

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

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Xu 2006 (<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).
Braga 2002 (<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.
Gianotti 2002 (<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). A significant reduction in LOS was also noted for the intervention formula group (p=0.01)

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Marano 2013 (<i>Ann Surg Oncol</i> ; July 10 2013 DOI: 10.1245/s1043401330881)	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).
Shirakawa 2011 (<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)
Suzuki 2010 (<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- γ , 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).
Okamoto 2009 (<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)	RCT 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-hemipancr-tectomy	40	Oral formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Iso-caloric, iso-nitrogenous 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, iso-nitrogenous 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-hemipancr-tectomy	154	Oral and tube-feeding formula containing supplemental L-arginine, n-3 fatty acids and nucleotides	Iso-nitrogenous, 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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Braga 1999 (<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
Braga 1998 (<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 ($p<0.05$)
Gianotti 1997 (<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, $p=0.004$ $p=0.01$)

Immunonutrition and Upper GI Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Senkal 1997 (<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
Kemen 1995 (<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
Daly 1995 (<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

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Braga 2002 (<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
Rowan 2013 (<i>Presented at the Triological Society 2014 Combined Sections Meeting (COSM)</i>)	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	177	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.	44% of standard of care patients registered complications vs 24% in the immunonutrition group (p=0.006). Complications included wound infection, pharyngocutaneous fistula, and free flap failure. Mean LOS was reduced by 3.2 days in those receiving immunonutrition (p=0.026).
Felekis 2010 (<i>Nutr and Cancer; 62(8):1105-1112</i>)	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.	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).
Sorenson 2009 (<i>The Laryngoscope; 119:1358-1364</i>)	Randomized double-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. 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.

Immunonutrition and Head/Neck Surgery- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Snyderman 1999 (<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

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Tepaske 2007 (<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.
Tepaske 2001 (<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 ≥70 years or had an ejection fraction of ≤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).
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 ≥70 years or had an ejection fraction of ≤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.

Health Economics for Immunonutrition and Surgery - Studies Compendium

Author	Study Objective	Patient population	(n)	Source of Cost Data	Intervention	Control	Results
Barker 2013 (<i>Euro J of Clin Nutr</i> ; 67(8):802-807)	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 AUD1576 in the intervention groups compared with the control (p=0.37).
Mauskopf 2012 (<i>WJSO</i> ; 10(136):open access)	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%.
Braga 2005 (<i>Nutrition</i> ; 21:1078-1086)	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 for Immunonutrition and Surgery - Studies Compendium

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Strickland 2005 (<i>JPEN</i> ; 29(1 Suppl):S81-S91)	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.
Farber 2005 (<i>JPEN</i> ; 29(1 Suppl): S62-S69)	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 (Δ 5 days) resulted in an average cost savings of \$11,382 per patient when comparing immunonutrition and control groups.
Senkal 1997 (<i>Crit Care Med</i> ; 25(9):1489-1496)	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
Burden 2012 (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 ($p=0.0003$).
Marimuthu 2012 (<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.
Cerantola 2011 (<i>Br J Surg</i> ; 98:37-48)	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 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.

Meta-analysis of Immunonutrition- Studies Compendium

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Drover 2011 (<i>J Am Coll Surg</i> ; 212(3): 385-399)	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 ($p < 0.00001$).
Marik and Zaloga 2010 (<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.

Meta-analysis of Immunonutrition- Studies Compendium

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Bozzetti 2007 (<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.
Waitzberg 2006 (<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).
Beale 1999 (<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% reduction 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
McClave 2013 (<i>JPEN</i> ; 37(Supp 1):99S-105S)	Summary Points and Consensus Recommendations from the North American Surgical Nutrition Summit.	Adults having major elective surgery	<ol style="list-style-type: none"> 1. Increase metabolic preparation 2. Do a preoperative nutritional risk assessment 3. Give preoperative immunonutrition for 5-7 days 4. Consider carbohydrate loading immediately preop 5. Use protocols to implement surgical nutrition intervention 	Grade D, Consensus
McClave 2009 (<i>JPEN</i> ; 33(3):277-316)	SCCM/A.S.P.E.N. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient.	SICU and MICU	Guideline E1. "Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, omega-3 fatty acids, and antioxidants) should be used for the appropriate population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis."	Grade A for Surgical ICU. Grade B for Medical ICU. Guideline references 8 studies using immunonutrition containing arginine/n3/nucleotides.
August and Huhmann 2009 (<i>JPEN</i> ; 33(5):472-500)	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.
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"> •undergoing major neck surgery for cancer •undergoing major abdominal cancer surgery •after severe trauma." 	Grade A Guideline references 18 studies using immunonutrition containing supplemental L-arginine, n-3 fatty acids and nucleotides.

Other Studies of Interest

Author	Study Objective	Patient population	(n)	Intervention	Control	Results
Kassin 2011 (<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.
Celik 2009 (<i>Eur J Gynaec Oncol</i> ; 4:418-421)	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 ($p < 0.05$).
Harris 2007 (<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.