

Carol Rees Parrish, M.S., R.D., Series Editor

## Nutrition and Nutraceuticals for Muscle Maintenance and Recovery: Hero or Hokum?



Joe Krenitsky

**Muscle loss during hospitalization, especially during intensive care unit admissions, contributes to muscle weakness, functional limitations and the need for extended rehabilitation services. The elderly are particularly affected by muscle loss due to age-related sarcopenia at baseline and because they have delayed recovery due to anabolic resistance. Inadequate nutrition contributes to muscle loss during hospitalizations, but the provision of full nutrition alone is unable to completely prevent muscle loss due to illness and inactivity. Nutrition strategies and supplements offer a way to minimize muscle loss and potentially accelerate recovery from periods of catabolism and muscle loss during hospitalizations. Several amino acids or amino acid derivatives increase nitrogen retention in animal models and appear to have a favorable action on human muscle metabolism. This review will evaluate the data investigating the potential of nutraceuticals and nutrition strategies to minimize muscle loss and accelerate rehabilitation of muscle mass and strength.**

### Process and Significance of Muscle Loss

In the past 40 years there has been substantial progress in the ability to provide nutrition support to hospitalized patients, especially those that are critically ill. Small bore and percutaneous feeding tubes allow safe enteral nutrition (EN) in circumstances and disease states previously considered impossible or inadvisable.<sup>1, 2</sup> Patients with a dysfunctional gastrointestinal tract can receive their full nutrition needs via parenteral nutrition (PN). However, while providing

adequate nutrition reduces muscle breakdown, nutrition alone cannot completely preserve lean muscle mass in hospitalized adult patients.<sup>3, 4</sup> In the early phase of critical illness, catabolism is unavoidable.<sup>5</sup> Research has demonstrated that the negative nitrogen balance associated with the early stage of critical illness are not completely reversed even when calories and protein are provided far in excess of requirements.<sup>4</sup> Furthermore, the lack of exercise and general immobilization that occurs in hospitalized patients results in breakdown of skeletal muscle regardless of nutrition intake.<sup>5</sup> The loss of skeletal muscle during hospitalizations exacerbates muscle weakness, which can hamper weaning from

---

Joe Krenitsky MS, RD. University of Virginia Health System, Charlottesville, VA

mechanical ventilation, delay recovery, and increase the need for and duration of rehabilitation services.<sup>5</sup> A study of ARDS survivors revealed that discharge body weights were 18% less than preadmission weight, and there was a prolonged functional disability in many patients that persisted, even when pulmonary function returned to normal.<sup>6, 7</sup> Intensive Care Unit acquired weakness has been reported in 50% of patients ventilated > 1 week and was still present in 25% of ICU patients 7 days later.<sup>8</sup>

Elderly patients are particularly susceptible to the effects of muscle loss while hospitalized and have delayed recovery of skeletal muscle mass compared to younger patients.<sup>9</sup> Typically there is a progressive loss of skeletal muscle between 20 and 80 years of age that eventually amounts to 35-40% of total muscle mass, therefore older patients enter their hospitalization with less functional reserve.<sup>10</sup> The elderly are also resistant to the normal stimulating effects of dietary protein on muscle protein synthesis, which may be one of the reasons why the elderly experience delayed recovery from periods of immobilization and muscle loss.<sup>11</sup> The loss of skeletal muscle mass (sarcopenia) in elderly patients contributes to disability with reduced abilities for stair climbing, rising from a chair, load carrying and even walking.<sup>10</sup> Increased loss of muscle during hospitalizations further reduces leg strength and stability, and may increase the risk of falls.<sup>12, 13</sup> Nutritional strategies or supplements that minimize muscle loss during hospitalization and enhance recovery of muscle mass and strength during rehabilitation have the potential to decrease functional disability after an illness and decrease the need for, or duration of, rehabilitation services after surviving a critical illness. It is important that nutraceuticals with anabolic potential be adequately studied to understand the full effects on patient outcomes before they are routinely used in clinical practice. It is clear that some nutritional interventions that initially appeared promising had negative effects that were not apparent in animal, or small short-term studies, and are revealed only in large randomized trials.<sup>14-17</sup> This article will examine available research of agents with the potential to accelerate recovery from episodes of skeletal muscle loss and review nutritional strategies that may help reduce loss of muscle mass during hospitalizations.

### Arginine

Arginine is considered a conditionally essential amino acid because it functions as an essential amino acid

under conditions of growth, pregnancy, or injury.<sup>18</sup> Arginine is involved in the detoxification of ammonia through the urea cycle, the synthesis of creatine, nitric oxide, and in supraphysiologic doses increases the secretion of growth hormone, glucagon, insulin and prolactin.<sup>18</sup> Supplemental arginine improves nitrogen balance and measures of T-cell immune function of hospitalized adult patients.<sup>19</sup> Supplemental arginine also increased protein accumulation and collagen deposition in catheters implanted into muscle of healthy volunteers, suggesting that arginine could have a favorable influence on wound healing.<sup>20</sup>

However, studies of arginine supplemented enteral feedings have also revealed increased mortality in septic patients and a study of supplemental arginine in patients with cardiovascular disease was halted due to significantly increased mortality in the arginine supplemented group.<sup>16, 21</sup> Although there is data to suggest that supplemental arginine could have potential benefits for strength, muscle, rehabilitation and wound healing, there are no randomized studies of the effect of arginine on any functional endpoints that matter such as the need for rehabilitation after hospitalization, time for recovery, or actual healing of wounds. Considering that randomized studies have demonstrated unexpected negative effects of supplemental arginine in some circumstances, arginine supplementation appears to be an area worthy of further investigation rather than routine clinical use at this time.

