

## Immunonutrition and GI Surgery (Upper and Lower)- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Xu 2006</b> ( <i>WJS</i> ;30:1284-1289)	RCT to determine the effect of preoperative immunonutrition on nutritional status, immunity and incidence of post-operative complications in patients having UGI and LGI elective surgery.	Colorectal or gastric cancer surgery	60	Immunonutrition formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given preoperatively.	Standard isocaloric/isonitrogenous pre-op formula	Incidence of postop complications was significantly lower in the immunonutrition group (6.7% vs. 26% p<0.05). Postop IgG and CD4/CD8 ratio was significantly higher in the immunonutrition vs standard nutrition groups (p<0.05, <0.05, respectively).
<b>Braga 2002</b> ( <i>Arch Surg</i> ;137:174-180)	RCT to determine if perioperative use of immunonutrition is associated with a decrease in postoperative morbidity in malnourished upper and lower GI cancer surgery patients	GI cancer surgery: pancreatic, colorectal, and gastroesophageal	150	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard isocaloric/isonitrogenous post-op tube-feeding formula	ITT analysis revealed that patients fed study formula peri-op and pre-op had decreased post-op complications (18% and 28%, respectively) vs. the control group (42%, p=0.02, p=0.04, respectively). Reduction in LOS was observed in both intervention formula groups vs. control: 2.8 days in the peri-op group (p=0.001) and 2.1 days in the pre-op group (p=0.01) vs. control.
<b>Gianotti 2002</b> ( <i>Gastroenterol</i> ;122:1763-1770)	RCT to measure prospectively whether preoperative immunonutrition supplementation could be as efficacious as the perioperative approach, and superior to conventional treatment (no treatment) in reducing postoperative infectious complications and LOS in mostly weight-stable GI cancer surgery patients	GI cancer surgery: pancreatic, colorectal, and gastroesophageal	305	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional practice	Use of study formula pre-op (p=0.006) was as effective as study formula used peri-op (p=0.02) in reducing post-op infections in weight-stable patients, and is superior to conventional treatment. Significantly shorter post-op LOS in pre-op (p=0.008) and peri-op (p=0.03) study formula groups, compared to conventional (11.6, 12.2 vs. 14 days). Significantly fewer antibiotic therapy days for infected patients in pre- (p=0.01) and peri-op (p=0.03) study formula groups vs. conventional group (6, 6.3 vs. 9.2 days). Post-op study formula was well tolerated in the peri-op group, with 88% reaching goal feeding rate. Post-hoc analysis showed rate of infectious complications increased for BMI >30 vs. 18-25 (p=0.04)

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Braga 1999 ( <i>Arch Surg</i> ;134:428-433 )	Double-blind RCT to evaluate the effect of perioperative immunonutrition on clinical outcomes in GI cancer surgery patients	GI cancer surgery: gastric, pancreatic and colorectal cancer surgery	207	Formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isocaloric, isonitrogenous control formula	Patients who received the intervention formula vs. control had significant reduction in post-op infections (9/85 vs. 21/86, p=0.02) and received significantly fewer days of antibiotic therapy (6.7 vs 9 days, p=0.001). A significant reduction in LOS was also noted for the intervention formula group (p=0.01)

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<b>Martin 2017</b> ( <i>EJSO; published on line</i> )	RCT to determine if preoperative immunonutrition improves outcomes in patients undergoing irreversible electroporation (IRE) surgery for locally advanced pancreatic cancer (LAPC).	LAPC patients undergoing IRE for non-resectable pancreatic cancer.	71	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given preoperatively for 5 days.	No supplementation.	Postoperative complications in the immunonutrition group were significantly lower than in the control group (22% vs. 41%, p=0.05), and the most common reduction in complications was infectious (p=0.014). A significant reduction in LOS was also noted for the IM vs control group (10.7 vs 17.4 days, p=0.01).
<b>Aida 2014</b> ( <i>Surg;155:124-133</i> )	RCT to investigate the effect of preoperative immunonutrition on postop complications and immune response.	Pancreaticoduodenectomy (PD)	50	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides combined with a 50% reduction in the amount of regular food x 5 days prior to surgery. Std tube feeding postop.	No supplementation preop followed by early postop standard tube feeding postop.	Infectious complications in the immunonutrition group were significantly lower than in the control group (28% vs. 60%, p<0.05), and the severity of complications were also lower (p<0.05). EPA, EPA:AA were higher and PGE2 levels lower in the immunonutrition vs control group (p<0.05). This preoperative modulation was associated with higher levels of T-Bet vs. GATA3 mRNA expression (p<0.05), showing favorable Th1/Th2 differentiation in the immunonutrition group. This demonstrates a decrease in stress-induced immunosuppression.
<b>Marano 2013</b> ( <i>Ann Surg Oncol; July 10 2013 DOI: 10.1245/s1043401330881</i> )	RCT to investigate the effect of early post-op immunonutrition can have on outcomes in gastric cancer patients.	Total gastrectomy	109	6 hours post-op, tube feeding containing supplemental L-arginine, n-3 fatty acids and nucleotides was administered	6 hours post-op, isocaloric/isonitrog standard feeding was administered	Infectious complications in the intervention group were significantly lower than in the control group (7.4% vs. 20%, p<0.05), as was the rate of anastomotic leak (3.7% vs 7.3%, p<0.05). LOS for the intervention group was 3.2 days less than for the control group (p=0.029).

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<b>Shirakawa 2011</b> ( <i>J Hepatobiliary Pancreat Sci</i> ; 3: 249-258 )	Ascertain the feasibility and effectiveness of preoperative immunonutrition in patients having upper GI cancer surgery.	PD	31	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Retrospective clinically matched group that received conventional treatment	82.6% compliance with preoperative immunonutrition was noted and associated with less wound infection (0 vs 30.8%, p=0.012). Change in systemic severity as measured by APACHE II score was milder in the intervention group (p=0.033)
<b>Suzuki 2010</b> ( <i>Surg</i> ;148:573-581 )	RCT to investigate whether perioperative immunonutrition can influence cell-mediated immunity, T helper cell differentiation and response, and can reduce the rate of infectious complications after upper GI cancer surgery.	PD	30	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Post-op isocaloric TPN	The perioperative intervention group was found to have significantly higher levels of lymphocyte proliferation, natural killer cell activity, mRNA levels of T-bet, interferon- $\gamma$ , related orphan receptor, and interleukin-17F than post-op intervention or control groups. The perioperative immunonutrition group was found to have a significantly lower rate of infectious complications than either of the other groups (10% vs 60% vs 60%, p<0.05). A significant difference in SIRS days between the perioperative group and the control group was also noted (2.4 vs 3.6 days, p<0.05).
<b>Okamoto 2009</b> ( <i>WJS</i> ; 33:1815-1821 )	RCT designed to evaluate the effect of preoperative oral immunonutrition on cellular immunity, duration of SIRS and postoperative complications after upper GI cancer surgery.	Distal and total gastrectomy	60	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isocaloric standard oral formula	Post-operative infectious complications in the intervention group were significantly lower than in the control group (6% vs. 28%, p<0.05), as was the duration of SIRS (0.77 vs. 1.34 days, p<0.05). Postoperative lymphocyte and CD4+T-cell counts decreased in both groups (p<0.05), however the CD4+T-cell counts on pre-op day 1 and post-op day 7 were higher in the interventional than control group (p<0.05).

