.[99–102]

Two randomized, prospective trials comparing different enteral formulas have been performed in burn patients. Gottschlich and associates[103] found that a high-protein tube feeding formula enriched with arginine, ω-3 PUFA, and other nutrients specific for burn recovery was associated with lower infection rates and decreased length of hospital stay compared with two commercially available formulas. On the other hand, Saffle and associates[104] found no significant benefit to the use of a commercially available "immune-enhancing" diet that contained, among other features, ω-3 PUFA. Other differences in formula composition, such as the amounts of arginine, glutamine (GLN), and nucleic acids, between the control and test diets in these studies prevent any direct conclusions about the role of ω-3 PUFA.

In the only study done to date that examines the appropriate type and amount of dietary lipid in burn patients, Garrel and associates[105] assigned patients to three different groups: control (35 en% fat from a mixture of soy and fish oils (ω-6 to ω-3 ratio of 1.5:1), low fat (15 en% fish and soy oils), and low fat with soy oil only (ω-6 to ω-3 ratio of 9:1). The results indicate that low-fat nutrition decreases infectious morbidity and insulin requirements, and that it shortens length of hospital stay for burn patients; however, the addition of ω-3 PUFA in fish oil does not provide additional clinical benefits beyond the effects noted by lowering the total amount of dietary fat.

Current recommendations for dietary lipids in burn patients limit intake to 15 to 25% of nonprotein calories, providing some in the form of essential fatty acids.[106] Consumption of 1 to 2 en% as linoleic acid is sufficient to prevent essential fatty acid deficiency, but a truly balanced formula must also include ω-3 PUFA. Although the absolute amount of essential fatty acids is not known, the ω-6 to ω-3 PUFA ratio should be approximately 2:1.[94,107]

Many laboratory studies suggest that manipulation of dietary lipids has the potential to alter the the host response to infection, but this has not yet been borne out conclusively by clinical studies. In addition, the choice of lipids in intravenous emulsions or in enteral products is limited at this time, but an increasing diversity of choices is expected in the near future. Future research into the use of monounsaturated fatty acids and defining the appropriate ratio of ω-6 to ω-3 fatty acids should clarify the correct amount and type of lipids for the burn patient.

Carbohydrates. Carbohydrates are the major source of energy both in the regular North American diet and in enteral formulas. The form of carbohydrate greatly influences the flavor and digestibility of the enteral product. Formula osmolarity is also influenced by the sources and amounts of glucose, sucrose, and other carbohydrate fragments and polymers; it is also determined to a lesser extent by free amino acids and electrolyte concentration.[108] Glucose polymers are common components of enteral formulas because they are more soluble than starch and are rapidly hydrolyzed by the small intestine. Most carbohydrates are easily digested and absorbed by the small intestine. Lactose

is the exception, and even patients who are not normally lactose-intolerant will become so following burn injury. Symptoms of carbohydrate intolerance range from abdominal discomfort to flatulence and diarrhea.

Burn injury significantly alters carbohydrate metabolism. For example, gluconeogenesis from alanine and other amino acids is significantly elevated in burn injury; this elevation is markedly increased in patients who are bacteremic.[109] The nitrogen residual, which is unavailable for reincorporation into body protein from gluconeogenesis, is excreted as urea, contributing to a progressive depletion of body nitrogen stores. The protein-sparing benefit of carbohydrate-containing solutions is directly related to the reduction in demand for glucose from gluconeogenesis when exogenous sugars are provided.[110]

Although oxidation of free fatty acids increases approximately linearly with the amount of substrate available, there is a limit to utilization of glucose as fuel in stress states. Burke and associates[111] found that there is little increase in direct glucose oxidation from increases in glucose infusion above approximately 5 mg/kg/min. Hepatocytes convert carbohydrates and protein in excess of the body's needs to triglycerides, which are released into the blood for transport to adipose tissue for storage. Keim and Mares-Perlman[112] studied the time course of lipid accumulation in the livers of rats infused continuously with lipid-free TPN at excessive energy and nitrogen levels and noted significant hepatomegaly within the first day. Initially, glycogen deposition accounts for the liver enlargement, but by the fourth day liver lipids have increased fourfold and are the major contributor to hepatomegaly. Autopsy studies of severely burned children confirm the association of fatty liver infiltration with high rates of caloric infusion.[111]

Therefore, the need for adequate caloric repletion following burn injury must be balanced with concerns about substrate disposition. Nonetheless, it is unusual to see fatty livers in burn patients at this point in time. First, the use of TPN and dependence on dextrose as the primary fuel source has declined because of the increased risk of infection. Second, the average number of calories delivered is less than in the era prior to early excision and grafting of burn wounds. For example, Burke and colleagues[111] administered several thousand calories each day to the children who later developed hepatomegaly; indirect calorimetry now shows us that these caloric loads are no longer necessary.