### Branched Chain Amino Acids and Leucine

Studies of isolated muscle tissue and animal models have provided evidence that the branched chain amino acids, particularly leucine, stimulate muscle protein synthesis.<sup>22, 23</sup> In healthy young adults, adding additional leucine to an oral amino acid supplement (3.5g leucine) increased muscle anabolic signaling, but did not stimulate muscle protein synthesis more than an amino acid supplement with a normal leucine content (1.7g leucine).<sup>24</sup> However, in an elderly population (66 +/- 2 years) increasing the concentration of leucine in an amino acid supplement to 2.8g increased protein synthesis by 20% compared to the standard amino acid supplement containing 1.7 gm leucine.<sup>25</sup> Healthy elderly subjects who ingested a leucine-rich amino acid supplement had rates of protein synthesis similar to younger patients (30 +/- 2 years).

Although leucine supplementation appears to acutely increase protein synthesis in older patients, there

is no evidence that long-term leucine supplementation will result in significant functional changes or influence patient outcomes. A randomized, placebo-controlled study investigated the effect of adding 2.5g supplemental leucine to each meal (3X/day) for 3 months in a group of healthy elderly (71 +/- 4 years) men.<sup>26</sup> There were no significant differences in muscle mass or strength between the placebo and leucine groups at the end of 3 months. There is evidence that resistance exercise may have a synergistic effect on protein synthesis with branched-chain enriched proteins, therefore it would be worthwhile to study the potential for leucine as an adjunct to resistance exercise in patients undergoing rehabilitation or in elderly patients with sarcopenia.<sup>27</sup> Due to the fact that leucine stimulates protein synthesis by increased signaling through a pathway that is increased in some forms of cancer, some experts have questioned if leucine could accelerate growth of existing tumors.<sup>25</sup> Colon cancers with an unfavorable prognosis were reported to have increased leucine uptake, and branched-chain enriched amino acid mixtures appear to stimulate tumor growth.<sup>28, 29</sup> While supplemental branched-chain amino acids or leucine may not be advisable during treatment of existing malignancy, there is sufficient evidence for an effect of leucine on protein synthesis to justify further investigations.

### **Beta-hydroxy-beta-methylbutyrate (HMB)**

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite derived from the amino acid leucine.<sup>30</sup> HMB has been studied in athletes, the elderly and in various pathological states after studies demonstrated an increase in lean muscle mass and protein synthesis in animals with HMB supplementation. Randomized studies in athletes have demonstrated that the beneficial effects of HMB on muscle appear to be limited to novice athletes, because elite or highly trained athletes do not appear to benefit from HMB supplementation.<sup>31, 32</sup> A small randomized study of HMB supplementation (3 gm/day) in 48 critically ill trauma patients, demonstrated that HMB significantly improved nitrogen balance from the first 7 days compared to the last 7 days, more than placebo or a combination of 3g HMB, 14 gm arginine and 14g glutamine (Juven).<sup>33</sup> Interestingly, the addition of arginine and glutamine to HMB in trauma patients appears to negate any benefits of HMB on protein metabolism. The group that received the combination of HMB with arginine and glutamine had numerically lower nitrogen balance compared to control patients,

and significantly worse nitrogen balance compare to the HMB group.

A year long randomized study of elderly patients investigated the effects of an HMB-arginine-lysine combination (HMB/Arg/Lys) on body composition, protein metabolism, strength and functionality.<sup>34</sup> Compared to the placebo group, HMB/Arg/Lys significantly increased body cell mass by 1.6% and lean mass by 1.2%. Despite these statistically different results there was only a trivial difference in lean mass between the groups at the end of 1 year of supplementation (average of 1.2 lbs lean mass), and there was no significant difference in strength or functional status between the two groups of patients. There was a gradual loss of handgrip and leg strength in both groups over the year, and the results of the functionality tests were not different between treatments groups. However, recently the authors published a post-hoc re-analysis of this data based upon the vitamin D status of the participants.<sup>35</sup> The investigators found that the 11 patients who received HMB/Arg/Lys supplement with adequate vitamin D status (25-OH vitamin D > 30ng/mL) had a significant improvement in strength. Those patients who received the control product, and subjects that received HMB/Arg/Lys, but were vitamin D insufficient or deficient (25-OH vitamin D <30 ng/ml), did not have a significant change in strength. Obviously, the number of patients in the cohort (n = 11) that received the HMB/Arg/Lys with adequate vitamin D status is so small that it prevents strong conclusions and points to the need for a larger study. However, these results do point out that it is difficult to study the effects of a potential treatment for muscle mass or strength if there are other deficiencies or pathologic states that would prevent accrual of lean muscle mass. Studies of HMB in other pathologic conditions such as cancer, rheumatoid cachexia, and HIV/AIDS, also suffer from very small numbers of patients, limited study time frames and reliance on surrogate markers rather than real functional outcomes that matter.<sup>36-39</sup>

### **Fish Oil**

Fish oil provides the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which influence a wide variety of cellular functions. Among other actions, EPA and DHA supplementation decreases production of proinflammatory cytokines in stressed states, alters the sensitivity of skeletal muscle

*(continued on page 34)*

(continued from page 29)

to the effects of insulin, and may decrease protein breakdown.<sup>40,41</sup>

Early unblinded studies of fish oil supplementation in cancer patients reported decreased weight loss, preserved lean muscle mass, and improved appetite.<sup>40,42,43</sup> However, larger randomized studies of fish oil supplementation in cancer patients did not report significant advantages compared to placebo.<sup>40-46</sup>

A recent randomized study (n = 45) reported that elderly women who took fish oil supplements had improved response to a strength training program compared to patients taking placebo and undergoing the same training program.<sup>40</sup> Women taking the fish oil supplements without exercising had no significant

difference in strength or functional capacity compared to the placebo group. All of the women had improved strength and functional capacity after the 90 day exercise program, but women taking the fish oil supplement during the exercise program had significantly greater gains in peak strength and functional capacity compared to the placebo group.<sup>40</sup> There is a need for larger and longer duration studies to evaluate the effect of fish oil supplements on body composition and outcomes in hospitalized and rehabilitation patients.

