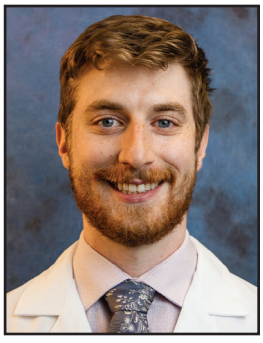
Carol Rees Parrish, MS, RDN, Series Editor

Enhanced Recovery After Surgery (ERAS) and Immunonutrition: An Evidence-Based Approach



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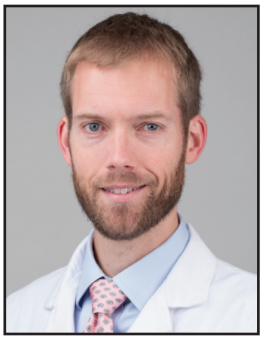

Robert Thiele

Nutrition is increasingly understood to play an essential role in optimization of perioperative outcomes. Pre-surgical nutritional status has a profound impact on perioperative outcomes and in the critically ill patient population, early adequate enteral nutrition has a clear positive impact on outcomes including mortality. Not surprisingly, nutritional optimization is a focus of many "Enhanced Recovery After Surgery" (ERAS) protocols. Additionally, manufacturers have developed "disease-specific" nutritional formulations designed for individual patient populations (e.g. acute respiratory distress syndrome). One such disease-specific category includes "immunonutrition" (IMN) formulations, most of which include arginine and are designed to enhance immune function in patients exposed to an immunological threat (e.g. undergoing surgery). While there are some theoretical benefits of IMN, a lack of credible, prospective data in the perioperative patient population suggest it would be premature to recommend their use in surgical patients, either within or outside of the context of an ERAS protocol. Furthermore, their safety in critically ill patients has recently been questioned, making it even harder to justify the routine use of these costly agents given the lack of data to support them.

INTRODUCTION

Perioperative management has experienced a sea change over the last two decades with the arrival and implementation of Enhanced Recovery After Surgery (ERAS) protocols. ERAS is a conceptual framework grounded on the application of evidence-based principles to improve outcomes in surgical patients. While ERAS was originally developed for patients undergoing colorectal surgery,[1] it has since expanded to a variety of other surgical subspecialties including thoracic surgery.[2] A key feature of ERAS is the development of standardized protocols based on best available evidence. Originally, ERAS for colorectal surgery focused on achievement of adequate pain control without excessive use of opioids, rational fluid management (either goal-directed or "restrictive"), early ambulation and feeding.[1] Not all early ERAS (or "fast track") protocols addressed fluid management.[3] However, around the time of ERAS

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development, the benefits of restrictive[4] or goal-directed[5] fluid management strategies became clear, and later, all protocols[6,7] addressed this important component of enhanced recovery. Many of these interventions were tried "all at once" and it was impossible to tease out the relative contribution of each to the observed improvement in outcomes, which included reductions in length of stay and surgical complications.[1]

With the advent and success of ERAS, interest has grown in understanding which components have the greatest impact, as well as whether other areas of the perioperative experience are being overlooked (e.g. the potential for pre-habilitation). Perioperative nutritional state is of particular interest for several reasons:

- First, all of the core concepts of ERAS (opioid minimization [less ileus], rational fluid administration [less bowel edema], ambulation [accelerated GI recovery], and early oral intake), either directly or indirectly impact nutrition
- Second, preoperative nutritional status is a powerful predictor of a variety of surgical complications;[8,9] and,
- Third, an enormous body of data from the ICU literature suggests that critically ill patients survive longer when they receive early, adequate nutrition.[10]

While there are distinct differences between surgical and critically ill patients, there is also extensive overlap in these patient populations that cannot be ignored. The recent development of "disease specific" nutrition formulations (e.g. omega-3 enhanced diets for acute respiratory distress syndrome[11]) is a testament to the crucial role played by nutrition in patients who are critically ill, undergoing surgery (or both). One of the more intriguing disease-specific dietary strategies is immune modification (referred to as immunonutrition [IMN]).

From the perspective of the patient as well as the clinician, increased certainty regarding the risks and benefits of a surgical procedure is desirable. The nutritional screening strategies described below are inexpensive to perform and can help risk-stratify surgical patients. However, whether and how nutritional status can be normalized in a short time period, whether or not this leads to improved outcomes, and how much this intervention costs are less clear.

