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Early Enteral Nutrition for Burn Injury

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Abbreviations and Acronyms

ICU = intensive care unit

IL = interleukin

ILGF1 = insulin-like growth factor 1

MOF = multiorgan failure

rhGH = recombinant human growth hormone

ROS = reactive oxygen species

TNF = tumor necrosis factor

Significance: Nutrition has been recognized as a critical component of acute burn care and ultimate wound healing. Debate remains over the appropriate timing of enteral nutrition and the benefit of supplemental trace elements, antioxidants, and immunonutrition for critically ill burn patients. Pharmacotherapy to blunt the metabolic response to burn injury plays a critical role in effective nutritional support.

Recent Advances: Further evidence is demonstrating long-term benefits from pharmacologic immunomodulation given the prolonged metabolic response to injury that may last for over a year following the initial insult.

Critical Issues: The majority of evidence regarding early enteral feeding comes from mixed populations and smaller studies. However, on balance, available evidence favors early feeding. Data regarding immunonutrition does not support the routine use of these products. Limited data regarding use of antioxidants and trace elements support their use.

Future Directions: Further evaluation of anti-inflammatory mediators of the immune response, such as statins, will likely play a role in the future. Further data are needed on the dosing and route of micronutrients as well as the utility of immunonutrition. Finally, little is known about nutrition in the obese burn patient making this an important area for investigation.

SCOPE AND SIGNIFICANCE

Burn injury continues to be a significant cause of morbidity and mortality. In 2011, there were 45,000 hospitalizations for burn injury and 3,500 deaths.[1] As resuscitation, surgical therapy, and critical care for burn patients have improved, the survival from burn injury has improved. According to data from the National Burn Repository, the survival rate for 2011 was 96.1%.[1] Despite this, major burns remain a devastating injury that can affect all organ systems. Additionally, all of these patients require careful wound management. Nutritional support has become an essential element of burn care. This review will cover the use of nutrition in burns, particularly the use of early enteral nutrition in the management of these patients.

CLINICAL RELEVANCE

Burn patients with >20% body surface area injury suffer a long and severe response to injury, including a hyperdynamic and hypermetabolic response with lipolysis, proteolysis, glycolysis, and fever. This catabolic state ultimately results in a profound reduction of lean body mass. Poor wound healing, immune dysfunction, multiorgan failure, and even death can ensue. Elements of a hypermetabolic state may persist for years following injury.[2] Whereas the primary intervention that blunts the catabolic state and promotes anabolism is wound closure by early excision and grafting, systemic support

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with optimal nutrition, and pharmacologic modulation of the metabolic response are also necessary. Starting enteral nutrition early (< 24 h after injury) is thought to blunt the metabolic response to burn injury and lead to improved outcomes.[3] Enteral nutrition may be oral; however, many burn patients will require an oral or nasoenteric feeding tube placement. Published practice guidelines currently exist, but vary in their recommendations regarding early enteral nutrition.[4–7]

TRANSLATIONAL RELEVANCE

Experimental evidence has demonstrated that enteral nutrition influences the physiologic response to injury. Animal models using guinea pigs demonstrate that early enteral nutrition significantly reduces the hypermetabolic response to injury.[8,9] Rat models show that enteral nutrition can decrease the levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α), when compared with parenteral routes.[10] Bacterial translocation and loss of gut mucosal integrity has also been shown in the host response to burn injury.[11,12] The resulting intestinal injury may influence systemic injury and multiorgan failure.[13] Enteral nutrition helps to maintain gut mucosa viability and decrease bacterial translocation.[14] Introduction of nutrients to enhance the immune response shows promise in blunting the inflammatory response and improving the intestinal immune response.[15–18] Finally, even in the acute phase of the injury, the bowel tolerates enteral feeding despite slower transit times.[19]

