Message to Surgeons: The Expected Norm in Elective Complex GI Cancer Surgery is Use of Perioperative Immunonutritional Therapy that also Saves Hospital Costs!

Michael M. Meguid, MD, PhD, FACS, and Carolina G. Goncalves, MD†*

A curious headline of a column in the January 2, 2007 issue of USA Today read: *"Omega-3 pours into cereal, orange juice, eggs, and pet food."* It stated that 'Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish, some nuts, and oils were the hottest food additive in 2007, because of their health and immuno-modulating effects in reducing inflammation, and thus thought to prevent heart disease, cancer, and arthritis. So, if our dogs are getting 'Omega-3 fatty acids' in their food, why not give it to our upper GI cancer patients, the majority of who suffer from debilitating cancer cachexia-anorexia syndrome and are at high risk of operative complications?

Thus we read with enthusiasm in this issue of *Annals,* the paper by Ryan et al of a well designed controlled clinical study in patients undergoing esophagectomy to examine the effects of perioperative EPA-enriched enteral nutrition therapy on the nutritional, metabolic, and immuno-inflammatory response and on postoperative complications.[1] The enthusiasm emanates, in part, from the success of demonstrating EPA's anticatabolic properties. This achievement reflects the culmination of a long and tortuous journey of nutritional support in cachectic cancer patients in an attempt to decrease their perioperative morbidity.

Warren in 1932 documented that cancer cachexia was a common cause of death in patients with cancer.[2] Studley in 1936 made the crucial observation in his gastrectomized patients, that the greater the preoperative weight loss in his patients, the higher the complication and mortality rate.[3] This seminal observation clearly linked nutritional status to postoperative outcome. Patients with upper gastrointestinal (GI) tumors have among the highest incidence of malnutrition, which correlates positively with high postoperative complication rates.[4] These complications are similar to those described by Studley 70 years ago: wound dehiscence, ileus, sepsis, pneumonia, prolonged hospital stays, poor quality of life and death.

In the intervening years, numerous studies examined the effects of both pre- and postoperative nutrition therapy, either parenteral or enteral, to decrease surgery related complications. Initially, these studies focused on providing supraphysiological concentrations of different substrates to induce positive nitrogen balance postoperatively. In many of these studies, the observed reversal of weight loss was due to an increase in fat mass and in total body water (TBW). Our concepts in clinical nutrition evolved to include the understanding that specific nutrients had immunologic effects, particularly when given in pharmacological amounts. Thus began the 'trial and error era' of immunonutrition, not only in cancer patients and high risk elective surgical patients, but also in critically ill postoperative patients. The 'immunonutritional mixtures' that were added to conventional substrates known to improve metabolic processes included arginine, glutamine, nucleotides, antioxidants, and omega-3 fatty acids, often in different permutations. It required meta-analysis of many studies to conclude that immunonutrition improved clinical outcomes.[5] In retrospect, it may seem curious that for almost 20 years, studies were done in which different experimental compounds were administered simultaneously in an effort to determine the nebulous postoperative beneficial metabolic effects. But such was our knowledge base and the sense of frustration and urgency of the times, underpinning the need to address the ongoing critical issues as to which 'immune compounds' and to what amounts were needed to reverse the processes of cancer cachexia.

The importance of Ryan et al's study is its simplicity in examining the effects of one compound, EPA, in an 'exemplar model of complex major surgery' that often includes patients who also require neoadjuvant combined chemo- and radiotherapy.[1] This is an ideal model for testing the stated primary end-point of exploring the anticatabolic effect of EPA by preserving lean body mass (LBM). The protocol is user friendly, and when applied to our patients, in consultation with a

From the *Professor of Surgery, Physiology and Neuroscience, Surgical Metabolism and Nutrition Laboratory, Department of Surgery, University Hospital, SUNY, Upstate Medical University, Syracuse, New York; and †Assistant Professor Surgery, Department of Surgery, Positivo University, Curitiba, PR, Brazil.
Corresponding Author: Michael M. Meguid, MD, PhD, FACS, Surgical Metabolism and Nutrition Laboratory, Department of Surgery, University Hospital, SUNY, Upstate Medical University, Syracuse, NY 13210. E-mail: meguidm@upstate.edu.

ISSN: 0003-4932/09/24903-0364
DOI: 10.1097/SLA.0b013e31819ab8ba

dietitian, is easily applicable in our current clinical practice climate: 1. Drink 200 mL of an oral supplement enriched with EPA (2.2 g EPA/d) twice daily for 5 days before surgery. 2. Place a jejunostomy tube intraoperatively and 3. On postoperative day one, start the EPA enriched enteral nutrition therapy and advance the feed volume, as tolerated, over the next 2–3 days, to reach a goal of approximately 30 kcals/kg/d and 1.2 g protein/kg/d. Ryan et al's practice called for switching from jejunostomy administration to oral supplementation after 14 days. Using this protocol, the patients obtained 96% of their daily calorie and protein goal. Measuring segmental (legs, arms, and trunk) bioelectrical impedance analysis, the EPA supplemented enteral nutrition therapy group maintained all aspects of body composition postoperatively, whereas patients with standard enteral nutrition therapy lost significant amounts of fat-free mass.