### Glutamine

Serum and intracellular concentrations of glutamine are decreased in critical illness, and provision of parenteral glutamine (PG) was reported to improve

**Table 1. Considerations for the Use of Anabolic Therapies**

#### Arginine

There are no randomized human studies demonstrating improvements in muscle mass or functional outcomes with arginine supplements. Arginine supplementation is worthy of further investigation rather than routine clinical use at this time.

#### Branched Chain Amino Acids and Leucine

Leucine and BCAA supplements do not appear effective for increasing muscle mass without exercise. Leucine supplements should be studied in patients undergoing rehabilitation and actively engaged in physical therapy or resistance exercise programs, especially in patients with marginal intake of high quality proteins.

#### Beta-hydroxy-beta-methylbutyrate (HMB)

A small short term study demonstrated improved nitrogen balance in ICU patient receiving HMB. Long term HMB supplementation in older patients resulted in trivial increases in muscle mass and no functional improvements. There is a need for adequately powered randomized studies to determine if HMB improves outcomes or functional status and whether there are risks, drawbacks or limitations of HMB supplementation for some populations. Current studies are too small and too short to establish the safety of HMB in patients with malignant disease.

#### Fish Oil

There is a need for large, longitudinal studies to evaluate the effect of fish oil supplements on body composition and outcomes in hospitalized and rehabilitation patients.

#### Glutamine

There are no human studies that support a role for glutamine supplements as effective agents to prevent muscle loss or restore muscle mass.

#### Ornithine alpha-ketoglutarate (OKG)

Small, controlled studies demonstrate an improvement in nitrogen balance, muscle mass and some outcomes with OKG supplements. There is sufficient evidence of OKG's action on enhancing nitrogen balance, appetite and weight to support larger properly controlled studies of OKG on patient outcomes.

nitrogen balance in adult patients after surgery or trauma.<sup>47</sup> Supplemental glutamine induces heat shock proteins, which allows cells and tissues to become more stress tolerant in experimental models.<sup>48</sup> Two studies in critically ill patients who received parenteral nutrition (PN) supplemented with PG reportedly had improved 6-month survival, compared to patients who received glutamine-free PN.<sup>49,50</sup> Supplemental PG did not result in any significant difference in short-term mortality (ICU or hospital) in these studies.<sup>49,50</sup> The improvement in long-term mortality without significant changes in short-term mortality could reflect the impact of glutamine on muscle loss or general nutrition status that only resulted in improved outcomes over a longer period of time. Unfortunately, there are no studies that have examined the effect of supplemental glutamine on long-term muscle changes, time to recovery of functional status, or need for rehabilitation after a hospitalization. PG may improve tolerance to the stressed state, but does not appear to affect protein synthesis or muscle breakdown in healthy adults. Svanberg et al demonstrated that there was no change in protein synthesis or breakdown with PG in healthy adults and reported that the provision of glutamine enriched parenteral amino acids appeared to negatively affect uptake of other amino acids into the muscle that are necessary for protein synthesis.<sup>51</sup>

The results of studies with PG supplementation may not apply to glutamine supplementation via the enteral route. Although there is no glutamine in standard PN, glutamine is available as a component of protein in both oral and enteral feedings. Additionally, the cells of the intestinal lumen and liver use enteral glutamine

for fuel, so there is much less glutamine reaching the systemic circulation than is ingested.<sup>52</sup> A randomized blinded study of 363 critically ill patients reported no significant difference in short term or 6 month outcomes with enteral glutamine supplementation compared to an isonitrogenous control group.<sup>53</sup>

Several studies have provided enteral glutamine in combination with HMB and arginine (HMB-ARG-GLUT). There was no significant improvement in lean body mass after gastric bypass with supplemental HMB-ARG-GLUT compared to controls.<sup>54</sup> In a study of patients with rheumatoid cachexia there was no significant improvement in fat-free mass or functional status with supplemental HMB-ARG-GLUT compared to controls.<sup>55</sup> While there may be a benefit of PG supplementation to improve outcomes and nitrogen balance in some ICU populations, there are no adequately powered studies of patient outcomes to support a role for oral glutamine as an agent to maintain, or restore, muscle mass in hospitalized or rehabilitation patients.

Glutamine may be beneficial for mitigating the side effects of a few chemo- and radiation therapy regimens; some experts have theorized that glutamine supplementation may help protect normal cells while sensitizing some tumor cells to the effects of chemotherapy and radiation therapy.<sup>56,57</sup> However, there are no large randomized studies investigating the effects of extended glutamine on oncology outcomes.

One of the few contraindications to glutamine supplementation is end-stage hepatic failure. Patients with decompensated cirrhosis had a significant increase

## Table 2. Strategies to Help Limit Loss of Lean Body Mass

- Decrease the time patients are without nutrition prior to procedures
- Accelerate the transition back to oral/enteral intake post-procedures
- Add D5 to standing IV fluids in patients not receiving nutrition support
- Evaluate the practice of NPO status prior to procedures and consider continuing nutrition (at least nutritional liquids/enteral feeding) until 2 hours before many procedures
- Enlist Early Recovery After Surgery (ERAS) pathway or modifications
- Keep EN going (especially in those jejunally fed) for tests/ procedures that require no, or only a local anesthetic.
- Provide an evening snack (or two) for patients that must be npo after midnight.
- Provide adequate amounts of high-quality protein.
- Evaluate protocols for mobility and physical therapy and collaborate with other disciplines to eliminate barriers for activity.
  - Consider nocturnal cycle of EN and PN when possible to facilitate daytime activity

in serum ammonia (75 to 169  $\mu\text{mol/L}$  cirrhosis vs. 52 to 78  $\mu\text{mol/L}$  control patients), 60 minutes after a single 20g dose of enteral glutamine.<sup>58</sup> Among the patients with cirrhosis, there was a significant increase in the number of patients meeting criteria for hepatic encephalopathy 60 minutes after the dose of enteral glutamine (44 vs. 69%).<sup>58</sup>