Fiber. Dietary fiber is necessary for normal gastrointestinal function. The recommended daily amount for healthy Americans is 10 to 13 g of dietary fiber per 1,000 calories.[113] Polysaccharides of plant cells and seeds are the unique source of dietary fiber. Nonfermentable fibers such as cellulose, hemicellulose, and lignin can increase gastric emptying, increase fecal bulk, and decrease intestinal transit time, thus preventing constipation. Fermentable or viscous fibers such as gums and pectins delay gastric emptying and slow small intestinal uptake of sugars and drugs such as acetaminophen and digoxin.[114,115] Dietary fiber acts as a barrier to diffusion by increasing the width of the unstirred layer and for this reason has been used successfully to treat diabetes mellitus, resulting in a reduction of the dose of antidiabetic medications.[116]

The major end products of metabolism of fermentable fibers are the short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. SCFAs are the preferential metabolic fuel for colonic epithelial cells and have been proposed as an alternate energy source during nutrition support of critically ill patients.[117] SCFAs influence gastrointestinal function by increasing intestinal blood flow,[118] stimulating pancreatic enzyme secretion,[119] and promoting sodium and water absorption in the colon.[120,121] Fermentable fibers also reduce the rate of bacterial translocation in experimental models and improve survival rates from experimental *Clostridium difficile* ileocecitis.[122]

Thus, there are two theoretical advantages to the inclusion of fiber in enteral formulas in burn patients. First, dietary fiber could reduce the morbidity and mortality associated with bacterial translocation and subsequent septic or systemic inflammatory response states. Second, fiber could reduce the incidence of diarrhea among critically ill patients. Unfortunately, clinical evidence is lacking to support either of these hypotheses, and there is little to support the routine use of dietary fiber in critically ill burn patients. Nonetheless, we have empirically added fiber to the enteral formulas of patients with troublesome diarrhea; in some cases resolution of the problem has been noted.

Soy polysaccharides, oat fiber, and modified guar gum are fibers that can supplement enteral formulas. Fiber can also be given to patients separately in other forms, such as natural bran, psyllium husk fiber (Metamucil®, Proctor & Gamble, Cincinnati, OH USA), pectin, or banana flakes. These fibers should not be added directly into enteral feeding bags because the solution will thicken and lead to tube occlusion. The mixture of fiber and small amounts of water should be administered with a syringe and followed by flushing. Patients receiving fiber from tube feedings or other sources should increase free water intake to prevent obstipation. Fiber formulas should also be initiated slowly to prevent discomfort and flatulence.

Arginine. Arginine is a non-essential amino acid for healthy adults, but is essential for wound healing, protein anabolism, and immunity following injury.[123,124] For example, Barbul and associates[125] found that arginine supplementation significantly increases the breaking strength of skin incisions. Similarly, there is an increase in reparative collagen deposition in subcutaneously implanted sponges. Arginine supplementation also modulates immune function, increasing thymic weight and cellularity in animals and increasing lymphocyte blastogenesis.[126,127] The mechanism by which arginine produces these effects is not known, but it has numerous biochemical roles, including as an intermediate in the urea cycle, as a precursor for nitric oxide, and as a stress hormone secretagogue.[123,128,129]

Arginine turnover in burn patients is increased. Yu and associates[130,131] found a low rate of net de novo arginine synthesis despite increased rates of arginine degradation. These investigators also studied urea production rates and plasma arginine and leucine kinetics in burn patients.[130,132] They proposed that there are at least two significant metabolic pools of arginine, one related specifically to urea synthesis and the other forming a systemic pool in equilibrium with plasma. Because the hepatic urea cycle does not

contribute substantially to making arginine available for protein synthesis, exogenous arginine is required for the larger systemic pool, thus making it available for maintenance of immune function and wound healing.

