Clinical study reference

Nestlé HealthScience

Evidence-based immunonutrition for the nutritional requirements of major surgery patients

IMPACT® Advanced Recovery is a food for special medical purposes specifically formulated for medical conditions where nutritional needs cannot be met by diet modification alone. Must be used under the supervision of a healthcare professional.

Information for healthcare professional use only.

Contents

Overview of IMPACT® Advanced Recovery

An evidence-based choice: IMPACT® Advanced Recovery is supported by extensive evidence showing positive outcomes in major elective surgery, including: Upper GI, Lower GI, Cardiac, Bladder Cancer, Gynaecological Oncology and Hip surgery.

Major guidelines support the use of immunonutrition:

- 2016 Critical Care Nutrition Guidelines (SCCM, A.S.P.E.N) recommends nutrition formulas containing immune-modulating nutrients perioperatively for major elective surgeries.[1]
- ESPEN recommends immunonutrition perioperatively for malnourished patients undergoing major cancer surgery.[2]
- Enhanced Recovery After Surgery (ERAS) Society recommends immunonutrition perioperatively in their guidelines for pancreaticoduodenectomy and colorectal cancer surgery.[3,4]

When compared to standard of care (SOC), use of IMPACT® products* in major elective surgery patients have shown reductions in the risk of:

37%
Surgical site infections
(p=0.005)[5]

44%
Anastomotic leaks
(p=0.004)[5]

54%
Abdominal abscesses
(p=0.001)[5]

47%
Urinary tract infections
(p=0.011)[5]

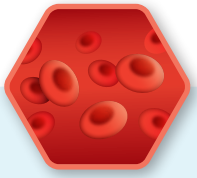
47%
Pneumonia
(p=0.001)[5]

1.9–2.7 days
Antibiotic use
(p=0.005)[6]

*From the IMPACT® product range, IMPACT® Advanced Recovery is the product that is available in Australia.

Mechanisms of action

IMPACT® Advanced Recovery contains a unique blend of three synergistic immunonutrients. This blend has documented outcomes in more than 80 publications, including several meta-analyses, which show these ingredients support the unique nutritional needs of the major elective surgery patient by helping support the immune and vascular systems to reduce the risk of postoperative complications.

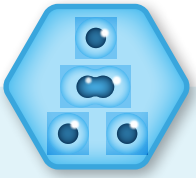


Arginine

- Enhances host immune response by promoting T-lymphocyte growth and replication, and nitrogen retention.[7–10]
- Increases levels of hydroxyproline, the main precursor for collagen, thereby playing a role during wound management.[7–11]
- Increases gut oxygenation and colonic microperfusion.[6]

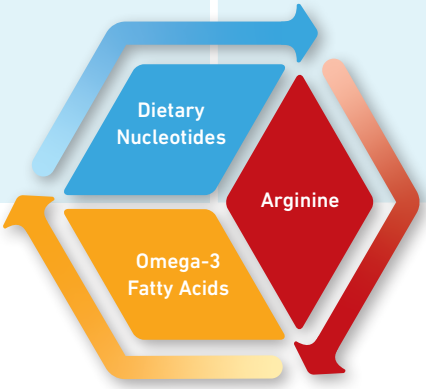
Omega-3 Fatty Acids (from fish oil)

- Modulate cytokines to produce less inflammatory and less immunosuppressive mediators.[12]
- May produce less inflammatory prostaglandins (PGE3) to help alleviate arginine deficiency by reducing induction of arginase 1.[13]



Dietary Nucleotides

- Support replication of the rapidly dividing cells of the immune system, i.e. T-lymphocytes, by providing a source of purine and pyrimidine bases for DNA/RNA production.[14,15]



Perioperative IMPACT® protocols benefit patients undergoing major elective surgery

It's a simple protocol:

Consume for 5 days before surgery and at least 5 days after surgery†.

†When oral consumption is reinitiated.