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Takeuchi 2007 ( <i>WJS</i> ; 31:2160-2167)	Retrospective comparison to measure the effect of preoperative and/or postoperative immunonutrition on post-op complications in patients undergoing upper GI cancer surgery	Esophageal	40	Formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard enteral formula	Significantly higher lymphocyte counts noted in the peri-op vs. post-op intervention groups on post-op day 7 ( $p=0.03$ ). Significantly shorter duration of post-op SIRS in peri-op intervention vs. control group (3 days vs. 4 days; $p=0.046$ ). Significantly shorter ICU LOS in peri-op intervention vs. standard nutrition group (5.5 days vs. 7 days, $p=0.047$ ). The incidence of incisional wound infection was significantly lower in the peri-op intervention than control group (0% vs 30%; $p=0.031$ ), but there were no significant differences in other postoperative complications such as pneumonia, anastomotic leakage or sepsis.
Senkal 2005 ( <i>JPEN</i> ; 29(4):236-240)	RCT to evaluate incorporation of omega-3 fatty acids into cell phospholipids in upper GI cancer surgery patients	Esophageal, gastric, duodeno-hemipancrea-tectomy	40	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Iso-caloric, isonitrogenous standard supplement	Increased levels of EPA and DHA in liver tissue, gut mucosa, and tumor tissue were observed in the pre-op intervention vs control group ( $p<0.05$ ), which indicates a possible effect on post-op inflammatory response after abdominal surgery
Farreras 2005 ( <i>Clin Nutr</i> ; 24:55-65)	RCT to assess the effect of early postoperative enteral immunonutrition on wound healing in upper GI cancer surgery.	Gastric	60	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Iso-caloric, isonitrogenous standard formula	The intervention formula group had significantly higher levels of hydroxyproline deposition ( $p=0.0018$ ), and no wound healing complications vs. 27% in the control group ( $p=0.005$ ). The intervention group also had a significantly lower rate of infectious complications (6.7% vs. 30% in the control group, $p=0.01$ )
Senkal 1999 ( <i>Arch Surg</i> ; 134:1309-1316)	Double-blind RCT to determine effects of perioperative immunonutrition in upper GI cancer surgery	Esophageal, gastric, duodeno-hemipancrea-tectomy	154	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isonitrogenous, iso-caloric standard supplement and tube feeding	Patients who received the intervention formula had significantly fewer infections occurring after post-op day 3 ( $p=0.04$ ) and fewer complications overall (48% reduction, $p=0.05$ ) than patients receiving the standard diet.

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<b>Braga 1999</b> ( <i>JPEN; 23(1):S2</i> )	RCT to measure the effect of postoperative immunonutrition support in upper GI cancer surgery	PD	182	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides initiated 6 hours after surgery	Iso-caloric, isonitrogenous standard enteral feeding or TPN initiated 6 hours after surgery	Compared to the TPN group, there was a 36% reduction into the number of patients with infectious complications ( $p < 0.05$ ), and the hospital LOS was 4 days shorter for patients fed intervention formula ( $p < 0.05$ ). Early post-op enteral feeding was well tolerated and did not increase the rate of complications
<b>Braga 1998</b> ( <i>Crit Care Med; 26(1):24-30</i> )	RCT conducted to measure the effect of postoperative immunonutrition support in upper GI cancer surgery	Gastric, Pancreatic	166	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides initiated within 12 hours after surgery	Iso-caloric, isonitrogenous standard enteral formula or TPN initiated 12 hours after surgery	Patients receiving intervention formula had the fewest number of post-op infections ( $p < 0.05$ ) and a shorter hospital stay compared to standard formula or TPN. In subgroups of malnourished patients and patients who received homologous transfusions, administration of intervention formula compared more favorably than TPN, and decreased severity of infection and LOS ( $p < 0.05$ )
<b>Gianotti 1997</b> ( <i>Arch Surg; 132:1222-1230</i> )	RCT to evaluate the effect of delivery route and formulation of postoperative nutrition in upper GI cancer surgery	PD, Gastrectomy	260	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isonitrogenous, iso-caloric standard enteral formula and TPN	Intervention formula group showed significantly lower sepsis scores than patients on either standard enteral or TPN ( $p < 0.01$ ). Mean hospital LOS was shorter for patients in the intervention formula group compared to either of the other groups (16.1 days for the immunonutrition formula group vs. 19.2 days for the standard enteral and 21.6 days for TPN, $p = 0.004$ $p = 0.01$ )

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<b>Senkal 1997</b> ( <i>Crit Care Med</i> ;25(9):1489-1496 )	Perform an outcome and cost-benefit analysis on a RCT of early postoperative immunonutrition in upper GI cancer surgery patients	Gastrectomy (various), PD, other	164	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given within 12-24 hours after surgery	Isonitrogenous, isocaloric control formula given 12-24 hours after surgery	Patients who received the intervention formula had 53% fewer infectious and wound complications occurring after post-op day 5 ( $p<0.05$ ). The average cost for treating complications was 32% lower for the intervention formula group
<b>Kemen 1995</b> ( <i>Crit Care Med</i> ;23(4):652-659 )	RCT measuring the effect of early postoperative administration of immunonutrition formula on immune function of upper GI cancer surgery patients	Gastrectomy (various), PD	42	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides initiated on post-op Day 1	Isonitrogenous, isocaloric control formula initiated on post-op day 1	The intervention group had significantly improved immune function as measured by Immunoglobulin M (IgM) ( $p<0.05$ ) and Immunoglobulin G (IgG) ( $p<0.05$ ). Significantly higher T-lymphocyte concentrations ( $p<0.05$ ) were also noted for the intervention formula in comparison to control
<b>Daly 1995</b> ( <i>Ann Surg</i> ;221(4):327-338 )	Double-blinded RCT to measure the effect of early postoperative immunonutrition vs. standard high protein formula in upper GI cancer patients undergoing abdominal surgery	Esophageal, gastric, pancreatic	60	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard enteral formula	Immunonutrition group had 77% fewer infectious and wound complications ( $p<0.005$ ), and a 6-day shorter mean length of hospitalization ( $p=0.02$ )

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Daly 1992 ( <i>Surgery</i> ;112:56-67)	RCT to measure effect of early postoperative immunonutrition formula on surgical outcomes (immunologic, metabolic and clinical)in upper GI cancer surgery patients	Esophagogastrectomy, gastrectomy, PD, laparotomy and miscellaneous	85	Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard enteral formula	Patients fed the intervention formula had better nitrogen balance ( $p=0.05$ ), a quicker return of immune function to pre-op levels ( $p<0.01$ ), 70% fewer infectious/healing complications ( $p=0.02$ ), and a 22% (1.2 day) reduction in length of hospital stay ( $p=0.01$ ).