Arginine possesses numerous pharmacologic actions that can have great potential benefit in immune function. Saito and associates[133] found that either 1 or 2 en% of supplemental arginine increased delayed-type hypersensitivity and decreased mortality in burned guinea pigs. Gennari and associates[134] studied the benefit of different combinations and amounts of arginine and other immune-enhancing nutrients on bacterial translocation and related mortality during gut-derived sepsis in burned mice. Results indicated that the animals fed arginine in combination with either GLN or fish oil have improved gut barrier function and enhanced ability to kill translocated organisms in the liver. Supplementation of the diet of burn patients with 2 en% arginine is associated with enhanced T-cell blastogenesis, CD4 expression, CD4/CD8 ratio, IL-2 production, and IL-2r expression.[135]

Glutamine. The most abundant amino acid in the body, GLN is important for the function of lymphocytes and macrophages, as well as for nourishment of enterocytes. Mobilization of muscle amino acids, especially branched-chain amino acids (BCCAs), during stress states provides necessary precursors for GLN.[136] GLN can be synthesized in skeletal muscle, but this endogenous production of GLN cannot keep up with demands after injury, sepsis, or surgical stress. Whole body GLN flux increases after burn injury, but skeletal muscle fails to augment de novo GLN synthesis, leading to parallel decreases in muscle GLN utilization unless exogenous GLN is available.[137] For example, Snelling and associates[138] found plasma GLN in burn patients is approximately 64% that of control patients. Supplementation of GLN either enterally or parenterally may be necessary for maintenance of immunity, gut barrier function, and wound healing.

GLN contributes amide groups for purine and pyrimidine synthesis, which are critical for rapidly proliferating cells.[139] In addition, it serves as an energy source for lymphocytes and phagocytes. PMN cells from burn patients were isolated by Ogle and associates[140] and studied for their ability to phagocytose and kill *Staphylococcus aureus* in the presence and absence of GLN. Although GLN has no effect on phagocytosis, it does improve bacterial killing. Similarly increasing the concentration of GLN in culture media improves the blastogenic response of lymphocytes from burned mice.[141]

Enterocytes have exceptional needs for GLN during stress states. GLN supplementation increases intestinal blood flow and oxygenation, secretion of secretory IgA, and absorption of nutrients following burn in miniswines.[130–132] Mice fed GLN-supplemented diets following burn injury have lower rates of bacterial translocation and higher rates of bacterial killing of translocated organisms.[142,143] These findings are consistent with observations in other animal models or clinical settings in which GLN has been studied.[144,145]

Currently, commercially available parenteral amino acid solutions do not contain GLN because it is unstable and hydrolyzed in a relatively short time at room temperature. GLN dipeptides are stable in solution after 121°C sterilization and have a long shelf-life; they will soon be available in the United States.[146] On the other hand, GLN-enriched enteral formulas and GLN supplements in bulk form and single packets are now available for clinical use.

Branched-chain amino acids. BCAAs are oxidized predominately in the periphery, notably in skeletal muscle rather than liver. BCAAs taken up by skeletal muscle are use primarily for nitrogen transfer via transamination, for the formation of GLN and alanine.[147–149] (GLN, as mentioned above, plays many roles in the stressed host; alanine serves as a fuel source of gluconeogenesis in the liver, especially important once glycogen stores have been depleted after injury.) However, the oxidation of some keto acids indicates that in human skeletal muscle BCAAs provide some energy as well as nitrogen. Nonetheless, transfer of nitrogen to GLN and alanine following burn injury is the key physiologic process in skeletal muscle rather than the generation of energy.[150]

Yang and Birkhahn[151] studied female and male rats on the BCCA oxidizing pathway after thermal injury. The ability of the skeletal muscle to oxidize the BCCA was estimated by BCCA transaminase (BCTA) and branched-chain α-keto acid dehydrogenase (BCKDH). The results indicated that both BCTA and BCKDH activity in red and white muscles from male rats is elevated. (Female rat muscle does not show the same pattern.) Studies in burn patients show that the arterial plasma concentrations of BCAAs are approximately 50 to 61% those of the control patients, although net arterial-venous flux is unchanged.[138]

The theoretical advantage of BCAA supplementation in correcting some of the metabolic problems in stress states is to provide an exogenous source of energy and nitrogen as an alternative to skeletal muscle.[152] However, the studies of Sax et al.[153] with burned rats and Brown et al.[154] with burn patients indicate that solutions enhanced with BCAAs do not significantly increase nitrogen balance compared with standard amino acids. At the present time, there are no well-founded clinical studies to support the routine supplementation of BCAAs following burn injury.

Micronutrients. Micronutrients function as coenzymes and cofactors necessary for biochemical reactions. Protein and energy sources cannot be utilized efficiently if the intake of vitamins and minerals is inadequate. Micronutrient requirements still remain undefined in the severely burned patient. However, it is well known that the burn patient has higher requirements due to altered digestion, absorption, utilization, excretion, and fuel metabolism arising from tissue injury, infection, and surgery.