Clinical evidence of IMPACT® products by surgery type

The evidence in this folder comes from Oral IMPACT® and IMPACT® Advanced Recovery, which both contain the immunonutrients – arginine, fish oil and nucleotides. The recommendation for both products is to consume 3 serves for 5 days pre and postoperatively. Consuming IMPACT® Advanced Recovery provides higher amount of the immunonutrients than the Oral IMPACT® product per serve, therefore the benefits seen from consuming Oral IMPACT® would also be expected for IMPACT® Advanced Recovery. IMPACT® Advanced Recovery is the product that is available in Australia.

Bladder cancer surgery

PREOPERATIVE

Impact of preoperative immunonutrition on morbidity following cystectomy for bladder cancer: A case-control pilot study.

***World J Urol* 2014;32:233-237.**

Bertrand J, Siegler N, Murez T, Poinas G, Segui B, Ayuso D, Gres P, Wagner L, Thuret R, Costa P, Droupy S.

A prospective, multicentre, case-controlled pilot study to compare the rate of postoperative complications in patients with bladder cancer (n=60) who received preoperative immunonutrition (Oral IMPACT®) with those that did not prior to cystectomy. The immunonutrition group had a lower incidence of postoperative complications (40% vs. 77%; p=0.008) including paralytic ileus and infections than the control group. Mortality, pulmonary embolism, anastomotic fistula and wound dehiscence were similar between groups.

PERIOPERATIVE

Effects of immunonutrition for cystectomy on immune response and infection rates: A pilot randomized controlled clinical trial.

***Eur Urol* 2016;69(3):389-392.**

Hamilton-Reeves JM, Bechtel MD, Hand LK, Schleper A, Yankee TM, Chalise P, Lee EK, Mirza M, Wyre H, Griffin J, Holzbeierlein JM.

A pilot randomized controlled clinical trial to compare immune response and postoperative complications between a group of bladder cancer surgery patients (n=29) that received perioperative immunonutrition (IMPACT® Advanced Recovery Drink) vs. a group that received isocaloric perioperative oral nutrition supplement (ONS). The immunonutrition and control groups had myeloid derived suppressor cell (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 IMPACT® Advanced Recovery 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.

Cardiac surgery

PREOPERATIVE

Nutritional effect of oral supplement enriched in ω-3 fatty acids, arginine, RNA on immune response and leukocyte-platelet aggregate formation in patients undergoing cardiac surgery.

***Nutr Met Ins.* 2014;7:39-46.**

Iwase H, Kariyazono H, Arima J, Yamamoto H, Nakamura K.

RCT completed to investigate if preoperative use of immunonutrition (Oral IMPACT®) vs. no supplementation would influence immune response and leukocyte platelet formation in patients (n=14) having cardiac surgery. HLA–DR expression, CD4/CD8 ratio and the production of IFN–γ 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.

PREOPERATIVE

Glycine does not add to the beneficial effects of perioperative oral immune-enhancing nutrition supplements in high-risk cardiac surgery patients.

***JPEN.* 2007;31(3):173-180.**

Tepaske R, Velthuis HT, Oudemans-Van Straaten HM, Bossuyt PMM, Schultz JM, Eijsman L, Vroom M.

A prospective, randomized study to measure outcomes from the addition of glycine to an oral immune-enhancing nutrition supplement (Oral IMPACT® + glycine) as compared to a standard oral immune-enhancing nutrition supplement (Oral IMPACT®) and a control group receiving standard nutrition. Each nutrition supplement was administered for a minimum of 5 preoperative days. Patients (n=70) were 70+ years of age, had compromised left ventricular function or the need for mitral valve surgery. Outcomes of morbidity, organ function and postoperative recovery were analyzed. In both groups receiving the Oral IMPACT® formula, infectious morbidity was decreased (23%/17% vs. 50%) as compared to the control ($p=0.02$). Conclusions of the study were that use of preoperative Oral IMPACT® formula reduces the rate of infectious morbidity and results in more hemodynamic stability. The addition of glycine did not result in any additional benefit.

GI cancer surgery

PREOPERATIVE

Preoperative immunonutrition decreased postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy.

***Surg* 2014;155:124-133.**

Aida T, Furukawa K, Suzuki D, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Miyazaki M.