### Ornithine alpha-ketoglutarate (OKG)

Ornithine alpha-ketoglutarate (OKG), also known as ornithine oxoglutarate, is the salt of 2 molecules of ornithine linked to one molecule of  $\alpha$ -ketoglutarate. OKG was initially proposed as a possible treatment for hepatic encephalopathy in the 1960's, and marketed under the name Ornicitil.<sup>59</sup> Controlled trials suggested that OKG was not efficacious for resolving hepatic coma, but clinicians noted that patients treated with OKG appeared to have improved nutrition status.<sup>60</sup> OKG was reported to improve nitrogen balance in the 1980's in patients with trauma, after surgery and burn injury.<sup>61-63</sup> OKG causes a transient increase in growth hormone secretion, and supports glutamine levels post injury in humans.<sup>60, 64</sup> Two double-blind randomized studies of adult burn patients demonstrated that 10g of OKG given 2X/day significantly decreased wound healing times and improved nitrogen balance compared to control patients.<sup>65, 66</sup>

Several studies have investigated the effect of OKG supplementation in elderly patients.<sup>67, 68</sup> A double-blind randomized trial of OKG investigated the effects of 10g OKG/day for 2 months (patients monitored for 4 months total) in 185 elderly ambulatory patients.<sup>67</sup> There was a significant improvement in appetite, body weight and independence in the OKG group compared to the placebo group after 30 days, and also after 60 days. Two months after OKG was stopped, there was still a significant improvement in the quality-of-life and medical-cost index in the OKG group, and the investigators reported that there was an overall cost saving of 37% related to OKG use.<sup>67</sup>

A second study randomized 370 non-hospitalized healthy adults that had recently recovered from various illnesses to receive either 10g of OKG/day or an isocaloric placebo.<sup>69</sup> Patients who received OKG had a significant improvement in appetite and weight gain after 60 days compared to the placebo group.<sup>69</sup>

Although there is a long history of use and a number of studies documenting that OKG increases nitrogen balance in various pathologic states, there are some

limitations to existing evidence. A number of early trials did not provide isonitrogenous controls, and there is limited data regarding patient outcomes due to the limited size or duration of the studies.<sup>68</sup> There is evidence in animal models that OKG decreases muscle breakdown without stimulating tumor growth, but minimal human data about the potential risk of OKG use in humans with malignant disease.<sup>70</sup> The use of any agent that has the potential to enhance protein synthesis should raise concern for its potential to function as an accelerant for tumor growth. OKG supplementation increases arginine production, and thus could invoke synthesis of nitric oxide with a potential detrimental effect on septic critically ill patients in a fashion similar to arginine supplemented feeding.<sup>71</sup> There is sufficient evidence of OKG's action on enhancing nitrogen balance and appetite to support larger properly controlled studies of OKG on patient outcomes.

### Nutrition and Feeding Strategies

Although full nutrition does not completely prevent muscle loss in hospitalized patients, it is clear that inadequate nutrition accelerates muscle loss, and prolonged or recurrent periods without nutrition cause large amounts of body protein to be burned for energy.<sup>4, 72</sup> Healthy adults that are deprived of food have an adaptation to starvation within several days, with decreased metabolic rate and protein oxidation and increased utilization of fat for fuel. However, patients with illness or injury experience hypermetabolism and rapid protein breakdown even when starved. Fat cannot be converted directly into glucose, therefore, when glycogen stores are quickly depleted, large amounts of body proteins are catabolized to meet the needs of cells that are dependent on glucose.<sup>4, 73</sup> Many patients arrive at the hospital with a history of weight loss or decreased oral intake, and thus have depleted glycogen stores on admission. Acutely ill hospitalized patients with depleted glycogen stores will have urinary nitrogen losses of 10-15g/24 hrs.<sup>4, 73, 74</sup> Providing as little as 300-400 dextrose calories per 24 hours (75-100mL/hr of 5% dextrose) decreases muscle breakdown in half, as evidenced by a decrease in urinary nitrogen losses to 5-7g/24 hrs.<sup>73</sup> While short periods of time without significant nutrition are not overtly injurious, the cumulative effect of periods of semi-starvation undoubtedly contributes to muscle loss during hospitalization. Decreasing the amount of time

*(continued on page 38)*

(continued from page 36)

that a patient is without food is one of the most concrete, feasible and cost-effective interventions to implement.

### **Cumulative calorie deficit while in the hospital**

Patients that take food by mouth or receive enteral nutrition support (EN) inevitably have repeated interruptions in their nutrition and develop a large cumulative calorie and protein deficit during their hospitalization.<sup>75, 76</sup> A randomized study comparing full feeding with reduced calorie and protein “trophic” feeding in patients with acute respiratory distress syndrome (ARDS) demonstrated that patients receiving reduced feeding during the early part of their admission had significantly increased need for rehabilitation services after their hospitalization.<sup>77</sup> The use of PN to supplement inadequate enteral intake appears to create more problems than it cures however.<sup>78, 79</sup> Supplemental PN provided to those patients with functional GI tracts who were receiving inadequate EN resulted in significantly increased infectious complications, and increased the duration of hospitalization.<sup>78, 79</sup> Although supplemental PN carries excessive risk and expense, there are a number of less invasive strategies that can be used to limit cumulative nutrition deficit during hospitalizations. Oral nutrition supplements significantly decreased weight loss and increased muscle strength in postoperative hospitalized patients and when provided to malnourished patients after hospital discharge significantly increased muscle strength and improved quality of life.<sup>80-82</sup> EN support is frequently held due to outdated practices with poor, or no supporting evidence. Involvement of nutrition support professionals and adoption of evidence-based feeding protocols can increase nutrition delivery to patients that require EN.<sup>1, 76</sup>