## Immunonutrition and Lower GI Surgery- Studies Compendium

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<b>Banerjee 2017</b> ( <i>Nutrition;published on-line:1-8</i> )	Comparative effectiveness analysis of real world data to assess the effects of preoperative arginine-based immunonutrition (IM) on post-surgical utilization and cost outcomes in adult patients.	Colorectal patients in Washington State Strong for Surgery® (S4S) hospitals in the Surgical Care Outcomes Assessment Program (SCOAP) database.	n=722	An oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides x 5 days.	Regular diet, no supplementation	After controlling for demographic and patient health conditions, readmissions for the S4S-IM group vs. control were lower at 30 days post-discharge ( $p<0.05$ ), as well as at 90 and 180 days ( $p<0.01$ ). S4S-IM group patients had a lower rate of surgical site infection (SSI) than S4S-control patients (0% vs. 2.65%; $p=0.04$ ). S4S-IM group patients had a lower rate of venous thromboembolism than S4S-control patients (1.3% vs. 5%; $p=0.05$ ). From index hospitalization to 180 days post-discharge, mean cost of care was \$5300 less for the S4S-IM group vs. control (NSS), and the mean increase in total costs was reduced by 10%. Strong for Surgery is a Quality Program of the American College of Surgeons.
<b>Thornblade 2017</b> ( <i>Dis Colon Rect;60:1</i> )	Prospective cohort study to determine if preoperative immunonutrition (IM) improves outcomes in a community of colorectal surgery patients.	Colorectal patients in Washington State hospitals in the Surgical Care Outcomes Assessment Program (SCOAP)	n=3375; 960 for propensity score matched comparative effectiveness evaluation	An oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides x 5 days.	Regular diet, no supplementation	The rate of serious adverse events (SAEs) was not significantly different between groups, however patients receiving IM were in a higher ASA class ( $p=0.01$ ) or more likely to require an ostomy ( $p=0.02$ ). The rate of prolonged LOS was lower in the immunonutrition group for the full analysis (13.8% vs 17.3%, $p=0.04$ ), as well as among patients with similar covariates (RR, 0.77;95% CI, 0.58-1.01 $p=0.05$ ).
<b>Horie 2006</b> ( <i>Surg Today;36:1063-1068</i> )	Prospective study to measure the effect of preoperative immunonutrition on surgical site infection (SSI) in patients with colorectal cancer.	Colorectal CA, well-nourished	67	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Regular diet, no supplementation	Patients reported 100% compliance to the oral intervention. Frequency of SSI was reduced in the immunonutrition vs. the control group (0% vs. 14.7%, $p<0.05$ ). Superficial incision and organ/space SSI contributed to the data.

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<b>Braga 2002</b> ( <i>Surgery</i> ;132:805-814)	RCT measuring the effect of preoperative immunonutrition on immunometabolic host response and outcome after lower GI cancer surgery in mostly well-nourished patients.	Colorectal	200	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isonitrogenous/isocaloric standard pre-op supplement and conventional therapy	Immune response ( $p < 0.05$ ), gut oxygenation ( $p < 0.01$ ) and microperfusion ( $p < 0.02$ ) were significantly better for pre-op and peri-op study groups than control groups. ITT analysis shows pre- and peri-op study groups had a significantly lower infection rate (12%, 10%) compared to control and conventional groups (32%, 30%; $P < 0.04$ ). Hospital length of stay was shorter by 2.5 days on average for patients receiving study formula ( $P < 0.0005$ for pre-op group and $P < 0.0001$ for peri-op group) vs. control and conventional). Length of antibiotic therapy was significantly shorter in the patients receiving study formula who developed postoperative infections ( $P < 0.004$ for pre-op group and $P < 0.005$ for peri-op group vs. control and conventional).

## Immunonutrition and Head/Neck Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Rowan 2016</b> ( <i>Oral Onc</i> ;54:42-46 .)	Identify outcomes associated with implementing perioperative immunonutrition as part of a quality practice improvement (QPI) initiative with high-risk head and neck cancer surgical patients.	High-risk head and neck cancer surgery	195	5-day pre- and post-operative courses of oral and tube feeding immunonutrition formula, respectively. Formulas contained supplemental L-arginine, n-3 fatty acids and nucleotides.	Standard of Care (regular diet, no supplementation preoperatively; standard TF postop)	47.5% of standard of care patients registered complications vs 25.2% in the immunonutrition group (p=0.0021). Pharyngeal leaks or fistulas were the most common complication in both groups and more common in patients not receiving supplementation (p=0.007). Mean LOS was reduced by 2.8 days in those receiving immunonutrition (p=0.02). Readmission rates between the two groups were similar.
<b>Falewee 2014</b> ( <i>Clin Nutr</i> ;776-784 .)	Multicenter, prospective, randomized double-blind study to investigate if preoperative or perioperative immunonutrition could reduce post-operative infectious complications and surgical site infections.	Head and neck surgery patients with oropharyngeal and pharyngolaryngeal tumor	312; 205 ITT; 64 per protocol	Preop immunonutrition/postop standard formula compared with perioperative immunonutrition.	Isocaloric, isonitrogenous perioperative standard nutrition.	No differences in outcomes were found when compliance to the formula on POD 0-10 was <75%. In patients with >75% compliance, the perioperative immunonutrition group showed decreased SSI (43.5% vs 11.8%; p=0.04), infections complications (23.5% vs. 56.3%;p=0.05) and LOS (25 vs 18 days; p=0.05) vs. the control. Preoperative IM vs control did not make a significant difference in outcomes.
<b>Felekis 2010</b> ( <i>Nutr and Cancer</i> ; 62(8):1105-1112)	Randomized double-blinded prospective study that evaluated outcomes in head/neck cancer patients receiving perioperative immunonutrition vs standard formula post-op.	Squamous cell carcinoma of the head/neck.	40	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given perioperatively.	No nutritional support preoperatively and standard formula post-op.	Incidence of major complications (pneumonia, UTI, fistula and wound infection) was significantly lower in the immunonutrition group than the standard group; 5% vs. 25%; p<0.05).

## Immunonutrition and Head/Neck Surgery- Studies Compendium

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<b>Sorensen 2009</b> ( <i>The Laryngoscope</i> ; 119:1358-1364)	Randomized blinded pilot study that examined the nutritional, immunologic and wound healing outcomes in head/neck cancer patients receiving perioperative immunonutrition vs. standard.	Squamous cell carcinoma of the head/neck. Tumors located primarily in the oropharynx, tongue, tonsils or floor of mouth. 53% were moderately malnourished.	15	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given perioperatively. Intervention tube feeding was also higher in glutamine than standard formulas.	Standard enteral supplement and formula	CD3+ and CD4+ T cells were significantly higher on POD 1 for the intervention group (p=0.03), and CD56 NK cells on POD 8 (p=0.04) for the control group. In general, wounds healed without complications except for a tracheoesophageal fistula in two patients in the control group.
<b>Snyderman 1999</b> ( <i>The Laryngoscope</i> ;109:915-921)	Double-blinded RCT undertaken to determine if perioperative immunonutrition supplementation was superior to standard formula in decreasing postoperative infectious complications in head and neck oncology surgery patients.	Tumors of the oral cavity, pharynx, larynx, other (Stage 1-4)	136	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard enteral supplement and formula	Incidence of postoperative infectious complications for the intervention group (9/40 [23%]) compared significantly with standard therapy (13/31 [45%]); ITT (p=0.02) and actual (p=0.04). No difference in wound healing noted. LOS was prolonged in patients with infections (median 20 days vs 12 days, p<0.001), suggesting potential cost savings with use of immunonutrition.