RCT to investigate the effect of preoperative immunonutrition (Oral IMPACT®) vs. early postop standard tube feeding on postop complications and immune response in patients having pancreatoduodenectomy (n=50). 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 favourable Th1/Th2 differentiation in the Oral IMPACT® group. This demonstrates a decrease in stress-induced immunosuppression.

PREOPERATIVE

Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition.

***World J Surg* 2009;33:1815-1821.**

Okamoto Y, Okano K, Izuishi K, Usuki H, Wakabayashi H, Suzuki Y.

RCT designed to evaluate the effect of preoperative oral immunonutrition (Oral IMPACT®) vs. postop isocaloric TPN on cellular immunity, duration of SIRS and postoperative complications after upper GI cancer surgery (n=60). Postoperative 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+Tcell counts decreased in both groups ($p<0.05$), however the CD4+T-cell counts on preop day 1 and postop day 7 were higher in the interventional than control group ($p<0.05$).

PREOPERATIVE

Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition.

***Surg Today* 2006;36:1063-1068.**

Horie H, Okada M, Kojima M, Nagai H.

Prospective study to measure the effect of preoperative immunonutrition (Oral IMPACT®) vs. no supplementation on surgical site infection (SSI) in patients with colorectal cancer (n=17). 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.

PREOPERATIVE & PERIOPERATIVE

Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer.

***Surgery.* 2002;132:805-814.**

Braga M, Gianotti L, Vignali A, Di Carlo V.

A prospective, randomized, controlled trial of 200 patients with colorectal neoplasm requiring surgical resection. The 4 groups were randomized to: Group 1, perioperative supplementation with Oral IMPACT® formula for 5 days preoperatively + Oral IMPACT® or IMPACT® tube feeding postoperatively; Group 2, preoperative Oral IMPACT® for 5 days; Group 3 (control), isonitrogenous/caloric oral supplement preoperatively for 5 days; and Group 4; no supplementation before or after surgery (conventional therapy). Immune response ($p<0.05$), gut oxygenation ($p<0.01$) and microperfusion ($p<0.02$) were found to be significantly better for Groups 1 and 2. Overall, Groups 1 and 2 fed IMPACT® formula both perioperatively and preoperatively had outcomes of decreased infectious complications ($p<0.02$ $p<0.04$); reductions in antibiotic therapy days ($p<0.005$, $p<0.004$) and length of hospital stay ($p<0.0005$), as compared to the control and conventional therapy groups.

GI cancer surgery (continued)

PREOPERATIVE & PERIOPERATIVE

Nutritional approach in malnourished surgical patients: A prospective randomized study.

***Arch Surg.* 2002;137:174-180.**

Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V.

Prospective, randomized, controlled trial of 150 patients requiring major elective surgery of the GI tract for malignancy. All enrolled patients were malnourished with ≤10% body mass loss and randomized to 3 groups. Group 1 (Perioperative Treatment Group) was supplemented preoperatively with 1 litre per day Oral IMPACT® formula for 7 consecutive days and tube fed with IMPACT® formula postoperatively. Group 2 (Preoperative Group) was supplemented with 1 litre per day of Oral IMPACT® formula for 7 consecutive days preoperatively and standard formula postop. Group 3 (Control Group) received standard tube feeding postoperatively. All formulas were isocaloric and isonitrogenous. ITT analysis reveals patients fed study formula preop and periop had decreased postop complications (28% and 18%, respectively) vs. the control group (42%, p=0.04, p=0.02, respectively). Reduction in LOS was observed in both intervention groups vs. control: 2.1 days in the preop group (p=0.01), and 2.8 days in the periop group (p=0.001).

Hip surgery

PREOPERATIVE

Multimodal perioperatrive care plus immunonutrition verses traditional care in total hip arthroplasty: A randomized pilot study.

***Nutrition Journal* 2016;15:34.**

Alito Aprelino M and de Aguilar-Nascimento JE.

Prospective, randomized pilot study to test the effect of adding preoperative immunonutrition (Oral IMPACT®) to multimodal perioperative protocols vs. traditional care in patients having elective total hip arthroplasty (n=32). 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 postoperative Day 2 were lower in the study than traditional group (66.5 mg/L vs. 80.6 mg/L; p<0.01).