It is obvious that some periods without full nutrition for hospitalized patients are unavoidable due to the need to be NPO for tests and procedures. However it is equally obvious that many protocols stipulating no oral/enteral intake prior to a test are based more on convention than necessity. The results of several studies reported that patients may continue to receive nutrition until 2 hours before many procedures without increasing complications.<sup>83-85</sup> Carbohydrate and protein feeding pre-procedure may also decrease postoperative insulin resistance and appears to decrease postoperative muscle loss.<sup>86</sup> Although patients that are unable to protect their airway are at increased risk of reflux if they receive

gastric EN while supine, feedings often do not need to be held for a protracted time period pre-procedure. Furthermore, patients that receive EN into the small intestine can often have nutrition infusion continue until shortly before the test.

Although there is evidence that extended periods without food before many procedures is not necessary, actually changing hospital protocols and practices can be difficult to achieve. There is an extended history to the “NPO after midnight” practice and it is difficult to overcome the tremendous inertia of tradition. Updating outdated protocols to minimize periods of fasting pre-procedure may not be adequate by itself. Education about the potential advantages of reduced preoperative fasting and conducting follow-up quality evaluations to determine if the new protocols are being followed may help increase compliance and eventually decrease the nutrition deficit that patients accrue in the hospital setting.

In addition to decreasing the time that a patient is without nutrition prior to procedures, it is often possible to accelerate the transition back to oral intake post-procedure. There is copious evidence that rapid removal of nasogastric tubes and earlier introduction of food after surgical procedures does not have significant disadvantages, and may have benefits.<sup>87, 88</sup> There is a need for studies that investigate protocols to minimize non-essential downtime of oral and EN support to determine if more consistent nutrition provision can minimize muscle loss during hospitalizations and affect outcomes, functional status, or rehabilitation needs.

### **Protein**

Normally, muscle protein synthesis is transiently increased after ingestion of dietary protein. Ingestion of dietary protein has an enhanced ability to increase muscle protein synthesis in healthy people after exercise. Doses as small as 5g of high quality protein increase the rate of muscle protein synthesis, with maximal effects being reached at 20g in young adults. Elderly patients appear less sensitive to the effect of dietary protein after exercise because muscle protein synthesis was not stimulated in doses lower than 20g, and maximal effects were not reached until 40g of protein were ingested.<sup>11</sup> High quality protein such as whey increases protein synthesis after exercise compared to lower quality proteins.<sup>11</sup>

Unfortunately, immobilization or bedrest (unloading) blunts the ability of protein or amino acids

to stimulate muscle protein synthesis.<sup>72</sup> Protein or amino acid supplements were ineffective in decreasing muscle catabolism in patients that had no physical activity.<sup>72,89</sup> However, amino acid supplementation was effective in reducing muscle mass loss when combined with a minimal amount (5 minutes/day) of physical activity.<sup>90</sup> There is a need for further studies of exercise combined with high quality protein supplements to determine optimal protein dosing and exercise requirements to preserve and restore muscle mass.

## Discussion

The loss of lean muscle mass during hospitalizations very likely contributes to functional impairments, reduced quality of life and increased costs for rehabilitation.<sup>11,91,92</sup> The elderly, who are an expanding segment of our population, are especially susceptible to the negative effects of muscle loss. While there are a number of nutritional supplements that show promise and are worthy of additional research, there is a need for adequately powered studies that investigate meaningful outcomes and cost effectiveness before they are routinely used in clinical practice (see Table 1). OKG is the only anabolic nutraceutical with demonstrated outcome improvements in controlled studies, but there is limited data in acutely or critically ill patients receiving OKG.<sup>67</sup> Some nutraceuticals that increase anabolism may have the potential to accelerate tumor growth and available research does not adequately address potential safety risks. Randomized studies over the past 20 years have repeatedly demonstrated unexpected harmful effects of relatively benign nutrients or nutraceuticals that initially appeared promising in animal or small scale human studies.<sup>14-17</sup> Some critically or acutely ill populations may be at particular risk from enhancing protein synthesis because it is possible that reversing catabolism in the earlier stages of illness may have unexpected negative effects. The use of anabolic steroid oxandrolone in ventilator dependent surgical patients resulted in a significantly longer period of mechanical ventilation and intensive care unit stay, which may be related to increased collagen deposition leading to increased fibrotic pulmonary changes.<sup>93</sup> In two large multicenter randomized studies of surgical and medical critically ill patients, the administration of human growth hormone resulted in a significantly longer ICU and hospital stay, duration of mechanical ventilation and mortality compared to patients that received placebo.<sup>94</sup> There is insufficient evidence to

assume that nutraceuticals with anabolic potential would necessarily share the same risk factors as pharmacologic anabolics in similar populations. However, it would be similarly unreasonable to assume that nutraceuticals with anabolic potential would be safe in critically ill populations without randomized studies that have a sufficient number of patients with the power to examine patient outcomes.

Nutrition strategies may help limit the amount of muscle that is lost (see Table 2), but nutrition alone, even when optimized, cannot prevent muscle loss during inactivity or critical illness.<sup>4</sup> Exercise, particularly resistance exercise, is especially potent for preventing and restoring muscle loss.<sup>91</sup> Optimizing physical activity and implementing resistance exercise programs appears to be considerably more effective for restoring muscle mass than nutritional interventions alone.<sup>11,91</sup> Considering the evidence that some nutrition interventions only demonstrate anabolic potential when administered in concert with resistance exercise,<sup>40</sup> there is a clear need for adequate studies of this kind to fully evaluate the potential of combined therapies. Recent research has demonstrated that even isolated vitamin inadequacy can potentially become a factor that limits the ability to respond to anabolic therapies.<sup>35</sup> There is also the need to explore the potential of combining nutritional and pharmacologic, as well as nutrition, pharmacologic and exercise efforts to counteract muscle loss. Studies of pharmacologic approaches to enhance anabolism have rarely considered nutritional factors as a potential rate limiting step for muscle response. Likewise, studies of nutritional supplementation have not evaluated potential endocrine or metabolic abnormalities that can potentially influence the ability to respond to nutritional interventions.