In 2018, the American Society of Enhanced Recovery (ASER) released guidelines on nutrition as a component of ERAS.[12] This review will discuss those guidelines as well as additional evidence that has been subsequently published. The primary purpose of this manuscript is to discuss evidence supporting the use of IMN in ERAS protocols, however it is not possible to discuss IMN in isolation, thus other nutritional concepts (e.g. screening) will be covered as well.

Previously Published Guidelines

Current recommendations for perioperative nutrition come from three sources: the ESPEN Clinical nutrition in surgery guideline,[13] the American College of Surgeons (ACS) Strong For Surgery campaign[14] and the 2018 ASER perioperative nutrition guidelines.[12] The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines are the most comprehensive (37 recommendations) and focus on ERAS patients undergoing cancer surgery. The ESPEN guidelines include recommendations for nutritional screening, attention to perioperative nutrition, and use of IMN in malnourished patients undergoing major cancer surgery. The Strong for Surgery (S4S) campaign is a multifaceted perioperative optimization platform, of which nutrition is but one component.[14] S4S includes three nutritional components - a clinical screening questionnaire (and registered dietitian referral if positive), preoperative albumin screening in all patients undergoing inpatient procedures, and use of IMN supplements in any patient undergoing complex surgical procedures. The 2018 ASER recommendations are similar to the S4S guidelines (with several important differences) and are also more prescriptive (Table 1).

Actionable recommendations proposed by ASER include[12]:

1. Nutritional screening with a clinical questionnaire (and serum albumin if triggered by the questionnaire).

2. Dietitian referral with a positive screen.
3. Lean body mass evaluation by CT if available.
4. Oral nutritional supplements (ONS) for "at risk" patients (either high in protein or IMN).
5. Placement of a home feeding tube for "at risk" patients in whom ONS is not possible.
6. Parenteral nutrition for when enteric nutrition is not possible in "at risk" patients.
7. Consideration of IMN in any patient undergoing elective major abdominal surgery.

The use of albumin was discussed in all three sets of guidelines. Albumin, which is clearly correlated to surgical outcomes,[3] has been used to quickly and inexpensively measure nutritional risk, but has unfortunately been misconstrued as a universal marker of malnutrition. Albumin is a negative acute phase reactant and in isolation is not a sensitive or specific marker for malnutrition.[15-17] The utility of albumin as a modifiable risk factor has not been thoroughly explored and deserves further research.

The guidelines differ somewhat on their recommendations related to administration of nutrition before surgery. ESPEN writes that "*Patients with severe nutritional risk shall receive nutritional therapy prior to major surgery*" and that "*Peri- or at least postoperative administration of specific formula enriched with immunonutrients (arginine, omega-3-fatty acids, ribonucleotides) should be given in malnourished patients undergoing major cancer surgery*." However, they also acknowledge that "*There is currently no clear evidence for the use of these formulae enriched with immunonutrients vs. standard oral nutritional supplements exclusively in the preoperative period*".[13] S4S suggests that any patient undergoing complex surgery receive supplementary IMN for a week preoperatively, and supports this assertion with a compendium of studies available on their website. The ASER Guidelines, in contrast, recommend some type of high protein oral nutrition before major surgery and that IMN be *considered*, but noted in the online supplementary data file that "*The role of IMN was an area of great controversy in our discussions. Without question, additional definitive clinical trials comparing IMN to high protein ONS in the preoperative setting and pre-op IMN alone versus pre- and post-op IMN versus post-op IMN alone are needed. Further, additional trials of IMN within ERAS pathways are needed. Ultimately, a definitive, adequately-powered, randomized, multi-center trial of IMN is needed to finally define the previously observed benefits of perioperative IMN in many smaller trials*".[12]

Table 1. Key Features of the ESPEN, ACS, and ASER Perioperative Nutrition Guidelines

Clinical Question	ESPEN	ACS	ASER
Clinical Screen (CS)?	Yes	Yes	Yes
RD Consultation	n/a	If CS (+)	If CS (+)
Albumin Screen?	n/a	If inpatient surgery	if CS (+)
Oral Nutritional Supplements	Any patient with severe nutritional risk or if the following are anticipated: no intake for 5 days, or low intake for 7 days	All patients undergoing complex surgery	All patients screened as being high risk before major surgery
Immunonutrition	Malnourished patients undergoing major cancer surgery	All patients undergoing complex surgery	Considered for all patients undergoing elective major abdominal surgery