Non-small cell lung cancer surgery

PREOPERATIVE

Is preoperative protein-rich nutrition effective on postoperative outcome in non-small cell lung cancer surgery? A prospective randomized study.

***J of Cardiothor Surg* 2016;11:14.**

Kaya SO, Akcam TI, Ceylan KC, Samancılar O, Ozturk O, Usluer O.

Prospective, randomized study to evaluate the benefit of a 10 day course of preoperative immunonutrition (Oral IMPACT®) vs. normal diet in well-nourished patients having anatomic resection for non-small cell lung cancer (n=58). Patients in the immunonutrition group reported fewer complications vs. the control group (19.4% vs. 44.4%; p=0.049). Study patients also reported a reduced chest tube drainage time vs. the control group, on average (4 days vs. 6 days; p=0.019).

Gynaecologic oncology surgery

POSTOPERATIVE

Post-operative enteral immunonutrition for gynecologic oncology patients undergoing laparotomy decreased wound complications.

***Gyn Onc* 2015;137:523-528.**

Chapman JS, Roddy E, Westhoff G, Simons E, Brooks R, Ueda S, Chen L.

Retrospective cohort study of postoperative immunonutrition (IMPACT® Advanced Recovery Drink) and no supplementation as a quality practice improvement for patients having laparotomy for gynaecological malignancy (n=338). 75% patient compliance to postop intervention was noted. Fewer wound complications were observed 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.

Meta-analyses including IMPACT® formulas

A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery.

***Ann Surg* 2012;255:1060-1068.**

Marimuthu K, Varadhan KK, Ljungquist O, Lobo DN.

Evaluate 26 RCTs on the effect immunonutrient combinations vs. isonitrogenous, isocaloric standard enteral formulas had on complications and LOS after open abdominal surgery. 15/26 trials utilized immunonutrition containing supplemental arginine, n-3 fatty acids and nucleotides (IMPACT® formulas). 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). This reduction was statistically significant in all subgroups: preoperatively (52%; P=0.001), perioperatively (47%; P=0.0004), and postoperatively (32%; P<0.00001). A sub-analysis of perioperative studies showed a 47% reduction in risk of postop 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 this evidence was low.

Perioperative use of arginine-supplemented diets: A systematic review of the evidence.

***J Am Coll Surg* 2011;212(3):385-399.**

Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PE, Ochoa JB, Heyland DK.

Thirty-five randomized controlled trials (n=3,438) of major elective surgical patients are reviewed in this meta-analysis to compare outcomes with enteral nutrition supplemented with arginine vs. standard formula. Twenty-five studies involved GI surgery patients and the other 10 studies represented other elective surgical procedures. Twenty-three of 35 studies utilized IMPACT® formula administered pre-, peri- or post-surgically. Although, no difference in mortality was noted, arginine-supplemented diets were associated with a 41% reduction in infectious complications (p<0.00001 and a 2.38 day reduction in length of stay (LOS) (p<0.00001), on average. Tests for heterogeneity were not significant in regards to reduced overall infectious complications (p=0.11), but were significant in regards to reduced LOS (p<0.00001). Sub-analyses found greater reductions in infectious complications and LOS associated with perioperative vs. pre- or postoperative use (p=0.03, p=0.001), and significant benefit associated with IMPACT® formula vs. other immunonutrition formulas (p<0.0001).

For example, IMPACT® formula reduced risk of infectious complications by 51% (p=0.00001), whereas other arginine supplemented immunonutrition did not reduce the risk significantly. Authors support implementing use of perioperative nutritional therapy containing arginine and omega-3 fatty acids to support considerable reduction in morbidity for high-risk elective surgery patients and a substantial reduction in costs for the health care system.

Postsurgical infections are reduced with specialized nutrition support.

***World J Surg.* 2006;30:1592-1604.**

Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Tsann-Long H, Mijares JM, Bihari D.