EXPERIMENTAL MODEL OR MATERIAL: ADVANTAGES AND LIMITATIONS

The gold standard for evidence in clinical practice remains a well-conducted, blind, randomized controlled trial. Whereas several prospective randomized studies evaluate the use of early enteral nutrition in burns, they are not blinded, do not have transparent randomization, or have mixed populations of adults and children.[20] These studies also demonstrate mixed results. Peng *et al.* showed decreased intestinal permeability with early feeding in 22 patients randomized to enteral nutrition within 24 h compared with those started after 48 h.[14] Gottschlich *et al.* randomized 77 acutely burned children to enteral nutrition within 24 h or standard care where enteral nutrition was held for at least 48 h. They showed that early enteral nutrition prevented calorie deficits after burn injury and decreased protein breakdown, but did not improve infection, mortality, or morbidity.[21] However, they did see a trend of more adverse events, including bowel necrosis in the early feeding group, although it was not statistically significant.[21] Peck *et al.* prospectively looked at 27 patients with severe burn injury randomized to receive early (within 24 h) enteral nutrition or late (7 days) enteral nutrition and showed no difference in energy expenditure.[22] Results showed 28% mortality in the early feeding group compared to 38% in the late group, but this was not statistically significant.[22]

In a larger randomized study, Khorasani and Mansouri randomized 688 children with burn injury to either early (within 3–6 h) or late (> 48 h) enteral nutrition. They demonstrated decreased mortality, 8.5% in the early group versus 12% in the late group ($p < 0.05$) and decreased hospital stay in the early nutrition group.[23]

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Route of administration

Enteral feeding is preferred over parenteral nutrition. There is direct evidence in the burn population from randomized studies that show decreased infection, decreased cost, and decreased length of stay with enteral nutrition.[7,24,25] Patients who do not tolerate enteral feeds, however, may have no option but parenteral nutrition. If previously healthy patients are not tolerating adequate enteral feeding by day 7 in spite of aggressive attempts to maximize GI motility, supplemental parenteral nutrition should be considered.[4,7]

Timing

While there are no definitive trials that indicate clear superiority of early nutrition, clinical practice guidelines recommend starting enteral nutrition in critically ill patients within 24 h in burns and 24–48 h in mixed intensive care unit (ICU) populations.[4–7] Barriers to implementation include provider preferences, concerns over risk, logistic issues, and injuries that may prevent tolerating enteral support. A retrospective review by Holt *et al.* showed a median time to feeding tube placement of 31.1 h postadmission and a median time to beginning enteral nutrition of 47.9 h.[26] A larger study by Mosier *et al.* of 153 ventilated patients compared 123 patients with enteral nutrition at < 24 h to 30 patients who received enteral nutrition after 24 h.[27] They found no increase in complications, a lower infection rate, and a lower length of ICU stay in the early nutrition group.

These two studies highlight both the logistic difficulty of starting early enteral feeding as well as the potentially low risk, especially when taken

with the overall trend of the randomized data. For early nutrition to be successful, practice guidelines may need to be actively instituted and disseminated to change practice.[28]

Interruption of enteral nutrition can also occur as a result of multiple operations to close wounds. There is evidence from a cohort study of 80 burn patients that intubated patients can safely receive tube feeds throughout an operation. Patients who did receive nutrition in the operating room had a lower caloric deficit and fewer infections.[29] Eliminating the practice of stopping enteral feeds in the perioperative and intraoperative periods can significantly increase the amount of nutrition delivered.

Nutritional requirements

Critical to starting and maintaining early enteral nutrition is an assessment of patient nutritional need. Over 200 published equations estimate the caloric need, although they are less accurate than indirect calorimetry, particularly in the obese.[7] Indirect calorimetry is the preferred method of measuring caloric need, although some have questioned its ability to measure over or underfeeding in the pediatric population.[30,31] Calorimetry is not always feasible, particularly in the acute setting. Given the anticipated metabolic responses to injury, initial enteral feeding at 1.2–1.4 times resting energy expenditure in kcal/m^2 per day provides adequate nutrients.[32]