The recommendation to prioritize protein intake over consumption of calories in the pre-operative period is based on solid experimental evidence showing that the addition of protein to a diet can have an anabolic effect,[18] as does consumption of food sources that cist primarily of protein.[19] There is at least one prospective randomized controlled trial in critically ill surgical patients demonstrating that a hyperproteineic, hypocaloric diet leads to improved sequential organ failure assessment (SOFA) scores despite receiving similar amounts of calories prior to surgery.[20]

The recommendation to consider IMN was based on a shakier foundation. The ESPEN guidelines cite 15 meta-analyses published between 1992 to 2012 and note that "*the methodological analysis of these meta-analyses and the included RCTs raise reservations to give a strong recommendation for the general use of immunomodulating formulae*." As the ASER manuscript notes, perioperative IMN was recently supported by a Cochrane Systematic Review published in 2012 (6 trials, 549 participants), which compared IMN to either no nutritional support or standard support and concluded "*Seven trials evaluating IMN nutrition were included in the review, of which 6 were combined in a meta-analysis. These studies showed a low to moderate level of heterogeneity and significantly reduced total post-operative complications (risk ratio [RR] 0.67)*.[21]" However, a more recent meta-analysis published in 2014 (7 trials, 404 participants), also included in the ASER manuscript, compared IMN to ONS and concluded that "*When compared to ONS, preoperative IMN was not associated with reduced wound infection (OR 0.97, 95% CI 0.45 to 2.11), all infectious complications (OR 0.71, 95% CI 0.30 to 1.68), non-infectious complications (OR 1.25, 95% CI 0.64 to 2.43), or LOS (mean difference 0.07 days, 95% CI -2.29 to 2.43)*".[22] A key difference between these two more recent meta-analyses is that the Cochrane Review included trials in which IMN was compared to no nutritional support, whereas the 2014 meta-analysis only included trials comparing one nutrition intervention against another.

Update on the Evidence

Significant work has been completed and published in the literature since publication of the S4S and ASER guidelines in 2018. Though the effects of nutrition protocols have been of interest throughout the medical community, particular attention to the role of nutrition in improved outcomes has been focused within surgical and critical care populations. In 2018, two Cochrane Reviews of IMN trials were published describing recent work in the head and neck cancer population (high risk for decreased nutritional intake)[23] and the acute respiratory distress syndrome (ARDS) critical care populations,[24] respectively. The head and neck cancer (19 trials, 1099 participants) review found no evidence for differences in LOS, postoperative infection, mortality, or adverse events between patients receiving IMN and standard nutrition.[23] There was some weak evidence that patients receiving IMN were less likely to develop postoperative fistulae. The review of the effects of IMN in adults with ARDS (10 trials, 1015 participants) concluded that there were no differences in all-cause mortality between IMN and those patients receiving standard nutrition.[24] Additionally, the effect of IMN with omega-3 fatty acids and antioxidants on LOS and number of ventilator days was inconclusive. Both reviews noted that the quality of evidence ranged from low to very low due to small sample sizes, wide confidence intervals, high risk of bias, and clinical and methodological heterogeneity. Neither review quantified adherence or compliance.

In addition to the Cochrane Reviews described above, the authors of this update conducted a search of the available literature (PubMed) for randomized control trials of IMN in the surgical and critical care populations between 2016 and 2020, identifying 23 additional prospective RCTs, only 12 of which studied IMN in the surgical or critical care populations. The results of these studies are summarized below in Table 2. Greater than half of the studied populations were oncological populations, including colorectal, hepatopancreaticobiliary, gastric, esophageal, urological, and head and neck cancer patients. Other studies included total knee arthroplasty, traumatic brain injury, surgical ICU, neurocritical care, elective craniotomy, pelvic exenteration, and ICU patients. With one exception, the included studies were small, with 12 of the 23 studies reporting less than 100 total participants and multiple studies reporting intervention and control groups of less

Table 2. Recent Randomized, Controlled Trials Studying Immunonutrition (2016-Present)