## Immunonutrition and Cardiac Surgery- Studies Compendium

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<b>Iwase 2014</b> ( <i>Nutr Met Ins</i> ;7:39-46)	RCT completed to investigate if preoperative use of immunonutrition would influence immune response and leukocyte-platelet formation in patients having cardiac surgery.	Cardiac surgery due to valve disease, aneurysm or angina.	14	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Regular diet; no supplementation	HLA-DR expression, CD4/CD8 ratio and the production of IFN- $\gamma$ by CD4-positive cells were increased in the immunonutrition group ( $p < 0.05$ ). Conversely, IL-10 level and the formation of leukocyte-platelet aggregates before and after surgery were suppressed to a greater extent in the immunonutrition group ( $p < 0.05$ ). These effects may decrease the incidence of complications after surgery.
<b>Tepaske 2007</b> ( <i>JPEN</i> ;31(3):173-180)	Double-blind RCT completed to see if adding glycine to pre-op oral immunonutrition would improve outcome after high-risk cardiac surgery.	Mitral valve surgery, age 70+	74	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides +/- glycine	Isocaloric/ isovolemic standard oral formula	Infectious morbidity was decreased in both intervention groups as compared to the control ( $p = 0.02$ ). The addition of glycine did not appear to make a difference.
<b>Tepaske 2001</b> ( <i>Lancet</i> ; 358(9293):696-701)	Double-blind RCT measured differences in pre-op host defense and post-op outcomes in high-risk cardiac surgery patients to determine the effects from pre-op oral immunonutrition.	Age $\geq 70$ years or had an ejection fraction of $\leq 40\%$ , or were scheduled for mitral valve replacement.	50	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides. Tube feeding containing same was used post-op as needed until extubation.	Isocaloric, isovolemic and isonitrogenous standard nutritional supplement. Standard IC/IV/IN tube feeding was used post-op as needed until extubation.	Intervention group had significantly higher pre-op vs. baseline expression of HLA-DR epitopes on monocytes (109%) than those in the control group ( $p = 0.02$ ). Concentration of IL-6 was lower in the intervention group (0.90 pg/L) vs. control group (1.94 pg/L) ( $p = 0.032$ ). The intervention group showed a reduction in total infectious complications (4 of 23 vs. 12 of 22), ( $p = 0.01$ ), and had fewer cases of pneumonia ( $p < 0.05$ ).

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Tepaske 1997 ( <i>Eur Soc Surg Infect abstract</i> )	Double-blind RCT measured differences in pre-op host defense and post-op outcomes in high-risk cardiac surgery patients to determine the effects from pre-op oral immunonutrition.	Age $\geq$ 70 years or had an ejection fraction of $\leq$ 40%, or were scheduled for mitral valve replacement.	45	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides.	Isocaloric, isonitrogenous standard nutritional supplement.	HLA-DR density on monocytes was significantly higher for the intervention group vs control in the sample moments before surgery and 15 minutes after release of the aortic cross clamp (p=0.041, p=0.029). Less lower respiratory infections, excluding pneumonia, (0/22 vs. 5/23, p=0.022), as well as fewer total infections (4/22 vs. 12/23, p=0.009) were noted for the intervention vs control groups.

## Immunonutrition and Bladder Cancer Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Hamilton-Reeves 2016</b> ( <i>Euro Urol</i> ;69(3):389-392)	A pilot randomized controlled clinical trial to compare immune response and post-operative complications between a group of bladder cancer surgery patients that received perioperative immunonutrition vs. a group that received perioperative ONS.	bladder cancer (all male) being operated on according to the institution's ERAS protocols	29	Perioperative immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides was provided as 3 cartons per day for 5 days before and after surgery.	Iso-caloric ONS was provided as 3 cartons per day for 5 days before and after surgery.	The immunonutrition and control groups had MDSC counts that were significantly different over time ( $p=0.005$ ) and significantly lower in the immunonutrition group 2 days after surgery ( $p<0.001$ ). Neutrophil:lymphocyte ratio was lower in the immunonutrition group vs ONS 3 hours after the first incision ( $p=0.039$ ). Although not powered to detect outcome differences, the immunonutrition group had a 33% reduction in postop complication rate ( $p=0.060$ ) and a 39% reduction in infection rate ( $p=0.027$ ) during late-phase recovery.
<b>Bertrand 2014</b> ( <i>World J Urol</i> ;32:233-237)	A prospective, multicenter, case-controlled pilot study to compare the rate of postoperative complications in patients with bladder cancer who received preoperative immunonutrition with those that did not prior to cystectomy.	bladder cancer	60	Preoperative immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides.	No supplementation	The immunonutrition group had a lower incidence of post-operative complications (40% vs. 77%; $p=0.0080$ ) including paralytic ileus and infections than the control group. Mortality, pulmonary embolism, anastomotic fistula and wound dehiscence were similar between groups. Length of stay (LOS) was reduced by 3 days in the immunonutrition group (NS).

## Immunonutrition and Gyn-Onc Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Chapman 2015</b> ( <i>Gyn Onc;137:523-528</i> )	Retrospective cohort study of perioperative immunonutrition and no supplementation as a quality practice improvement for patients having laparotomy for gynecological malignancy.	Ovary/fallopian tube/peritoneal cancer, benign pathology, uterine cancer, cervix/vaginal cancers, GI cancer	338	Perioperative immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides. However, only 5 patients took immunonutrition preoperatively, so the study largely measures results from post-operative use.	no supplementation	75% patient compliance to postop intervention. Fewer wound complications were noted in patients receiving immunonutrition (19.6% vs 33%; p=0.049). After controlling for variables associated with development of wound complications, patients receiving immunonutrition had a 78% reduction in CDC SSI class 2 and 3 infections (OR = 0.22, CI 0.05-0.95, p=0.044) in comparison to control.
<b>Celik 2009</b> ( <i>Eur J Gynaec Oncol; 4:418-421</i> )	RCT of perioperative immunonutrition and standard nutrition in patients operated on with gynecological malignancies.	Endometrial and ovarian cancer surgery.	50	Perioperative immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides.	Isocaloric standard feed given perioperatively	WBC count, lymphocyte population and CRP levels were significantly higher in the intervention group (p<0.05). Post-op pulmonary and urinary infection rates were similar in both groups, but wound infection rate and LOS were significantly lower in the treatment group (p<0.05).



## Immunonutrition and Orthopedic Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Alito Aprelino and Aguilar-Nascimento 2016</b> (Nutr Journal;15:1-7)	Prospective, randomized pilot study to test the effect of adding preoperative immunonutrition to multimodal perioperative protocols vs. traditional care.	Mostly well-nourished elective total hip arthroplasty surgery patients under epidural anesthesia.	32	Multimodal perioperative protocols including preoperative immunonutrition (containing supplemental L-arginine, n-3 fatty acids and nucleotides) for 5 days prior to surgery, 6h preoperative fasting from solids, CHO-enriched drink up to 2h prior to anesthesia and restricted IV fluids.	No use of multimodal perioperative protocols.	The median LOS was 3 days for study patients and 6 days for traditional care patients ( $p < 0.01$ ). Preoperative C-Reactive Protein (CRP) values were similar between groups, however levels on post-operative Day 2 were lower in the study than traditional group (66.5 mg/L vs. 80.6 mg/L; $p < 0.01$ ).

Immunonutrition and Non-Small Cell Lung Cancer Surgery

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Kaya SO et al 2016</b> <i>(J Cardiothor Surg;11:14)</i>	Prospective, randomized study to compare the effect of adding preoperative immunonutrition vs. a normal diet in patients undergoing resection for non-small cell lung cancer (thoracotomy or videothoracoscopy)	Well-nourished non-small cell lung cancer patients who did not have diabetes or undergo bronchoplastic procedures or neoadjuvant therapy.	58	Preoperative immunonutrition (containing supplemental L-arginine, n-3 fatty acids and nucleotides) for 10 days prior to surgery, 6h preoperative fasting from solids, CHO-enriched drink up to 2h prior to anesthesia and restricted IV fluids.	Normal diet	Complications developed in 19% of the study group patients, but in 44.4% of the control group patients (p=0.049). Mean chest tube drainage time was 4 days in the study group and 6 days in the control group p=0.019).