The macronutrients in the formulation of burn nutrition include carbohydrates, proteins, and lipids. Some research suggests that given the inhibition of lipolysis in the acute response to injury, lipids should be limited as a source of calories.[32] Comparison of high carbohydrate, high protein, low fat enteral feeds with low carbohydrate, high protein, high fat formulas in a systematic way showed no clear benefit to either formula, although the risk of pneumonia appeared lower with the high carbohydrate formula.[33] Protein appears to be an essential macronutrient for wound healing, and protein requirements in burn patients may be 50% higher than in healthy individuals. Protein delivery should be 1.5–2 g/kg body weight daily.[32,34]

Careful evaluation of nutritional formula and ongoing measurements of caloric need is essential to prevent both overfeeding and underfeeding. Whereas overfeeding is more common with parenteral nutrition, it can occur with the enteral route as well, particularly if parenteral nutrition is used as a supplement. Excess carbohydrate intake leads to fat synthesis, increased CO_2 production, hepatic steatosis, and difficulty weaning from the ventilator.[31,35] Administration of excess protein has been associated with renal failure, sepsis, and death.[34,36]

Assessment of response to nutritional supplementation can be difficult to assess in the ICU setting. Anthropometrics as well as traditional serum proteins, such as albumin, prealbumin, and retinol binding protein, may be unreliable in the critical care setting.[7] Still, measurement of weekly prealbumin levels provides insight into the catabolic or anabolic state of the patient in the presence of concomitantly measured, stable acute-phase reactants.[37,38]

Micronutrients and immunonutrition

Critical illness and injury result in increased oxidative stress and release of reactive oxygen species (ROS). These molecules have been associated with multiorgan failure (MOF) and acute respiratory distress syndrome. ROS may produce tissue injury through oxidation of enzymes and structural proteins, peroxidation of cell plasma membranes, and induction of apoptosis.[39] Even in previously healthy individuals, the oxidative stress of critical illness depletes body stores of antioxidants.[40]

Whereas data in burn patients is lacking, randomized data from the trauma population demonstrate clinical benefit from supplementation with the antioxidants α-tocopherol (vitamin E) and ascorbic acid (vitamin C). Nathens *et al.* studied 591 patients (91% trauma) randomized to supplementation with enteral α-tocopherol 1,000 IU every 8 h and 1,000 mg IV ascorbic acid every 8 h compared to placebo for the duration of ICU stay or 28 days. They found decreased pulmonary morbidity, MOF, length of mechanical ventilation, and ICU stay in the antioxidant group.[39] Another randomized trial in a mixed ICU population comparing lower doses of enteral vitamin E and vitamin C for 10 days compared with placebo demonstrated a significantly reduced 28-day mortality in the antioxidant group (45.7%) compared with placebo (67.5%, $p < 0.05$.)

Further data are needed to determine the precise amount of antioxidants and preferred route. Supplementation of nutritional intake with vitamins E and C appears to benefit the critically ill. Given the more severe inflammatory and metabolic derangements produced by burn injury, it seems reasonable to generalize these findings to the burn population.[32]

An overlapping pathway for the processing of ROS is enzymatic detoxification. Enzymes, such as superoxide dismutase, catalase, and glutathione

peroxidase work to defend the body against ROS, but require cofactors, such as zinc, selenium, manganese, and iron to function.[41] Berger *et al.* randomized 20 patients with >30% total body surface area burn injuries to either placebo, or supplementation with increased amounts of selenium, zinc, and copper. Patients were supplemented parenterally for 8 days starting at admission. Patients who received the trace elements had a shorter hospital stay and decreased pulmonary infections.[42] This study supplemented multiple trace elements, but a systematic review showed that single trace element supplementation might reduce the risk of mortality, particularly high-dose selenium.[41] However, this review also concluded that there was no difference with antioxidants supplemented enterally.[41]

Whereas there is direct evidence that traces element supplementation improved outcome specifically in burn patients, the numbers are small. The best route, dose, and type of trace elements for burn patients remain to be elucidated. Given that many critically ill burn patients have acute kidney injury, caution should be used when supplementing trace elements in patients with renal failure. Despite shortcomings, some clinical practice guidelines recommend the routine use of trace elements and antioxidants given promising results and a good safety profile.[5,7]