Many studies have suggested increased requirements for vitamins B, C, and E (thiamin, biotin, riboflavin, nicotinic acid, pyridoxine, folic acid, ascorbic acid, and α-tocopherol) in burn patients.[155–160] Zinc and magnesium deficiencies are also present in burn patients.[161,162] Symptoms of magnesium deficiency such as depression, hallucinations, tremors, and muscle cramps disappear after magnesium repletion, leading some observers to suggest that some of the psychiatric symptoms exhibited by many burned pa-

tients may be due to or aggravated by magnesium deficiency.[161] Iron deficiency is very common because of hemolysis after burn and blood loss due to frequent surgery. Nonetheless, iron supplementation (e.g., ferrous sulfate) should be discouraged because the low iron environment is essential for bacteriostatic and bactericidal systems in blood, lymph, and exudates.[163]

The majority of formulas contains enough minerals and vitamins to meet most patient needs if the patient receives enough volume to meet the caloric and protein goals. However, formulas specific for hepatic and renal failure have limited mineral and vitamin contents that are necessary to avoid metabolic complications; micronutrient supplements are usually necessary.

A recent survey on the use of mineral supplements in burn units in the United States and Canada showed that 90% of respondents prescribe or recommend trace mineral supplements.[164] Of that group, 88% prescribe zinc, 75% prescribe iron, 26% prescribe chromium, and 13% prescribe selenium supplements. Less than 2% supplement molybdenum or vanadium and do so only when administering TPN. Another similar survey on vitamin supplements showed that 87% of the respondents routinely prescribed vitamin supplements, usually a multivitamin preparation[165]; 58% of the multivitamin dosages exceeded 100% of the Recommended Dietary Allowances. Several respondents indicated that extra vitamins were given in addition to multivitamin preparations, especially vitamins A and C. Further research on micronutrient requirements for burn patients is needed.

Monitoring nutritional supplementation

Monitoring becomes an important task after nutritional support has been started. Calories and protein received should be compared with the planned nutritional goal. For many reasons, patients' nutritional requirements will change, or they may not be able to tolerate the prescribed formula. The complexity and frequency of nutritional monitoring may vary according to patient acuity but should never be discontinued during hospitalization, especially for patients on tube feedings. The suggested protocol for monitoring burn patients is listed in *Table 3*.

To assess nutritional intake, protein and calorie intake must be calculated daily. Multiple sources of the patient's intake from enteral, parenteral, and oral intakes are included in this calculation. We strive to limit each patient's weight loss through multidisciplinary team efforts. In our burn center, the patient's nutritional data, including daily calorie and protein intakes, nutritional goals, and weight, are graphed and posted on the patient's door. The percentage weight loss of each patient is reported during team rounds to alert team members of the patient's weight loss, reminding us to avoid unnecessary discontinuation of tube feedings and to avoid neglecting supplements and snacks because of therapies or treatments.

Patients can lose 10 to 20 lb in a short period of time without being noticed, leading to profoundly deleterious effects on immune function and wound healing. If the patient's current weight is higher than the admission weight or does not reflect true weight due to anasarca, calculated weight will be used. The daily caloric deficit is used to calculate dry weight (*Table 4*).[166] This formula assumes that most acute weight lose is adipose tissue; oxidizing 1 lb of fat provides 3,555 cal.[167] Thus this formula underestimates weight loss of burn patients because some muscle is also oxidized as fuel due to increased gluconeogenesis; muscle has less caloric density because only 25% is protein. If the patient has amputation or deep surgical debridement of burned tissue, the weight of these tissue losses should be included in the calculations.

Table 3 Suggested nutritional monitoring

Parameter	Critically ill patient	Stable patient
Calorie count	Daily	PRN
Indirect calorimetry	Weekly	PRN
Weight	Daily	Weekly
Wound healing	Daily	Daily
Transthyretin	Weekly	PRN
Electrolytes	Daily	Weekly
Liver function tests	Weekly	PRN
Kidney function tests	Thrice weekly	PRN
Nitrogen balance	Weekly	PRN
Intake and output	Daily	PRN
Bowel function	Daily	Daily
Urine or blood glucose	Daily	Daily for diabetics/ PRN for others

PRN–Pro re Nata (as the need arises)

It is not always easy to predict energy needs with formulas alone because of variations among individuals and because of changes in the clinical condition during the recovery period due to infections, surgeries, sepsis, and other complications. Indirect calorimetry (IC) is useful to measure actual energy expenditure, especially in the patient whose clinical response is not optimal (e.g., a patient with slowly healing wounds). IC is performed in the morning before daily activities begin to obtain a more accurate estimate of REE. An additional 30% is added to the REE to account for activity and the stress of treatment.[168] In many circumstances the measurements of IC will not represent actual energy expenditure. The equipment, the technician's skill, and the time the measurement is performed will affect the results. The data derived from the metabolic chart should never replace the clinical judgment of the dietitian and physician responsible for the care of the patient.