## Conclusions

There are a number of nutritional supplements that have demonstrated potential as agents to help maintain or recover muscle during and after illness. However, there is a need for larger studies examining patient outcomes and cost effectiveness before routine clinical use can be recommended. Nutritional strategies and protocols that minimize time without nutrition during hospitalizations may reduce muscle loss and can generally be implemented without increasing costs. Optimizing existing efforts to prevent time without nutrition and increase physical activity are concrete

*(continued on page 44)*

(continued from page 39)

steps that can be implemented now to reduce and restore muscle mass until additional research with anabolic nutraceuticals are available. Future nutrition studies should investigate not only short term outcomes such as survival and ICU length of stay, but also include longer term outcomes such as functional status and requirements for rehabilitation as outcomes. Programs that optimize physical activity and combined exercise and nutrition programs should be studied in the future. ■

### References

1. Parrish CR. Enteral feeding: the art and the science. *Nutr Clin Pract*, 2003;18:76-85.
2. Krenitsky J, Makola D, Parrish C. Parenteral Nutrition in Pancreatitis is Passé: But Are We Ready for Gastric Feeding? A Critical Evaluation of the Literature—Part I. *Practical Gastroenterology*, 2007; 92-112.
3. Frankenfield DC, Smith JS, Cooney RN. Accelerated nitrogen loss after traumatic injury is not attenuated by achievement of energy balance. *J Parenter Enteral Nutr*, 1997;21:324-329.
4. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients. The response to glucose infusion and total parenteral nutrition. *Ann Surg*, 1987;205:288-294.
5. Puthuchery Z, Harridge S, Hart N. Skeletal muscle dysfunction in critical care: wasting, weakness, and rehabilitation strategies. *Crit Care Med*, 2010;38: S676-682.
6. Herridge MS, Cheung AM, Tansey CM et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*, 2003;348:683-693.
7. Herridge MS, Tansey CM, Matté A et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*, 2011;364:1293-1304.
8. De Jonghe B, Sharshar T, Lefaucheur JP et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*, 2002;288:2859-2867.
9. Suetta C, Hvid LG, Justesen L et al. Effects of aging on human skeletal muscle after immobilization and retraining. *J Appl Physiol*, 2009;107:1172-1180.
10. Bross R, Javanbakht M, Bhasin S. Anabolic interventions for aging-associated sarcopenia. *J Clin Endocrinol Metab*, 1999;84:3420-3430.
11. Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the ‘anabolic resistance’ of ageing. *Nutr Metab*, 2011;8:68-79.
12. Hvid L, Aagaard P, Justesen L et al. Effects of aging on muscle mechanical function and muscle fiber morphology during short-term immobilization and subsequent retraining. *J Appl Physiol*, 2010;109:1628-1634.
13. Whipple RH, Wolfson LI, Amerman PM. The relationship of knee and ankle weakness to falls in nursing home residents: an isokinetic study. *J Am Geriatr Soc*, 1987;35:13-20.
14. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*, 1994;330:1029-1035.
15. Besselink MG, van Santvoort HC, Buskens E, et al.; Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomized, double-blind, placebo-controlled trial. *Lancet*, 2008;371:651-659.
16. Schulman SP, Becker LC, Kass DA et al. L-arginine therapy in acute myocardial infarction: the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA*, 2006;295:58-64.

17. Lonn E, Bosch J, Yusuf S et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*, 2005;293:1338-1347.
18. Visek WJ. Arginine needs, physiological state and usual diets. A reevaluation. *J Nutr*, 1986;116:36-46.
19. Daly JM, Reynolds J, Thom A et al. Immune and metabolic effects of arginine in the surgical patient. *Ann Surg*, 1988;208:512-523.
20. Kirk SJ, Hurson M, Regan MC, et al. Arginine stimulates wound healing and immune function in elderly human beings. *Surgery*, 1993;114:155-159.
21. Mendez C, Jurkovich GJ, Garcia I, et al. Effects of an immune enhancing diet in critically injured patients. *J Trauma*, 1997;42:933-940.
22. Crozier SJ, Kimball SR, Emmert SW, et al. Oral leucine administration stimulates protein synthesis in rat skeletal muscle. *J Nutr*, 2005;135:376-382.
23. Anthony JC, Anthony TG, Kimball SR, et al. Signaling pathways involved in translational control of protein synthesis in skeletal muscle by leucine. *J Nutr*, 2001;131:856S-860S.
24. Glynn EL, Fry CS, Drummond MJ, et al. Excess leucine intake enhances muscle anabolic signaling but not net protein anabolism in young men and women. *J Nutr*, 2010;140:1970-1976.
25. Leenders M, van Loon LJ. Leucine as a pharmacconutrient to prevent and treat sarcopenia and type 2 diabetes. *Nutr Rev*, 2011;69:675-689.
26. Verhoeven S, Vanschoonbeek K, Verdijk LB, et al. Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men. *Am J Clin Nutr*, 2009;89:1468-1475.
27. Pasiakos SM, McClung HL, McClung JP, et al. Leucine-enriched essential amino acid supplementation during moderate steady state exercise enhances postexercise muscle protein synthesis. *Am J Clin Nutr*, 2011;94:809-818.
28. Hagemüller E, Kollmar HB, Günther HJ, et al. Protein metabolism in human colon carcinomas: in vivo investigations using a modified tracer technique with L-[1-<sup>13</sup>C]leucine. *Cancer Res*, 1995;55:1160-1167.
29. McNurlan MA, Heys SD, Park KG, et al. Tumour and host tissue responses to branched-chain amino acid supplementation of patients with cancer. *Clin Science*, 1994;86:339-345.
30. Van Koeveering M, Nissen S. Oxidation of leucine and alpha-ketoisocaproate to beta-hydroxy-beta-methylbutyrate in vivo. *Am J Physiol*, 1992;262:E27-31.
31. Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-beta-methylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: A review. *Nutr Metab*, 2008;5:1-17.
32. Rowlands DS, Thomson JS. Effects of beta-hydroxy-beta-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: a meta-analysis. *J Strength Cond Res*. 2009 May;23(3):836-46.
33. Kuhls DA, Rathmacher JA, Musngi MD, et al. Beta-hydroxy-beta-methylbutyrate supplementation in critically ill trauma patients. *J Trauma*, 2007;62:125-131.
34. Baier S, Johannsen D, Abumrad N, et al. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. *J Parenter Enteral Nutr*, 2009;33:71-82.
35. Fuller JC Jr, Baier S, Flakoll P, et al. Vitamin D status affects strength gains in older adults supplemented with a combination of β-hydroxy-β-methylbutyrate, arginine, and lysine: a cohort study. *J Parenter Enteral Nutr*, 2011;35:757-762.
36. Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin Nutr*, 2005;24:442-454.
37. Hsieh LC, Chien SL, Huang MS, et al. Anti-inflammatory