### Immunonutrition and Hernia Repair- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Majumder 2016 ( <i>J Am Coll Surg</i> ;222:1106-1115)	Prospective comparison of an Enhanced Recovery Protocol (ERP) Bundle including preoperative immunonutrition with a pre-ERP historical cohort to see if hospitalization could be shortened for ventral hernia repair (VHR) patients.	VHR patients who had retromuscular hernia repair and posterior component separation via transversus abdominis muscle release, along with placement of synthetic mesh.	200	ERP Bundle including preoperative immunonutrition (containing supplemental L-arginine, n-3 fatty acids and nucleotides) given for 5 days prior to surgery. Diet advancement post surgery was scheduled and a clear liquid ONS was provided on postop day one and transitioned to a high calorie ONS once tolerating food.	Normal diet	ERP Bundle patients demonstrated a 75% reduction in 90-day readmissions vs. the control group (4% vs. 16%, p=0.001). ERP Bundle patients also showed a reduction in LOS by 2.1 days (p<0.001), and a shorter time to: diet advancement, flatus, bowel movement and oral narcotics. The differences in these additional measures were also statistically significant (p<0.001).

## Health Economics

Author	Study Objective	Patient population	(n)	Source of Cost Data	Intervention	Control	Results
<b>Banerjee 2017</b> <i>(Nutrition; published on-line:1-8)</i>	Comparative effectiveness analysis of real world data to assess the effects of preoperative arginine-based immunonutrition (IM) on post-surgical utilization and cost outcomes in adult patients.	Colorectal patients in Washington State Strong for Surgery® (S4S) hospitals in the Surgical Care Outcomes Assessment Program (SCOAP) database.	n=722	Comprehensive Hospital Abstract Reporting System (CHARS), a Washington hospital discharge database.	An oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides x 5 days.	Regular diet, no supplementation	At index hospitalization and at 30, 90 and 180 days post-discharge, mean cost of care was less for the S4S-IM group vs. control at \$2400, \$3500, \$4500 and \$5300 per patient, respectively. The mean increase in total costs was reduced by 10%. Decreased cost was associated with significantly lower readmissions at 30, 90 and 180 days (p<0.05) and SSI (surgical site infection; p=0.04) for the S4S-IM group vs control patients. <i>Strong for Surgery® is a registered trademark of the American College of Surgeons.</i>
<b>Chevrou-Séverac 2014</b> <i>(Clin Nutr;33(4):649-654)</i>	Determine the impact on hospital costs of pre, peri and postoperative immunonutrition used in patients undergoing elective surgery for GI cancer.	Upper and lower GI cancer surgery patients from 21 RCTs included in Cerantola 2011 (Br J Surg)	2730	University Hospital of Lausanne DRG Database	17/21 studies utilized Oral and/or tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	standard formula	Average contribution of complications to cost of stay was CHF 14,949 (€10,901), independent of severity. Based on this cost, immunonutrition was shown to decrease costs of hospital stay by CHF 1638 to CHF 2488 (€1195-€1814).

## Health Economics

Author	Study Objective	Patient population	(n)	Source of Cost Data	Intervention	Control	Results
<b>Barker 2013</b> ( <i>Euro J of Clin Nutr; 67(8):802-807</i> )	RCT with the aim to measure the effect of preoperative immunonutrition on clinical outcomes and treatment costs in GI surgery.	79% well-nourished and 21% malnourished pts having primarily lower GI cancer surgery	95	Royal Melbourne Hospital	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional practice	An overall trend in reduced LOS (1.7 days, p=0.11) was observed and was stronger for malnourished pts receiving the preop intervention. (4 days, p=0.21). Positive trends were also shown for the intervention in regards to infection rate, antibiotic use and wound infections at 30 days. Average cost/stay was reduced by AUD 1576 in the intervention groups compared with the control (p=0.37).
<b>Mauskopf 2012</b> ( <i>WJSO; 10(136):open access</i> )	Determine the impact on hospital costs of perioperative immunonutrition used in patients undergoing elective surgery for GI cancer.	Upper and lower GI cancer surgery patients from 6 RCTs included in Waitzberg 2006 ( <i>WJS</i> )	889	US Hospital Cost/day and Cost/stay with and without complications are from HCUP (Healthcare Cost and Utilization Project) Nationwide Inpatient Sample	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isonitrogenous/ isocaloric standard enteral formula, standard enteral formula, IV solution, conventional treatment.	Estimates project use of immunonutrition to result in a savings of \$6000/pt when costs were based on LOS and \$3300 when costs were based on a reduction in complications. Sensitivity analysis showed cost savings were expected for baseline complication rates above 3.5%.
<b>Braga 2005</b> ( <i>Nutrition; 21:1078-1086</i> )	Blinded cost analysis to determine the impact of preoperative immunonutrition on hospital costs in elective GI cancer surgery.	Upper and lower GI cancer surgery patients studied in RCT from Gianotti 2002 ( <i>Gastroenterology</i> )	305	National list of Sanitary Costs, Italian Ministry of Health	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional	A shorter LOS and fewer complications in the immunonutrition group showed a net hospital savings of €1424/pt as compared to conventional care. This was based on a total cost per patient of €5668 for those receiving immunonutrition and €7092 for those receiving conventional support (no supplementation).

## Health Economics

Author	Study Objective	Patient population	(n)	Source of Cost Data	Intervention	Control	Results
<b>Strickland 2005</b> ( <i>JPEN; 29(1 Suppl):S81-S91</i> )	Application of published clinical outcomes to hospital costs to determine the potential economic benefit associated with immunonutrition in various populations.	Surgical, trauma and medical ICU patients - see Gianotti. Gastroenterol 2002 - See Beale. CCM 1999 - See Braga. Arch Surg 2002	*305 (GI cancer surgery, well-nourished) *150 (GI cancer surgery, malnourished) *1282 (Surg, Trauma and Med ICU)	Medical College of Georgia and the University Health Consortium Database	12/14 studies utilized formulas containing supplemental L-arginine, n-3 fatty acids and nucleotides	Various	Assuming a baseline infection rate of 5%, net cost savings was estimated at \$2066 for the medical ICU patient; \$688 for the surgical patient and \$308 for the trauma patient.
<b>Farber 2005</b> ( <i>JPEN; 29(1 Suppl): S62-S69</i> )	Difference in outcome and economics of ICU patients receiving post-op immunonutrition compared with a retrospective control.	Severe trauma, burns and sepsis	38	Published costs of ICU care from: Angus DC et al. CCM 2003.	High energy tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard high energy tube-feeding formula	A reduction in nosocomial pneumonia (12% vs 52%, p<0.01) and associated ICU LOS ( $\Delta$ 5 days) resulted in an average cost savings of \$11,382 per patient when comparing immunonutrition and control groups.
<b>Senkal 1997</b> ( <i>Crit Care Med; 25(9): 1489-1496</i> )	Perform an outcome and cost-benefit analysis on a RCT of early postoperative immunonutrition	Gastrectomy (various), PD, other	164		Tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides given within 12-24 hours after surgery	Isonitrogenous, isocaloric control formula given 12-24 hours after surgery	Patients who received the intervention formula had 53% fewer infectious and wound complications occurring after post-op day 5 (p<0.05). The average cost for treating complications was 32% lower for the intervention formula group.