Immunonutrition refers to the use of nutrients that modify a patient's immune response during critical illness. Nutrients that have been used in burn patients include omega-3 fatty acids (fish oil), glutamine, and arginine. Glutamine is thought to be a conditionally essential amino acid in burns. It provides a nitrogen source, a fuel for immune cells, fuel for enterocytes, serves as a precursor for the antioxidant glutathione, and potentially reduces insulin resistance.[43] Arginine, another conditionally essential amino acid in burns, serves as a precursor proline and glutamate, promotes t-cell proliferation, stimulates insulin, insulin-like growth factor 1 (ILGF1), and pituitary growth hormone, as well as promoting wound healing.[43] Omega-3 fatty acids replace omega-6 fatty acids in cell membranes and decrease inflammation due to less inflammatory breakdown products.[43]

Glutamine is the best studied of these nutrients and has been recommended as a nutritional supplement in the critical care population.[7] This recommendation stems largely from a randomized, double-blind, control trial conducted by Garrel *et al.* that examined 41 patients and showed a reduction in mortality for patients randomized to receive bolus glutamine supplementation.[44] However, the only other randomized trial that reported mortality as an outcome measure was in pediatric patients and failed to show a reduction.[43] While recognizing that glutamine may show promise, a recent review of immunonutrition in the burn population found insufficient evidence to routinely recommend the use of these agents.[43]

Pharmacologic adjuncts

As described previously, the metabolic response to burn injury is severe. In patients with 25% body surface area burns, the metabolic rate can be increased by 118%–210% of that predicted by the Harris–Benedict equation.[45] This increase in metabolic demand increases with the burn size.[46] Increases in catecholamines, corticosteroids, and inflammatory cytokines, including interleukin (IL)-1, IL-6, TNF, and platelet activating factor mediate this response and levels can remain elevated for months after injury.[32] Subsequent lipolysis, proteolysis, and glycolysis can lead to loss of lean body mass and in the pediatric population, delays in growth of up to 2 years following injury.[32] Furthermore, these increases result in a hyperdynamic state with an elevated heart rate, increased cardiac work, and increased myocardial oxygen consumption.

Early enteral nutrition plays a key role in blunting the metabolic response to burn injury, but is insufficient by itself. Several pharmacologic therapies have been identified that counteract this catabolic state.

Nonspecific beta blockade with propranolol has shown very good results in blunting the response to burn injury. In the pediatric population, propranolol has been shown to reverse muscle-protein catabolism and reduce resting energy expenditure in a randomized trial.[47] Furthermore, by achieving a 20% reduction in the heart rate with propranolol dosing, cardiac work is decreased.[48] Recently, the benefit of propranolol has been demonstrated to last for at least 12 months after injury.[49]

Oxandrolone is an anabolic steroid analog of testosterone that has only about 5% of the virilizing effect. It reduces muscle protein catabolism, maintains lean body mass, and decreased acute hospital length of stay.[50,51] More recently, oxandrolonegiven to children for 12 months after injury has demonstrated benefits that persist up to 5 years following injury. In addition to the effects on protein metabolism, children who received treatment showed improved height percentile and increased bone mineral content when compared with controls.[52]

The recombinant human growth hormone (rhGH) showed promise as an agent for blunting

catabolism postburn.[32] A double-blind, randomized, controlled trial showed increased morbidity and mortality in critically ill patients.[53] ILGF1 is a mediator of the effects of rhGH. The combination of ILGF1 and rhGH resulted in improved protein metabolism compared to use of rhGH alone.[32]

TAKE-HOME MESSAGES

- Burn injury is associated with a hypermetabolic response and a prolonged catabolic state
- Early excision and wound closure of burn wounds is the primary mode of controlling this response.
- Enteral feeding helps modulate host response to injury and maintain healthy intestinal mucosa.
- Enteral nutrition is preferred over parenteral nutrition when possible.
- Enteral nutrition should be started within 24 h of injury.
- Supplementation with antioxidants (vitamin E & C) and trace elements, particularly selenium appears beneficial.
- Routine use of immunonutrition is not yet proven in burn patients.
- Propranolol and oxandrolone have both demonstrated long-term attenuation of the metabolic response to burns.