Current evidence based medicine[6] indicates that the primary action of EPA is to increase LBM by a mechanism that attenuates inflammatory cytokine-driven expression and activity of the ATP-dependent ubiquitin-proteasome pathway, which is the primary pathway responsible for skeletal muscle atrophy in cancer cachexia. Consequently, a significant increase in LBM occurs, with no significant change in either fat mass or percent TBW, leading to improved postoperative physical activity with improved quality of life. Such benefits have been achieved using omega-3 fatty acids at a dose between 0.1 and 0.23 g/kg/d, and yielded lesser need for antibiotics and shorter ICU and hospital stays. The administration of omega-3 fatty acids results in its integration into cell membranes of normal and tumor tissue, maintaining the balance of pro- and anti-inflammatory cytokines with diminished infection rates and the attenuation of inflammatory associated skeletal muscle catabolism with its attendant sequelae of multisystem organ failure.[7–9]

In summary, the paper presented by Ryan et al[1] is a significant step forward because it underscores the message to surgeons of the importance of using immuno-nutrition as an adjunct therapy started at least 5 days before elective GI cancer operation, a therapy which is also vital to treat critically ill patients, as demanded by current evidence based medicine.[6] It should no longer be a surgeon's preference, but the standard of expected norm for the practice of elective complex GI cancer surgery.

Would such an explicit directive to use perioperative immunonutritional therapy in the practice of cutting edge surgery in complex GI cancer operations meet resistance by cost-conscious hospital administrators in the current cost cutting climate? Braga et al[10] have shown that elective GI cancer patients, randomized to perioperative nutritional therapy supplemented with omega-3 fatty acids compared with conventional therapy (no supplementation) had fewer postoperative complications. The greatest amounts of resources consumed, in rank order, were: anastomotic leaks, intraabdominal abscesses, and pancreatic fistulae. The mean costs per complication were approximately $9,200 in immunonutrition therapy versus approximately $12,200 in the conventional therapy group. Whereas the effectiveness values were approximately 63% and 50% between supplemented versus conventional groups, the total costs consumed was 78% and 95% of diagnosis-related group reimbursement rate, respectively.

These data should be welcome music to the ears of hospital administrators, showing that the failure to institute immunonutrition leads to a larger consumption of the diagnosis-related group reimbursement rate. Particularly in these challenging fiscal times, hospital administrators should facilitate the purchase of and encourage the routine use of immunonutrition as the accepted standard of surgical practice, not only because in 2009 it reflects the expected norm of surgical practice, but because it also reflects cost-effective treatment.

Finally, the relevance of this paper is even greater given the progress made since 'the days of yore,' when nutritional therapy was often considered as an after-thought and, that too, for only some patients at a time when the cost of nutrition therapy was truly exorbitant.

REFERENCES

1. Ryan A, Reynolds JV, Healey L, Byrne M, Moore J, Brannelly N, McHugh A, McCormack D, Flood P. Enteral Nutrition Enriched with Eicosapentaenoic Acid (EPA) Preserves Lean Body Mass Following Esophageal Cancer Surgery: Results of a Double-Blinded Randomized Controlled Trial. *Annals of Surgery.* 2009;249:355–363.
2. Warren S. The Immediate Causes of Death in Cancer. *Am J Med Sci*. 1932;184:610.
3. Studley HO. Percentage of Weight Loss as a Predictor of Surgical Risk. *JAMA* 1936;106(6):458–460.
4. Meguid MM, Debonis D, Meguid V, Hill LR, Terz JJ. Complications of Abdominal Operations for Malignant Disease. *Am J Surg*. 1988;156:341–345.
5. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should Immunonutrition Become Routine in Critically Ill Patients? *JAMA*. 2001;286: 944–953.
6. ESPEN Guidelines on Enteral Nutrition: Surgery Including Organ Transplantation. 2006. www.espen.org.
7. Tisdale MI. Inhibition of Lipolysis and Muscle Protein Degradation by EPA in Cancer Cachexia. *Nutrition*. 1996;12:S31–S33.
8. Fearon KCH, Von Meyenfeldt MF, Moss AG, et al. Effect of Protein and Energy Dense N-3 Fatty Acid Enriched Oral Supplements on Loss of Weight and Lean Tissue in Cancer Cachexia: A Randomized Double Blind Trial. *Gut*. 2003;52:1479–1486.
9. Heller AR, Rosseler AR, Litz RJ, et al. Omega-3 Fatty Acids Improve the Diagnostic-Related Clinical Outcome. *Crit Care Med*. 2006;34:972–979.
10. Braga M, Gianotti l, Vignali A, Schmid A, Nespoli L, DiCarlo V. Hospital Resources Consumed for Surgical Morbidity: Effect of Preoperative Argenine and ω-3 Fatty Acid Supplementation on Cost. *Nutrition.* 2005; 21:1078–1086.