## Meta-analysis of Immunonutrition- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<p><b>Mazaki 2015</b> (<i>Ann Surg</i> 2015;261(4):662-669)</p>	<p>Evaluate 74 RCTs of standard enteral (SEN), standard parenteral (SPN), immunoenhancing parenteral (IMPN) and immunoenhancing enteral (IMEN) nutrition to see which is best at reducing complications after GI surgery.</p>	<p>GI surgery</p>	<p>7572</p>	<p>IMEN formulas contained various combinations and amounts of supplemental arginine, glutamine, n-3 fatty acids (EPA + DHA) and nucleotides. 24/36 studies involving IMEN utilized formula containing supplemental arginine, n-3 and nucleotides. IMPN formulas contained coconut oil/ MCT, olive oil, fish oil or various combinations and amounts of two or three of these oils.</p>	<p>Standard enteral or parenteral nutrition</p>	<p>IMEN ranked first for reducing the incidence of 7 complications after GI surgery: any infection, overall complications, mortality, wound infection, intra-abdominal abscess, anastomotic leak and sepsis. IMEN was ranked second for reducing the incidence of pneumonia and UTI, whereas IMPN was ranked first for these complications. SPEN performed least well for almost all outcomes when compared to the other three types of nutrition. Authors conclude the results suggest IMEN outperformed other types of nutrition in the reduction of complications and should be considered the best available option for GI surgery.</p>

## Meta-analysis of Immunonutrition- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Vidal-Casariago 2014</b> (Clin Nutr; 33(6):951-957)	Evaluate effect of 6 RCTs of arginine-supplemented enteral formulas on the risk of complications and LOS after head/neck cancer surgery.	Head/Neck Cancer Surgery	<b>397</b>	2/6 studies utilized formula containing supplemental arginine, n-3 fatty acids and nucleotides, and all contained arginine (6.25 - 18.7 g/L). Studies contained 2 preoperative arms, 7 perioperative arms and 4 postoperative arms.	isocaloric/isonitrogen standard formula	An average of the results found a decrease in fistulas (OR=0.36;p=0.039) and LOS (-6.8 days;p=0.023) associated with arginine-supplemented formulas, however, no reductions in wound infections or other infections were found between the immunonutrition and standard formulas groups.
Osland 2013 ( <i>JPEN</i> ; Feb 14 2013 DOI: 10.1177/0148607112474825)	Evaluate 22 RCTs (21 data sets) of arginine-dominant pharmaconutrition in major elective surgery, specifically in regard to the timing of administration. 5 trials were pre-op, 2 peri-op and 14 post-op.	Major elective GI cancer surgery	2005	11/22 studies used formula containing supplemental L-arginine, n-3 fatty acids and nucleotides.. 6/22 studies contained arginine as the sole immunonutrient.	standard formulas	Peri-op and Post-op immunonutrition both showed decreases in risk of infectious complications (OR=0.44, p=0.001; 0.61, p<0.01) and LOS (-2.57 days, p=0.001; -2.3 days, p=0.001). Peri-op showed decreased risk of anastomotic leak (OR=0.39, p=0.03), and Post-op showed decreased risk of noninfectious complications (OR=0.70, p=0.02). Pre-op arginine-dominant nutrition did not show significantly improved decreases in risk vs. control.



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<b>Burden 2012</b> (Cochrane Database of Systematic Reviews;11: article number CD008879)	Review of the literature on preoperative nutritional support in patients having GI surgery. 7 studies were meta-analyzed in regards to preoperative immunonutrition.	GI surgery	549	6/7 pre-op immunonutrition studies used formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard nutrition or conventional management	Pre-op immunonutrition found to reduce risk of total complications from 42% in the control group to 27% in the intervention group ( $p=0.0006$ ), while infections were reduced from 27% in the control group to 14% in the interventional ( $p=0.0003$ ).
<b>Marimuthu 2012</b> ( <i>Ann Surg</i> ; 255:1060-1068 )	Evaluate 26 RCTs on the effect immunonutrient combinations in enteral formulas had on complications and LOS after abdominal surgery	Major open GI surgery	2496	Immunonutrition formulas containing at least 2 immunonutrients. 15/26 studies used formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	isocaloric/isonitrog standard formula	Immunonutrition was associated with strong evidence showing a significant reduction in LOS (-1.88, $p=0.0004$ ) and risk of postoperative complications (36%, $p<0.00001$ ). A sub-analysis of perioperative studies showed a 47% reduction in risk of post-op complications ( $p<0.00001$ ) and a difference in LOS of 2.71 days on average ( $p<0.00001$ ). Immunonutrition was associated with an 18% reduction in non-infectious complications ( $p=0.007$ ), however the quality of the evidence was low.
<b>Zhang 2012</b> ( <i>Surg Onc</i> ;21:e87-e95)	A systematic review of 19 randomized clinical trials to assess the use of immunonutrition in GI cancer surgery patients.	Major elective GI cancer surgery	2331	17/19 trials used formula containing supplemental L-arginine, n-3 fatty acids and nucleotides. This included 6 preop analyses, 6 periop analyses and 11 postop analyses.	Standard enteral formula, IV fluids or TPN. 12/19 studies utilized isonitrogenous, isocaloric standard formula.	Pooled results show immunonutrition given exclusively preoperatively or postoperatively reduces risk of infectious complications (RR 0.45; $p<0.001$ , RR 0.69; $p<0.01$ ) and LOS (WMD -2.95 $p<0.01$ ; ), but not the risk of non-infectious complications. Pooled results show immunonutrition given perioperatively reduces risk of infectious complications (0.44; $p<0.01$ ), non-infectious complications (RR 0.72; $p=0.03$ ) and LOS (WMD2.62; $p<0.01$ )

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Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Cerantola 2011</b> ( <i>Br J Surg; 98:37-48</i> )	A systematic review of 21 randomized clinical trials to assess the impact of immunonutrition on postoperative complications, in particular, infection, as well as LOS and mortality in GI cancer surgery patients	Major elective GI cancer surgery	2730	17/21 trials used formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	standard formula	Pooled results show immunonutrition reduces the risk of post-op complications and infections by 34% and 36%, respectively, and reduces hospital LOS by 2.12 days ( $p < 0.01$ ). Trials using immunonutrition lacking in nucleotides did not show a reduction in the risk of infection. An analysis of preoperative studies, favored use of immunonutrition (Odds Ratio (OR) = 0.48, 0.34 to 0.69), as did the perioperative (OR = 0.39, 0.28 to 0.54) and postoperative (OR=0.46, 0.25 to 0.84) analyses.
<b>Drover 2011</b> ( <i>J Am Coll Surg; 212(3): 385-399</i> )	To conduct a systematic review of all RCT evaluating arginine-supplemented diets in elective surgery patients	35 studies included elective GI surgery and 10 studies included other major elective surgical procedures	3487	23/35 studies used formulas containing supplemental L-arginine, n-3 fatty acids and nucleotides	standard formulas	Arginine-supplemented diets were associated with a 41% reduction in risk of infectious complications when compared with standard formulas ( $p < 0.00001$ ). Benefit was shown for pre-, peri- and post-op use, however, the greatest reduction in infectious complications was seen with peri-op administration ( $p < 0.00001$ ), and the difference between the subgroups was significant ( $p = 0.03$ ). Formula containing supplemental L-arginine, n-3 fatty acids and nucleotides was associated with a 51% reduction in the risk of infectious complications ( $p < 0.00001$ ) compared to the use of other immunonutrition formulations ( $p = 0.68$ ). The differences between these 2 subgroups was significant ( $p < 0.0001$ ). The use of formula containing supplemental L-arginine, n-3 fatty acids and nucleotides was also associated with a significant reduction in hospital LOS (-2.38 days, $< 0.00001$ ) compared to the use of other immunonutrition formulations (-0.89 days, $p = 0.45$ ). The difference between these 2 subgroups was also significant ( $p < 0.00001$ ).