Authors	Patient Population	N (Intervention vs. Control)	Intervention	Results
Mudge et al. 2018	Esophageal cancer undergoing esophagectomy	276	2x2 Randomization Preop: IMN vs. SN Postop: IMN vs. SN	No significant differences in infectious, clinical, or QoL outcomes
Thornblade et al. 2017	Adults undergoing elective colorectal surgery	3375	Non-randomized Preop: Arginine-enriched nutrition vs. SN	No significant differences in serious adverse events after propensity score matching. IMN group had increased LOS
Hogan et al. 2019	Pelvic Exenteration	108 (52 vs. 56)	Preop: IMN TID for 5 days vs. 3 SN for 5 days	No significant difference in LOS or postop complications
Lewis et al 2018	Veterans receiving elective GI oncologic surgery	108 (54 vs. 54)	Preop: IMN TID for 5 days preop vs. SN TID for 5 days	Significantly increased rate of complications in SN group.
Hamilton-Reeves et al. 2016	Bladder cancer patients undergoing radical cystectomy	29 (14 vs. 15)	Enteral IMN vs. SN; 3 cartons of supplement 5 days preop and 5 days postop	Significantly increased Th1 response, arginine, and decreased IL-6 in IMN group vs. control. No significant difference in appendicular muscle loss.
Seguin et al. 2016	Hepatic resection for liver cancer	35 (18 vs. 17)	10-day preop supplementation with Nestle Oral Impact (R) vs. Placebo	No significant differences in liver function recovery, immune response, number of infections, or tolerance
Gade et al. 2016	Elective surgery for pancreatic cancer	35 (19 vs. 16)	7 days preop oral supplementation with Nestle Oral Impact (R) vs. Habitual diet.	No significant differences in postop complications, LOS, functional capacity, or bodyweight.
Rai et al. 2017	TBI patient admitted to ICU	36 (18 vs. 18)	IMN enteral formula (enriched with arginine, glutamine, and omega-3 fatty acids) vs. SN	Significant decrease in IL-6 at day 5 and significant increase in glutathione at day 5.
Uno et al. 2016	Major hepatobiliary resection	40 (20 vs. 20)	EPA, arginine, nucleotide enriched oral supplement vs. No artificial supplement	Significant decrease in postop infections. Significantly decreased serum IL-6.
Kanekiyo et al. 2018	Thoracic esophageal carcinoma undergoing esophagectomy	40 (20 vs. 20)	IMN enteral nutrition vs. SN enteral nutrition	Significantly decreased postop infections and changes in postop antibiotics in IMN group. No differences in ICU or hospital LOS. Significantly increased retinol-binding protein in IMN group.
Martin 2nd et al. 2017	Patients receiving irreversible electroporation surgery for locally advanced pancreatic cancer	71 (44 vs. 27)	Supplemental preop IMN vs. SN	Significant decreases in postoperative complications, LOS, postop nutritional risk index, and albumin levels.
Klek et al. 2017	Adults undergoing surgery for gastric cancer	99 (45 vs. 54)	IMN (arginine, glutamine, omega-3 fatty acids) vs. SN	No difference in survival time. Significantly decreased 3-month mortality in IMN group.

IMN = Immunonutrition; SN = standard nutrition

than 20 participants each. Intervention and control nutrition protocols differed widely across the studies, as did reported primary and secondary outcomes. Conclusions on significant effects of IMN on mortality, LOS, postoperative infections, and complications were mixed. Additionally, reported results were of varying quality with levels of significance and confidence intervals inconsistently reported.

Limitations of the Literature

Though interest in perioperative nutrition (and IMN in particular), has grown exponentially, the current literature remains fractured and limited. Much of the early work in IMN has occurred within the various critical care populations. While critically ill patients differ from those presenting for elective surgery, it is reasonable to at least draw some inferences from the critical care literature given the size and quality of critical care trials focused on nutrition as well as similarities between populations. A recent, larger trial of early versus late parenteral nutrition in critically ill populations unable to achieve caloric goals by the enteric route demonstrated an increased complication rate in the early parenteral nutrition group.[25] On the other hand, a more recent study of critically ill patients able to tolerate enteral nutrition, but randomized to enteral vs. parenteral nutrition showed no difference between the two routes.[26] Whether or not these studies can be generalized to elective surgical procedures is not known. IMN may yet prove beneficial to both or either populations, but extrapolation of results across differing populations may not prove efficacy in improved outcomes.