- and anticatabolic effects of short-term beta-hydroxy-beta-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit. *Asia Pac J Clin Nutr*, 2006;15:544-550.
38. Clark RH, Feleke G, Din M, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. *J Parenter Enteral Nutr*. 2000;24:133-139.
  39. May PE, Barber A, D'Olimpio JT, et al. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg*, 2002;183:471-479.
  40. Rodacki CL, Rodacki AL, Pereira G, et al. Fish-oil supplementation enhances the effects of strength training in elderly women. *Am J Clin Nutr*, 2012;95:428-436.
  41. Murphy RA, Yeung E, Mazurak VC, et al. Influence of eicosapentaenoic acid supplementation on lean body mass in cancer cachexia. *Br J Cancer*, 2011;105:1469-473.
  42. Wigmore SJ, Fearon KC, Maingay JP, et al. Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. *Clin Science*, 1997;92:215-221.
  43. Wigmore SJ, Barber MD, Ross JA, et al. Effect of oral eicosapentaenoic acid on weight loss in patients with pancreatic cancer. *Nutr Cancer*, 2000;36: 177-184
  44. Fearon KC, Barber MD, Moses AG, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *J Clin Oncol*, 2006;24:3401-407.
  45. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut*, 2003;52:1479-1486.
  46. Jatoi A, Rowland K, Loprinzi CL, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol*, 2004;22:2469-2476.
  47. Wilmore DW. The effect of glutamine supplementation in patients following elective surgery and accidental injury. *J Nutr*, 2001;131:2543S-25949S.
  48. Peng ZY, Hamiel CR, Banerjee A, et al. Glutamine attenuation of cell death and inducible nitric oxide synthase expression following inflammatory cytokine-induced injury is dependent on heat shock factor-1 expression. *J Parenter Enteral Nutr*, 2006;30:400-406.
  49. Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med*, 2002;30:2032-2037.
  50. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition*, 1997;13:295-302.
  51. Svanberg E, Möller-Loswick AC, Matthews DE, et al. The effect of glutamine on protein balance and amino acid flux across arm and leg tissues in healthy volunteers. *Clin Physiol*, 2001;21:478-489.
  52. Wernerman J. Glutamine supplementation. *Ann Intensive Care*. 2011;18:1:25-30.
  53. Hall JC, Dobb G, Hall J, et al. A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med*, 2003;29:1710-1716.
  54. Clements RH, Saraf N, Kakade M, et al. Nutritional effect of oral supplement enriched in beta-hydroxy-beta-methylbutyrate, glutamine and arginine on resting metabolic rate after laparoscopic gastric bypass. *Surg Endosc*, 2011;25:1376-1382.
  55. Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin Nutr*, 2005;24:442-454.
  56. Kuhn KS, Muscaritoli M, Wischmeyer P, et al. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. *Eur J Nutr*, 2010;49:197-210.
  57. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev*, 2003;29:501-513.
  58. Ditisheim S, Giostra E, Burkhard PR, et al. A capillary blood ammonia bedside test following glutamine load to improve the diagnosis of hepatic encephalopathy in cirrhosis. *BMC Gastroenterol*, 2011;11:134-141.
  59. Chainuvati T, Plengvanit U, Viranuvatti V. Ornicetil on encephalopathy. Effect of ornithine (ornithine alpha-ketoglutarate) on encephalopathy in patients with acute and chronic liver disease. *Acta Hepatogastroenterol*, 1977;24:434-439.
  60. Blonde-Cynober F, Aussel C, Cynober L. Use of ornithine alpha-ketoglutarate in clinical nutrition of elderly patients. *Nutrition*, 2003;19:73-75.
  61. Leander U, Vesterberg K, FURst P, Vinnars E, Johnsson C. Nitrogen sparing effect of Ornicetil in trauma. Presented at the 4th Congress of European Society of Parenteral and Enteral Nutrition, Vienna, Austria, September 26-29, 1982.
  62. Leander U, FURst P, Vesterberg K, et al. Nitrogen sparing effect of Ornicetil in the immediate postoperative state clinical biochemistry and nitrogen balance. *Clin Nutr*, 1985;4:43-51.
  63. Cynober L, Saizy R, Nguyen Dinh F, et al. Effect of enterally administered ornithine alpha-ketoglutarate on plasma and urinary amino acid levels after burn injury. *J Trauma*, 1984;24:590-596.
  64. De Bandt JP, Cynober L. Therapeutic use of branched-chain amino acids in burn, trauma, and sepsis. *J Nutr*, 2006;136:308S-13S.
  65. Donati L, Ziegler F, Pongelli G, Signorini MS. Nutritional and clinical efficacy of ornithine alpha-ketoglutarate in severe burn patients. *Clin Nutr*, 1999;18:307-311.
  66. Coudray-Lucas C, Le Bever H, Cynober L, et al. Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med*, 2000;28:1772-1776.
  67. Brocker P, Vellas B, Albarede JL, Poynard T. A two-centre, randomized, double-blind trial of ornithine oxoglutarate in 194 elderly, ambulatory, convalescent subjects. *Age Ageing*. 1994 Jul;23(4):303-6.
  68. Walrand S. Ornithine alpha-ketoglutarate: could it be a new therapeutic option for sarcopenia? *J Nutr Health Aging*, 2010;14:570-577.
  69. Deby G, Poyard T. Value of ornithine alpha-ketoglutarate for nutritional support in convalescent, malnourished elderly subjects. *Facts Res Gerontol*, 1995;9:1.
  70. Le Bricon T, Cynober L, Baracos VE. Ornithine alpha-ketoglutarate limits muscle protein breakdown without stimulating tumor growth in rats bearing Yoshida ascites hepatoma. *Metabolism*, 1994;43:899-905.
  71. Cynober L. Ornithine alpha-ketoglutarate as a potent precursor of arginine and nitric oxide: a new job for an old friend. *J Nutr*, 2004;134:2858S-2862S.
  72. Biolo G, Ciocchi B, Stulle M, et al. Calorie restriction accelerates the catabolism of lean body mass during 2 wk of bed rest. *Am J Clin Nutr*, 2007;86:366-372.
  73. Wolfe BM, Culebras JM, Sim AJ, et al. Substrate interaction in intravenous feeding: comparative effects of carbohydrate and fat on amino acid utilization in fasting man. *Ann Surg*, 1977;186:518-540
  74. Wernerman J, von der Decken A, Vinnars E. Protein synthesis in skeletal muscle in relation to nitrogen balance after abdominal surgery: the effect of total parenteral nutrition. *J Parenter Enteral Nutr*, 1986;10:578-582.
  75. Hise ME, Halterman K, Gajewski BJ, et al. Feeding practices of severely ill intensive care unit patients: an evaluation of energy sources and clinical outcomes. *J Am Diet Assoc*,