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Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Marik and Zaloga 2010</b> ( <i>JPEN</i> ; 34(4):378-386)	Meta-analysis of 21 RCT to evaluate the effect of immunonutrition vs. control formula on clinical outcomes of high-risk elective surgery patients	GI cancer, general abdominal, head/neck cancer, and cardiac surgery	1918	18/21 studies used formulas containing supplemental L-arginine, n-3 fatty acids and nucleotides	standard	Immunonutrition significantly reduced hospital acquired infections (OR 0.49; 0.39-0.62, $p < 0.0001$ ), wound complications (OR 0.60; 0.40-0.91, $p = 0.02$ ), and on average, a 3-day reduction in hospital LOS ( $p < 0.0001$ ). Benefits were found to be similar for peri- and postoperative use; however, formulas containing both arginine and fish oil were required, presumably due to synergistic effect. Authors state that given the majority of studies used a product containing arginine, fish oil, nucleotides, and antioxidants, it is unclear if the outcomes can be extrapolated to other immunonutrition formulas of differing ingredient composition.
<b>Bozzetti 2007</b> ( <i>Clin Nutr</i> ; 26(6):698-709)	Meta-analysis of 7 RCT comparing postoperative morbidity in GI cancer surgery patients receiving various nutrition regimens. Correlating factors studied included pancreatic surgery, advanced age, weight loss, and low serum albumin.	GI cancer surgery	1410	Formulas containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard enteral formula, IV fluids or TPN	Patients who received immunonutrition had significantly reduced post-op morbidity ( $p < 0.0010$ ). Pancreatic surgery, advanced age, weight loss, and low serum albumin were identified as independent risk factors for the onset of post-op complications.
<b>Waitzberg 2006</b> ( <i>WJS</i> ; 30:1592-1604)	Review of 17 RCTs to examine the relationship between specialized nutrition support with immunonutrients and postoperative morbidity in patients undergoing major elective surgery	GI cancer, head/neck cancer, and cardiac surgery	2305	Pre-op, peri-op or post-op formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional treatment, standard enteral formula, and/or IV solution	Pre-, peri-, and post-op supplementation with immunonutrition was associated with a significantly reduced risk of post-op infectious complications (RR 0.49, $p < 0.0001$ ). Supplementation with immunonutrition was associated with a 3.1 day average reduction in LOS ( $p < 0.05$ ). Use of immunonutrition was associated with a 44% lower risk of anastomotic leaks ( $p = 0.04$ ), 47% lower risk of pneumonia ( $p < 0.0001$ ), 40% lower risk of wound infection ( $p = 0.005$ ), 54% lower risk of abdominal abscesses ( $p = 0.001$ ) and a 47% lower risk of UTI ( $p = 0.0011$ ).

## Meta-analysis of Immunonutrition- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Beale 1999</b> ( <i>CCM</i> ; 27(12):2799-2805)	Meta-analysis of 12 RCTs to examine the relationship between immunonutrition and infection rate, hospital stay and ventilator days in ICU patients.	Surgical, trauma and medical ICU patients	1582	10/12 studies used formulas containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard, high-nitrogen enteral formulas	ITT analysis showed the immunonutrition group had a 30% reductions in infection rate (p=0.006), a 3 day shorter LOS (p=0.0002) and were off the vent 2.6 days sooner (p=0.04).

## Studies Compendium- Immunonutrition Guidelines and Recommendations

Author	Study Objective	Patient population	Guideline/Recommendations	Grade
<b>McClave 2016</b> (JPEN;40(2):159-211.	SCCM/A.S.P.E.N. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient.	Adult ICU patients	*Suggest immune-modulating formulations (arginine with other agents including EPA, DHA, glutamine, nucleic acid) be considered perioperatively for SICU patients. (E2,O3,M1b) *Suggest routine use of an immune-modulating formula (containing both arginine and fish oils) in the SICU for the post-operative patient who requires EN therapy. (O3) *Suggest immune-modulating formulations containing arginine and fish oil be considered in patients with severe trauma. (M1b) *Immune-modulating formulations (arginine with other agents) are suggested for consideration in patients with traumatic brain injury (E2, M2b)	The GRADE system utilizes the quality of evidence (RCTs vs Observational studies) and a risk vs benefit analysis to determine whether the Guideline is a 'Recommendation,' a 'Suggestion,' or 'Expert Consensus Suggests.'
<b>Mariette 2015</b> ( <i>J Visc Surg;152 (Supp 1):S1-S22</i> )	Guidelines for perioperative nutritional support in gastrointestinal cancer	Adults having major elective surgery for GI Cancer	*Based on Grade A Evidence, immunonutrition (nutrition product containing a high protein, high energy mixture, supplemented with specific nutrients, mostly arginine, omega-3 fatty acids and nucleotides) should be given to all GI Cancer patients 5 to 7 days preoperatively, regardless of nutritional status. *Immunonutrition should be continued postoperatively in malnourished patients for 5 to 7 days or until patients are able to consume 60% of their needs orally.	Referenced to Grade A evidence
<b>McClave 2013</b> ( <i>JPEN; 37(Supp 1):99S-105S</i> )	Summary Points and Consensus Recommendations from the North American Surgical Nutrition Summit.	Adults having major elective surgery	<ol style="list-style-type: none"> <li>1. Increase metabolic preparation</li> <li>2. Do a preoperative nutritional risk assessment</li> <li>3. Give preoperative immunonutrition for 5-7 days</li> <li>4. Consider carbohydrate loading immediately preop</li> <li>5. Use protocols to implement surgical nutrition intervention</li> </ol>	Grade D, Consensus
<b>August and Huhmann 2009</b> ( <i>JPEN; 33(5):472-500</i> )	A.S.P.E.N. Guidelines on nutritional support during adult anti-cancer treatment.	Adult anticancer treatment patients and those undergoing hematopoietic cell transplantation	Guideline 10 "Immune-enhancing enteral formulas containing mixtures of arginine, nucleic acids, and essential fatty acids may be beneficial in malnourished patients undergoing major cancer operations."	Grade A Guideline references 10 studies using immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides.

## Studies Compendium- Immunonutrition Guidelines and Recommendations

Author	Study Objective	Patient population	Guideline/Recommendations	Grade
Weimann 2006 ( <i>Clin Nutr</i> ;25:224-244 )	ESPEN (European Soc of Parenteral and Enteral Nutrition) Guidelines on Enteral Nutrition: Surgery	Adults having major elective surgery	<p>"Use EN preferably with immuno-modulating substrates (arginine, omea-3 fatty acids and nucleotides) perioperatively independent of nutrition risk for those patients:</p> <ul style="list-style-type: none"> <li>•undergoing major neck surgery for cancer</li> <li>•undergoing major abdominal cancer surgery</li> <li>•after severe trauma."</li> </ul>	Grade A Guideline references 18 studies using immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides.

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### Immunonutrition and Surgery- Neutral Studies

Author	Study Objective	Patient population	(n)	Intervention	Control	Results	Note
<b>Mudge 2018</b> ( <i>BJS 2018</i> ; <i>published on-line</i> <i>DOI:</i> <i>10.1002/bjs.1092</i> 3)	Multicenter RCT with objective to compare preoperative and postoperative IM vs. standard nutrition and determine if immunonutrients or simply more calories/protein make a difference.	Esophagectomy; ~80% had neoadjuvant chemo/radio therapy; well-nourished by PG-SGA	n=276	1) Preop IM/Postop IM 2)Preop IM/Postop Std 3)Preop Std/Postop IM 4)Preop Std/Postop Std  (IM contained supplemental L-arginine, n-3 fatty acids and nucleotides)	Standard nutrition (isonitrogenous/ isocaloric)	No difference in infectious complications or LOS shown across groups.	A major limitation of the study which made the objective difficult to achieve was that significantly less protein was provided after surgery to the periop and postop IM groups [70%, 71% vs. 89% of needs (1.5 g/kg)], respective to the periop standard control. Further, all groups only received 62-64% of postop caloric needs. If immunonutrients, i.e. arginine, were increasingly used to meet protein/calorie needs, the benefits of using IM may be more difficult to identify. Patients were included from 11 centers across 24 surgeons, and this may have also introduced considerable variability in other protocols and technique.
<b>Hegazi 2014</b> ( <i>JACS</i> ;219(5):1078-1087)	Meta-analysis of 8 RCTs comparing preoperative immunonutrition (IM) with standard ONS and 9 RCTs comparing preoperative immunonutrition with regular diet to compare outcomes after major elective surgery.	GI Surgery	n=561 (IM vs. std ONS); n=895 IM vs.reg diet	16/17 studies utilized a formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Standard ONS; Regular diet with no supplementation	No difference in risk of complications or LOS was found when preop IM was compared with preop standard ONS. A decreased risk of infectious complications (p<0.01) and reduced LOS (p<0.01) was found when preop IM was compared to no supplementation.	The results of preop IM vs standard ONS conflict with those from the Marimuthu meta-analysis, a study where RCTs of immunonutrition were only included that used isocaloric/isonitrogenous controls. The preoperative studies compared by Hegazi et al and Marimuthu et al differ only in Hegazi's inclusion of the Giger-Pabst 2013 and Hübner 2012 studies. See below.