The respiratory quotient (RQ) is an indicator of substrate utilization and can be used to determine over- or underfeeding.[169] An RQ of less than 0.8 suggests underfeeding and total caloric intake should be increased. An RQ between 0.8 to 0.95 suggests appropriate mixed substrate utilization. An RQ over 1.0 suggests carbohydrate overfeeding and

Table 4 Equations for calculation of weight loss and dry weight

- Daily weight loss (kg) = (caloric goal − caloric intake)/3,555 calories/2.2
- Accumulated weight loss (kg) = weight loss of day 1 + day 2 + . . . day # *n* . . . + today's weight loss
- Calculated current weight (kg) = admission weight − accumulated weight loss − tissue loss from surgery

lipogenesis; carbohydrate or total calories should be decreased.[170]

It is equally challenging to assess the ongoing need for and adequacy of protein supplementation. Transthyretin, also known as prealbumin, is recognized as a sensitive marker of visceral protein status, largely because of its short half-life of 2 to 3 days.[171] Cynober and associates[172] have suggested that in burn patients transthyretin should be selected over other visceral protein markers because of its simplicity, low cost, and predictive value. Church and Hill[173] compared levels of transthyretin with serum albumin, plasma transferrin, and retinol-binding protein in surgical patients treated with intravenous nutrition. They found that transthyretin has better sensitivity, specificity, and positive and negative predictive values than the other protein markers. Cynober and associates[172] also studied 61 patients with burn injury, observing that transthyretin levels fall to a minimum between postburn days 6 and 8. (Interestingly, transthyretin levels are not significantly related to the extent or depth of burn in surviving patients without complications.) Levels return to normal gradually in survivors but remain low in nonsurvivors. In addition, persistently low transthyretin values are associated with a higher risk of sepsis in the survivors.

Nitrogen balance studies have also been used to monitor protein status and efficacy of nutritional support for burn patients. Total urinary nitrogen (TUN) and urinary urea nitrogen (UUN) are commonly used, but UUN is less expensive, hazardous, and laborious, and the technology is more widely available than TUN.[174] The validity of UUN as a substitute for TUN in burn patients, however, has been questioned.[175–177] On the one hand, Konstantinides and associates[176] found that the formula for calculating TUN from UUN underestimates nitrogen loss by 20 to 60% in burn patients. In their study of 27 burn patients, UUN represented a mean of approximately 65% of the directly measured TUN rather than 80% as assumed by commonly used formulas. On the other hand, Milner and associates[177] measured UUN and TUN simultaneously in 200 24-hour urine specimens from 45 burn patients and found that there was a linear relationship with excellent correlation ($r = 0.936$) between TUN and estimated TUN ($1.25 \times$ UUN). In addition the mean difference between TUN and UUN was only 0.6 g, a number that is statistically significant but has little clinical significance. TUN is more direct and accurate, but UUN offers practical advantages and is acceptably accurate for routine calculation of nitrogen balance in burn patients.

Unfortunately, there is a poor correlation between serum visceral protein levels and nitrogen balance. Carlson and associates[178] found weak correlations between nitrogen balance (TUN plus nitrogen losses from the burn wound estimated by formula[85]) and serum prealbumin, retinol-binding protein, and transferrin ($r^2 = 0.14$, 0.15, and 0.12, respectively) during the first 4 weeks following burn injury. Parallel changes in direction (e.g., higher serum protein levels and more positive nitrogen balance) between serum proteins on the one hand and nitrogen balance studies on the other occurred less than 50% of the time. One of the major drawbacks of nitrogen balance studies is their dependence on estimated insensible nitrogen losses, which from the burn wound can be considerable and quite variable. Our own experience has been that positive changes in serum proteins are associated with clinical progress, such as healing of wounds, and that these changes are often attributable to the amount of dietary protein.

In addition to caloric and protein intake, patients' vitamin and mineral intakes need to be monitored. These micronutrients play important roles in wound healing, maintenance of immune function, and overall recovery. Burn patients receive vitamin and mineral supplements daily, but because of prolonged hospitalizations and numerous complications, deficiencies can occur. However, routine laboratory monitoring of micronutrients is not cost effective and should be reserved for patients who demonstrate clinical signs of deficiencies.

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