INNOVATION

Research into nutritional supplementation for burn patients is ongoing. Currently, several U.S. Department of Defense–funded, American Burn Association–sponsored ongoing multicenter trials will further elucidate the role of micronutrients and specific amino acids and metabolic manipulation in burn patients. More information is needed regarding the duration, amount, and route of these supplements. Others are attempting to clarify further the effects of the macronutrients in nutrition, particularly the anti-inflammatory effects of increased lipids.

Major areas of innovation will likely come from the pharmacologic adjuncts to enteral nutrition. Agents that blunt the body's metabolic response help to improve the benefits of early nutrition and long-term outcomes. Statins are a class of molecules with anti-inflammatory properties that are only beginning to be investigated in the burn population. However, evidence already suggests that statins decrease insulin resistance in burned animals, and may improve mortality in septic burn patients.[54,55]

Finally, little is known about the effect of obesity on nutrition in burn patients. A survey of practices in the United States demonstrated that providers are adjusting clinical practice based on perceptions that complications and poor outcomes are more frequent in obese patients.[56] As the obesity rate rises, it will be important for future research to identify how the metabolic response varies in this population and the optimal method of providing them with nutritional support.

CAUTION, CLINICAL REMARKS, AND RECOMMENDATIONS

Early enteral nutrition appears to have significant benefits to burn patients with few adverse events. Sufficient evidence exists to recommend starting enteral feeding within 24 h of injury. However, studies from both pediatric and adult populations are relatively small so generalization should be done with caution. Institutional guidelines and protocols will likely be necessary to ensure that feeding starts in a timely fashion. The routine use of antioxidants and trace elements is also reasonable given the current data and limited downside. It should be noted, however, that there is currently little evidence regarding the preferred dose, route, or combinations of these supplements. Experimental regimens may act as a guideline, but the precise dosing and use of these supplements require clinical judgment. Data regarding the use of pharmacologic adjuncts are also sufficient to recommend their use; however, it should be noted that currently much of the data comes from a single center as well as a pediatric population. While prolonged use of these medications appears safe and beneficial, the exact duration and dosing for optimal benefit is not yet clear.