This article reviewed 17 studies (n=2,305) where IMPACT® formula was used before and/or after major elective surgery and the clinical outcomes reported were included in this meta-analysis. Ten studies compared preoperative or perioperative IMPACT® formula provision vs. control and 7 studies looked at postoperative nutrition. Fourteen studies examined IMPACT® formula used with gastrointestinal (GI) cancer surgeries. IMPACT® formula supplementation was associated with significant reductions in postoperative infectious complications (39–61%) and a significant decrease in hospital stay by an average of 2 days. Anastomotic leaks were found to be less prevalent in gastrointestinal surgery patients who received IMPACT® formula perioperatively. Overall, 500mL–1 litre of IMPACT® formula 5–7 days preoperatively contributed to improved outcomes in GI, cardiac, and head/neck elective surgery patients.

Health economics‡

Immunonutrition for patients undergoing elective surgery for gastrointestinal cancer: Impact on hospital costs.

***WJSO* 2012:10:136; doi:10.1186 1477-7819-10-136.**

Mauskopf JA, Candrilli SD, Chevrou-Séverac H, Ochoa JB.

This study was completed to create a health economic model to determine the impact on hospital costs of immunonutrition (IMPACT® formulas) used in patients having major elective surgery for gastrointestinal (GI) cancer. United States (US) hospital costs were taken from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (HCUP-NIP) database. These costs were used to estimate the effect of immunonutrition on hospital costs using reductions in length of stay (LOS) and risk of complications from a meta-analysis of 6 RCTs studying perioperative use of IMPACT® formulas in GI cancer surgery patients (n=889). Meta-analysis estimates show perioperative use of IMPACT® resulted in savings per patient of US$6000 when costs were based on reduction in LOS, and a US$3300 savings when costs were based on a reduction in infectious complications. The sensitivity analysis showed cost savings were present for baseline complication rates above 3.5%. When US baseline rates for LOS and infectious complications for upper and lower GI cancer surgery were inserted in the model, cost savings continued to present (range, US$1200 to US$6300). Use of immunonutrition for patients undergoing elective surgery for GI cancer was concluded an effective and cost-saving intervention.

‡The data was based on a US population, which may or may not be translatable into the Australian Healthcare System.

References

1. McClave et al. *J Paren & Enter Nut,* 2016.
2. Weimann A et al. *Clinical Nutrition,* 2017.
3. Lassen K et al. *Clin Nutr* 2012;31:817-830.
4. Gustafsson UO et al. *World J Surg.* 2019 Mar;43(3):659-695.
5. Waitzberg DL et al. *World J Surg* 2006;30:1592-1604.
6. Braga M et al. *Surg* 2002;132:805-14.
7. Ochoa JB et al. *NCP* 2004;19(3):216-225.
8. Zhu X et al. *Ann Surg* 2014;259(1):171-178.
9. Wu G et al. *Amino Acids* 2009;3(0)153-168.
10. de Aguilar-Nascimento JE et al. *Nutr* 2010;26(4):354-358.
11. Chow O and Barbul A. *Adv Wound Care* 2014;3(1):46-53.
12. Calder PC. *Biochem Biophys Act* 2015;1851:469-484.
13. Bansal V et al. *JPEN* 2005;29(1):S75-S80.
14. Grimble GK et al. *Curr Opin Clin Nutr Metab Care* 2001;4(1):57-64.
15. Hess JR and Greenberg NA. *NCP* 2012;27(2):281-294.

An oral nutritional formula specifically developed for the nutritional needs of patients at risk of infections

Contains dietary nucleotides, L-arginine and omega-3 fatty acids

Each drink (178mL) contains:

- **200** Calories
- **18g^** Protein
- **4.2g** Supplemental L-arginine
- **1.1g** Omega-3 (EPA+DHA)
- **430mg** Dietary Nucleotides

^Includes 4.2g L-arginine per 178mL.

IMPACT® Advanced Recovery is a food for special medical purposes specifically formulated for medical conditions where nutritional needs cannot be met by diet modification alone. Must be used under the supervision of a healthcare professional.

For more information call **1800 671 628** or visit **www.nestlehealthscience.com.au**

Information for healthcare professional use only. Printed in June 2020.

Nestlé HealthScience