- 2007;107:458-465.
76. Soguel L, Revelly JP, Schaller MD, et al. Energy deficit and length of hospital stay can be reduced by a two-step quality improvement of nutrition therapy: The intensive care unit dietitian can make the difference. *Crit Care Med*, 2011; 15.
  77. Rice TW, Mogan S, Hays MA, et al. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med*, 2011;39:1-398.
  78. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*, 2011;37:601-609.
  79. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*, 2011;11;365:506-517.
  80. Rana SK, Bray J, Menzies-Gow N, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*, 1992;11:337-344.
  81. Price R, Daly F, Pennington CR, McMurdo ME. Nutritional supplementation of very old people at hospital discharge increases muscle strength: a randomised controlled trial. *Gerontology*, 2005;51:179-85.
  82. Norman K, Kirchner H, Freudenreich M, et al. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease--a randomized controlled trial. *Clin Nutr*; 2008;27:48-56.
  83. de Aguilar-Nascimento JE, Dock-Nascimento DB. Reducing preoperative fasting time: A trend based on evidence. *World J Gastrointest Surg*. 2010 Mar 27;2(3):57-60.
  84. Kaska M, Grosmanová T, Havel E, et al. The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery--a randomized controlled trial. *Wien Klin Wochenschr*. 2010 Jan;122(1-2):23-30.
  85. Power S, Kavanagh DO, McConnell G, et al. Reducing preoperative fasting in elective adult surgical patients: a case-control study. *Ir J Med Sci*. 2012 Mar;181(1):99-104.
  86. Perrone F, da-Silva-Filho AC, Adorno IF, et al. Effects of preoperative feeding with a whey protein plus carbohydrate drink on the acute phase response and insulin resistance. A randomized trial. *Nutr J*, 2011;10:66.
  87. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. *J Parenter Enteral Nutr*, 2011;35:473-487.
  88. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. *Cochrane Database Syst Rev*, 2006;(4):CD004080.
  89. Brooks NE, Cadena SM, Vannier E, et al. Effects of resistance exercise combined with essential amino acid supplementation and energy deficit on markers of skeletal muscle atrophy and regeneration during bed rest and active recovery. *Muscle Nerve*, 2010;42:927-935.
  90. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab*, 2004;8:4351-4358.
  91. Glover EL, Phillips SM. Resistance exercise and appropriate nutrition to counteract muscle wasting and promote muscle hypertrophy. *Curr Opin Clin Nutr Metab Care*, 2010;13(6):630-4.
  92. Rennie MJ. Anabolic resistance in critically ill patients. *Crit Care Med*, 2009;37(10 Suppl):S398-S399.
  93. Bulger EM, Jurkovich GJ, Farver CL, et al. Oxandrolone does not improve outcome of ventilator dependent surgical patients. *Ann Surg*. 2004, 240:472-478.
  94. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*, 1999;341:785-792.

# PRACTICAL GASTROENTEROLOGY

## REPRINTS

Special rates are available for quantities of 100 or more.

For further details email us at:  
[practicalgastro1@aol.com](mailto:practicalgastro1@aol.com)

*Celebrating  
 Over 3 Decades  
 of Service*