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REFERENCES

1. Burn Incidence and Treatment in the United States: 2011 Fact Sheet. 2011; www.ameriburn.org/resources_factsheet.php (accessed October 27, 2012).
2. Jeschke MG, Gauglitz GG, Kulp GA, *et al.*: Long-term persistance of the pathophysiologic response to severe burn injury. PLoS One 2011; **6:** e21245.
3. Hart DW, Wolf SE, Chinkes DL, *et al.*: Effects of early excision and aggressive enteral feeding on hypermetabolism, catabolism, and sepsis after severe burn. J Trauma 2003; **54:** 755; discussion 761.
4. Jacobs DG, Jacobs DO, Kudsk KA, *et al.*: Practice management guidelines for nutritional support of the trauma patient. J Trauma 2004; **57:** 660; discussion 679.
5. Kreymann KG, Berger MM, Deutz NE, *et al.*: ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr 2006; **25:** 210.
6. Heyland DK, Schroter-Noppe D, Drover JW, *et al.*: Nutrition support in the critical care setting: current practice in canadian ICUs—opportunities for improvement? JPEN J Parenter Enteral Nutr 2003; **27:** 74.
7. Martindale RG, McClave SA, Vanek VW, *et al.*: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine and american society for parenteral and enteral nutrition: executive summary. Crit Care Med 2009; **37:** 1757.
8. Mochizuki H, Trocki O, Dominioni L, Brackett KA, Joffe SN, and Alexander JW: Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg 1984; **200:** 297.
9. Dominioni L, Trocki O, Fang CH, *et al.*: Enteral feeding in burn hypermetabolism: nutritional and metabolic effects of different levels of calorie and protein intake. JPEN J Parenter Enteral Nutr 1985; **9:** 269.
10. Cui XL, Iwasa M, Kuge H, Sasaguri S, and Ogoshi S: Route of feeding influences the production and expression of tumor necrosis factor alpha in burned rats. Surg Today 2001; **31:** 615.
11. Carter EA, Tompkins RG, Schiffrin E, and Burke JF: Cutaneous thermal injury alters macromolecular permeability of rat small intestine. Surgery 1990; **107:** 335.
12. Deitch EA: Intestinal permeability is increased in burn patients shortly after injury. Surgery 1990; **107:** 411.
13. Deitch EA, Shi HP, Lu Q, Feketeova E, Skurnick J, and Xu DZ: Mesenteric lymph from burned rats induces endothelial cell injury and activates neutrophils. Crit Care Med 2004; **32:** 533.
14. Peng YZ, Yuan ZQ, and Xiao GX: Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. Burns 2001; **27:** 145.
15. Berger MM, Binnert C, Chiolero RL, *et al.*: Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. Am J Clin Nutr 2007; **85:** 1301.
16. Cui XL, Iwasa M, Iwasa Y, and Ogoshi S: Arginine-supplemented diet decreases expression of inflammatory cytokines and improves survival in burned rats. JPEN J Parenter Enteral Nutr 2000; **24:** 89.
17. Falder S, Silla R, Phillips M, *et al.*: Thiamine supplementation increases serum thiamine and reduces pyruvate and lactate levels in burn patients. Burns 2010; **36:** 261.
18. Fan J, Meng Q, Guo G, *et al.*: Effects of early enteral nutrition supplemented with arginine on intestinal mucosal immunity in severely burned mice. Clin Nutr 2010; **29:** 124.
19. Sallam HS, Kramer GC, and Chen JD: Gastric emptying and intestinal transit of various enteral feedings following severe burn injury. Dig Dis Sci 2011; **56:** 3172.
20. Wasiak J, Cleland H, and Jeffery R: Early versus delayed enteral nutrition support for burn injuries. Cochrane Database Syst Rev 2006; **2006:** CD005489.
21. Gottschlich MM, Jenkins ME, Mayes T, Khoury J, Kagan RJ, and Warden GD: The 2002 Clinical Research Award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional, and endocrine outcomes after severe burns. J Burn Care Rehabil 2002; **23:** 401.
22. Peck MD, Kessler M, Cairns BA, Chang YH, Ivanova A, and Schooler W: Early enteral nutrition does not decrease hypermetabolism associated with burn injury. J Trauma 2004; **57:** 1143; discussion 1148.
23. Khorasani EN and Mansouri F: Effect of early enteral nutrition on morbidity and mortality in children with burns. Burns 2010; **36:** 1067.
24. Chen Z, Wang S, Yu B, and Li A: A comparison study between early enteral nutrition and parenteral nutrition in severe burn patients. Burns 2007; **33:** 708.
25. Lu G, Huang J, Yu J, *et al.*: Influence of early post-burn enteral nutrition on clinical outcomes of patients with extensive burns. J Clin Biochem Nutr 2011; **48:** 222.
26. Holt B, Graves C, Faraklas I, and Cochran A: Compliance with nutrition support guidelines in acutely burned patients. Burns 2012; **38:** 645.
27. Mosier MJ, Pham TN, Klein MB, *et al.*: Early enteral nutrition in burns: compliance with guidelines and associated outcomes in a multicenter study. J Burn Care Res 2011; **32:** 104.
28. Jain MK, Heyland D, Dhaliwal R, *et al.*: Dissemination of the Canadian clinical practice guidelines for nutrition support: results of a cluster randomized controlled trial. Crit Care Med 2006; **34:** 2362.
29. Jenkins ME, Gottschlich MM, and Warden GD: Enteral feeding during operative procedures in thermal injuries. J Burn Care Rehabil 1994; **15:** 199.
30. Saffle JR, Larson CM, and Sullivan J: A randomized trial of indirect calorimetry-based feedings in thermal injury. J Trauma 1990; **30:** 776; discussion 782.
31. Liusuwan Manotok RA, Palmieri TL, and Greenhalgh DG: The respiratory quotient has little value in evaluating the state of feeding in burn patients. J Burn Care Res 2008; **29:** 655.
32. Williams FN, Branski LK, Jeschke MG, and Herndon DN. What, how, and how much should patients with burns be fed? Surg Clin North Am 2011; **91:** 609.