### Immunonutrition and Surgery- Neutral Studies

Author	Study Objective	Patient population	(n)	Intervention	Control	Results	Note
<b>Giger-Pabst 2013</b> (Nutr;29:724-729.	Double-blind RCT designed to evaluate a 3-day period of preop immunonutrition on outcomes in major elective abdominal cancer surgery.	Well-nourished patients (NRS<3). (9 esophageal, 13 gastric, 15 pancreatic, 11 hepatic, 35 colonic and 25 rectal)	108	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isocaloric, isonitrogenous standard oral supplement	No differences were noted in post-op complications overall nor in postop infectious complications. LOS did not differ between the groups	Average intake of preoperative immunonutrition supplementation was 1920 mL over three days, whereas a proven 5 day protocol = 3750 mL. Authors comment that it appears at least 5 days of preoperative and/or postoperative immunonutrition is needed to achieve a positive effect.
<b>Hübner 2012</b> (J Clin Nutr; 66(7):850-855)	Double-blind RCT designed to evaluate preoperative immunonutrition on postoperative morbidity in major abdominal surgery.	Upper and lower GI surgery patients with a nutritional risk score (NRS) ≥3. (22 UGI, 62 hepatobiliary, 46 colorectal and 15 misc. 30 if the procedures were laparoscopic.	145	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides in powder form	Isocaloric/ isonitrogenous standard oral supplement in powder form	At 30 days, no significant differences were noted in complications. Secondary endpoints of infections and hospital stay also did not differ between groups.	Compliance was comparable but poor for both groups with only 53% of intervention and 60% of control patients able to drink 2/3 of the prescribed amounts. Actual intake was below current recommendations in 43% of subjects, and may have been influenced by the products being powders vs. RTU. Previous studies (Braga Arch Surg 2002) show malnourished GI cancer surgery patients have better outcomes with perioperative use of



### Immunonutrition and Surgery- Neutral Studies

Author	Study Objective	Patient population	(n)	Intervention	Control	Results	Note
<b>Fujitani 2012</b> ( <i>BJS</i> ; 99:621-629)	Multi-center RCT that assessed effects of preoperative enteral immunonutrition given to patients having major upper GI surgery. Primary endpoint was surgical site infection.	Well nourished patients (<10% preop wt loss) having total gastrectomy due to cancer.	244	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional treatment	No significant differences were shown in SSIs or infectious complications overall.	Overall compliance to immunonutrition was 94.5%. Post-hoc subgroup analysis comparing patients with and without 5-10% preoperative weight loss across groups showed a 44% decreased risk of SSI in the immunonutrition group with weight loss (p=0.031). Another consideration is that given that all subjects were Japanese and the Japanese have a higher intake of n-3 fatty acids in their diet and presumably cell membranes, it may have been more difficult to see a treatment effect of preop immunonutrition in a well nourished
<b>Ghosh 2012</b> (e- <i>SPEN Journal</i> 7:e107-e114)	Double-blinded RCT undertaken to determine if perioperative immunonutrition supplementation was superior to standard formula in decreasing postoperative infections in head and neck oncology surgery patients.	Squamous cell carcinoma of the head and neck	57	Formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Isocaloric/isonitrogenous standard formula	No differences were observed between the groups.	Statistical considerations mentioned in the study show the need for 160 total patients to achieve statistically significant outcomes. With only 57 participants, the study was underpowered.

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<b>Finco 2007</b> ( <i>Surg Endosc; 21:1175-1179</i> )	RCT that followed loop relaxation, intestinal cleanliness, nutritional and immunologic parameters associated with use of perioperative immunonutrition and a low fiber diet.	Laparoscopic colorectal	28	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides, low fiber diet x 5 days preop. 3L of iso-osmotic laxative on day before surgery. Intervention diet for 3 days post-op, starting on PO Day 1.	Low fiber diet preop, 3L/d of iso-osmotic laxative for two days prior to surgery. Return to conventional diet on post-op Day 3.	There was s significant increase in CD4 lymphocytes on the day before surgery as compared with baseline in the intervention group ( $p < 0.05$ ), but no statistically significant differences between groups in regards to intestinal loop relaxation, cleanliness or in postoperative infectious complications.	A period of only 3 days of post-operative use may not have been sufficient to see a difference in infectious complications.
<b>Helminen 2007</b> ( <i>Scand J of Surg; 96:46-50</i> )	RCT purposed to determine if perioperative immunonutrition would decrease infectious complications after major GI surgery.	Primarily colo-rectal resection	100	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Conventional treatment	No significant differences were shown in infectious complications, complications overall or LOS.	Study was underpowered, in that authors comment that a power calculation showed the need for over 300 pts in each arm. Preoperative compliance to the study formula was good, but post-operatively only 30% of subjects reached the target of 12-15 doses.

### Other Studies of Interest

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
<b>Wachira JK 2014</b> ( <i>BJN</i> ;111:1652-1662)	Review article written after surveying recent publications that directly study the effects of n-3 fatty acids on bleeding risk or reported effects on bleeding while measuring different endpoints.	Multiple clinical settings including various surgeries, critical care, subarachnoid hemorrhage, MI, dialysis, statin therapy and sickle cell disease.	>30K	N/A	N/A	This overview found no support for discontinuing the use of n-3 fatty acid treatment before invasive procedures or when given in combination with other agents that affect bleeding. In several settings studied, use of n3 fatty acids improved clinical outcomes.
<b>Kassin 2011</b> ( <i>JACS</i> ; 215:322-330)	Retrospective chart review of factors associated with 30-day hospital readmission after surgery.	General surgery	1442	N/A	N/A	GI surgeries have highest incidence of readmission. Post-op complications increased risk of readmission by factor of 4, wound complications by a factor of 3.5. Surgical infection listed as an ICD-9 code reason for readmission 22% of the time.
<b>Harris 2007</b> ( <i>Am J Cardiol</i> ; 99(Suppl):44C-46C)	Review article of 19 trials addresses concerns about fish oil supplementation and bleeding.	Coronary surgery	4397	Doses ranged from 1.4 g/d to 6.9 g/d of combined EPA and DHA. Most of the study subjects were also given aspirin or other anticoagulation therapy such as warfarin.	Absence of fish oil (EPA and DHA) supplementation.	Concerns about clinically significant bleeding associated with fish oil supplementation are unfounded. As always, clinicians need to be aware of the amount of EPA and DHA administered and the time over which it is administered, and patients on anticoagulant therapy need to be monitored according to clinician orders.