Drover et al.'s 2011 systematic review of arginine-supplemented diets highlights the difficulties associated with analysis of the IMN data. Many of the studies included in this analysis were small (e.g. 20 subjects per group), and not all were blinded.[27] Many of the studies included in these analyses were funded by commercial entities that produce the products in question,[28-33] received some other form of industry support,[34] or failed to report who funded the study.[35] Some of the authors of these systematic reviews have, appropriately, disclosed the receipt of industry-sponsored research grants, honoraria, or consulting fees related to nutrition research.[36]

The relationship between industry and academia is complex and a detailed analysis is beyond the scope of this review. We, along with many other authors, acknowledge that in order for an effective therapeutic agent to make it to the bedside, a commercial entity needs to produce it. The massively important role of the pharmaceutical industry in funding cutting edge research is undeniable and their continued contributions to science must be acknowledged. That said, industry-sponsored studies do present unique challenges in terms of conflict of interest management, which are certainly not limited to the nutrition literature and have been described in detail elsewhere.[37-40] We find the Oxepa® (Abbot Laboratories, Abbott Park, IL) experience particularly instructive. In 2008, an industry-sponsored, highly favorable meta-analysis of Oxepa® in critically ill patients was published in *Journal of Parenteral and Enteral Nutrition*, based on three small studies including 296 subjects.[41] Three years later a single larger, randomized controlled trial including 276 subjects and sponsored by the National Heart, Lung, and Blood Institute (NHLBI) was negative.[11]

In fact, the critical care literature is filled with small, high impact studies which have subsequently been disproven,[42-47] and thus, while the majority of the IMN data is promising, it is prudent to wait for the results of large, independent, multicenter studies before recommending widespread adoption of this promising (albeit expensive) therapeutic modality. The Oxepa® experience should give clinicians pause before practice changes are made based on small, industry-funded trials, as the potential for bias is higher.

Also important is reconciliation of the mostly favorable perioperative arginine data with data from other patient populations – in both critically ill patients and those suffering myocardial infarctions, arginine supplementation may also have the potential to cause harm.[48-50] This may be, in part, due to the complex nature of arginine metabolism and its variety of effects in humans.[48] Further complicating the interpretation of IMN data are the lack of data to even support basic perioperative nutrition as compared to no nutrition. The above-referenced Cochrane review was only able to identify three studies (263 subjects) comparing

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preoperative oral nutrition to no intervention (as opposed to standard oral supplementation), with no difference in outcomes.[21]

For ERAS specifically, the reality is that there is not enough data directly comparing IMN to either standard supplementation or no intervention in the context of an established ERAS pathway to make any meaningful determination as to efficacy. There is one moderate sized trial comparing IMN to other nutritional products in the context of ERAS. Moya et al. randomized 264 patients to IMN versus a hypercaloric hypernitrogenous supplement starting 7 days before surgery and finishing 5 days post-operatively and found a significant reduction in infectious complications (attributable solely to decreased surgical site and deep wound infections) although no difference in length of stay or re-admission rates.[51] Of note, the surgical site infection rate reported by the authors in the control group was considerably higher (~ 3X) than that reported by other authors.[7,52]

Recommendation

While we agree with much of the ESPEN, S4S, and ASER recommendations, based on the most up-to-date analysis of the literature, we believe that the evidence does not support the use of IMN in the context of ERAS at this time for the following reasons:

1. There is only one trial specifically studying the use of IMN in ERAS.[51]
2. Data on IMN in other populations (surgical, critical care) are equivocal.[13,24]
3. There is some data that IMN can be harmful in certain populations.[53-57]
4. The use of IMN incurs cost (3-5 x that of standard ONS) which might be more effectively used (e.g. for registered dietitian consultation in high risk patients) in a healthcare environment in which expenses are increasingly constrained.

Future work should be focused first on larger multicenter randomized control trials, adequately powered for analysis of both primary and secondary outcomes, specifically studied in patients enrolled in ERAS programs. These trials should also explicitly report the "dose" of IMN actually received by the patient (many published trials do not actually report this). Much of the perioperative nutrition literature is based on studies conducted outside the context of ERAS. What is not known and deserves further investigation is whether or not nutritional assessment and intervention is useful in patients who receive care in a structured pathway that encourages enteral intake of carbohydrate-containing fluids up to two hours before surgery, in addition to other modifications (opioid minimization, rational fluid administration, and ambulation), when compared to traditional care.

Additionally, though mortality, LOS, and postoperative complications have been the most commonly studied outcomes to date, greater emphasis should be placed on economic analysis. In an era of increasing cost constraints and limited resources, the cost of any potential intervention must also be weighed. These two competing realities (the desire to improve outcomes while decreasing costs) have been captured by the term "value," which indexes marginal improvements to cost. Going forward, it is increasingly expected that healthcare systems will make investments in equipment, supplies, and infrastructure that offer them the largest return on investment. Expensive interventions with weak or no evidence will likely be abandoned, and these cost-savings reinvested in proven technologies and strategies. ■

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