33. Masters B, Aarabi S, Sidhwa F, and Wood F: High-carbohydrate, high-protein, low-fat versus low-carbohydrate, high-protein, high-fat enteral feeds for burns. Cochrane Database Syst Rev 2012; **2012:** CD006122.

34. Stroud M: Protein and the critically ill; do we know what to give? Proc Nutr Soc 2007; **66:** 378.

35. Mittendorfer B, Jeschke MG, Wolf SE, and Sidossis LS: Nutritional hepatic steatosis and mortality after burn injury in rats. Clin Nutr 1998; **17:** 293.

36. Klein CJ, Stanek GS, and Wiles CE 3rd: Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc 1998; **98:** 795.

37. Raguso CA, Dupertuis YM, and Pichard C: The role of visceral proteins in the nutritional assessment of intensive care unit patients. Curr Opin Clin Nutr Metab Care 2003; **6:** 211.

38. Crimi E, Liguori A, Condorelli M, *et al.*: The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. Anesth Analg 2004; **99:** 857, table of contents.

39. Nathens AB, Neff MJ, Jurkovich GJ, *et al.*: Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 2002; **236:** 814.

40. Goode HF, Cowley HC, Walker BE, Howdle PD, and Webster NR: Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. Crit Care Med 1995; **23:** 646.

41. Heyland DK, Dhaliwal R, Suchner U, and MM: Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med 2005; **31:** 327.

42. Berger MM, Spertini F, Shenkin A, *et al.*: Trace element supplementation modulates pulmonary infection rates after major burns: a double-blind, placebo-controlled trial. Am J Clin Nutr 1998; **68:** 365.

43. Kurmis R, Parker A, and Greenwood J: The use of immunonutrition in burn injury care: where are we? J Burn Care Res 2010; **31:** 677.

44. Garrel D, Patenaude J, Nedelec B, *et al.*: Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. Crit Care Med 2003; **31:** 2444.

45. Herndon DN and Tompkins RG: Support of the metabolic response to burn injury. Lancet 2004; **363:** 1895.

46. Jeschke MG, Mlcak RP, Finnerty CC, *et al.*: Burn size determines the inflammatory and hypermetabolic response. Crit Care 2007; **11:** R90.

47. Herndon DN, Hart DW, Wolf SE, Chinkes DL, and Wolfe RR: Reversal of catabolism by beta-blockade after severe burns. N Engl J Med 2001; **345:** 1223.

48. Baron PW, Barrow RE, Pierre EJ, and Herndon DN: Prolonged use of propranolol safely decreases cardiac work in burned children. J Burn Care Rehabil 1997; **18:** 223.

49. Herndon DN, Rodriguez NA, Diaz EC, *et al.*: Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. Ann Surg 2012; **256:** 402.

50. Hart DW, Wolf SE, Ramzy PI, *et al.*: Anabolic effects of oxandrolone after severe burn. Ann Surg 2001; **233:** 556.

51. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, and Herndon DN: The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. Ann Surg 2007; **246:** 351; discussion 360.

52. Porro LJ, Herndon DN, Rodriguez NA, *et al.*: Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg 2012; **214:** 489; discussion 502.

53. Takala J, Ruokonen E, Webster NR, *et al.*: Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999; **341:** 785.

54. Fogerty MD, Efron D, Morandi A, Guy JS, Abumrad NN, and Barbul A:Effect of preinjury statin use on mortality and septic shock in elderly burn patients. J Trauma 2010; **69:** 99.

55. Bonab AA, Carter EA, Paul K, *et al.*: Effect of simvastatin on burn-induced alterations in tissue specific glucose metabolism: implications for burn associated insulin resistance. Int J Mol Med 2010; **26:** 311.

56. Coen JR, Carpenter AM, Shupp JW, *et al.*: The results of a national survey regarding nutritional care of obese burn patients. J Burn Care Res 2011; **32:** 561.