Winnipeg Regional Health Authority / Office régional de la santé de Winnipeg
Caring for Health / À l'écoute de notre santé

PRACTICE ISSUE EVIDENCE SUMMARY

Best Practice Issue (state as a question, PICO):

Does Impact AR® (an immune-enhancing formula) reduce infectious complications and length of stay compared to standard formulas in elective surgery (head and neck and gastrointestinal) patients?

Member: WRHA Surgery RD Network (Kathy Vagianos, Heather Howie, Jacqueline Proulx, Jing Zuo, Stephanie Verleih, Leanne Lawless, Kim Hutchison, Laura Toews)	**Site:**

Purpose: (goals, scope, intended users, settings, and patient/client groups)

Issue: Immunonutrition has been associated with modulation of inflammatory response, enhancement of cell-mediated immune response, and up-regulation of gut function parameters early after surgery[1]. Early clinical trials showed that immunonutrition improves surgical outcomes in elective gastrointestinal cancer surgeries[2, 3, 4, 5]. Impact AR® is an example of an immune-enhancing enteral formula which is not currently on the WRHA formulary and therefore not available for use. In order to determine if including Impact AR® on the next enteral contract is warranted, a comprehensive review of the benefits of Impact AR® has been recommended.

Goal: To determine the effect of Impact AR® on surgical outcomes (infectious complications and hospital length of stay).

Intended users & settings: Dietitians & all Nutrition and Food Service staff; Surgeons; All nursing staff; Patients admitted for elective head and neck and GI surgery; Preoperative clinic staff.

Scope: Literature review is limited to Adults only. Studies where Impact products were administered via oral intake or feeding tube in elective head and neck and GI surgery patients are included. Studies including total parenteral nutrition as a part of intervention are excluded. Studies which did not report clinical outcomes (LOS, infection, post-operative complications) are excluded.

Definitions/ Abbreviations:

IN: Immunonutrition

LOS: Length of hospital stay

GI: Gastrointestinal

Pre-op: Pre-operative

Post-op: Post-operative

Peri-op: used both pre and post operatively

Arginine: a *conditional* essential amino acid; endogenous production may be inadequate during periods of growth, illness, or injury.

EPA (Eicosapentanoic Acid): an omega -3 polyunsaturated 20 carbon fatty acid molecule derived from linolenic acid. It is the precursor of sets of prostacyclins, prostaglandins, thromboxanes and leukotrienes that are considered less pro-inflammatory compared to those derived from omega-6 fatty acids.

DHA (Docosahexanenoic acid): an omega-3 polyunsaturated 22 carbon fatty acid derived from EPA. It is also the precursor of sets of prostacyclins, prostaglandins, thromboxanes and leukotrienes that are considered less pro-inflammatory compared to those derived from omega-6 fatty acids.

Nucleotides: organic molecules that consist of a nitrogenous base bound to a pentose and at least one phosphate groups. Nucleotides are the building blocks of DNA, RNA, ATP, and many metabolic regulators and coenzymes.[10]

Impact AR® (Impact Advance Recovery): is the immune-enhanced oral formulation that contains a unique and patented blend of arginine, omega-3 fatty acids (DHA+EPA), and nucleotides.

Impact products: general term that refers to any of the following enteral fomulations: Impact AR®, Impact®, Oral Impact®, Impact RTD®

Evidence Review: (Please list type and grade of evidence reviewed)

Background:

Despite significant changes in elective surgery techniques and new antimicrobial agents, post-operative infectious complications remain common, adding to length of hospital stay, and potential increase in mortality[1].

It has been well known that major abdominal surgeries lead to post traumatic dysregulation of the immune system characterized by suppression of immune functions. Causes of post-operative infection are multifactorial and dependent to an extent on the primary disease diagnosis, the type and the magnitude of the operation, length of operation, loss of blood, and malnutrition[6].

The benefits of nutrition provision in post-operative patients are traditionally thought to provide adequate macronutrients such as calories and protein for wound healing and to reduce the impact of catabolism. However, it has been theorized that due to the complex inflammatory, immune and oxidative responses during the post-operative period, providing specific nutrients in supraphysiological doses may provide vital substrates that modulate immune and metabolic responses and thus may improve clinical outcomes[7].

A term called Immunonutrition (IN) has become popular since the 1990s. It is used to describe the

administration of higher amounts of specific nutrients, or combinations of nutrients, that can aid to minimize the inflammatory response to surgery and tissue injury and can assist in restoring immune and inflammatory response to prevent infections and morbidity[8].

Glutamine, arginine, N-acetyl cysteine, branch-chain amino acids, nucleotides, long-chain omega-3 fatty acids, antioxidant vitamins, and taurine are the nutrients that have been considered as a component in immune-modulating artificial nutrition formulations. Among these nutrients, arginine, omega-3 fatty acids, and nucleotides have gained most of the attentions.

Arginine

Arginine serves as a substrate for the production of nitric oxide. Arginase and nitric oxide synthase compete for arginine as a substrate. The metabolic products of these enzymes are important modulators of T-cell function. Arginine also functions as a secretagogue, increasing growth hormone, insulin-like growth factor-1, and prolactin levels. Arginine is a conditionally essential amino acid as endogenous production will be inadequate during the periods of growth, illness, and injury[9].

Arginine is converted to nitric oxide (NO). A small amount of NO has an anti-inflammatory effect, however excessive NO production, due to NO synthase induction by inflammatory cytokines or bacterial endotoxins, has a pro-inflammatory effect by increasing vasodilatation. Arginine supplementation increases NO formation and the mitotic response of peripheral lymphocytes to standard stimuli in healthy subjects and postoperative patients. Some evidence suggest arginine in combination with other immunonutrients reduces infectious complications, days on a ventilator and length hospital stay, particularly in patients undergoing elective surgery[10]. However caution should be used in other patient groups. For example, an early meta-analysis suggests arginine may have a detrimental toxic effect in critical care patients[24].

Omega-3 fatty acids

Omega-3 fatty acids (EPA+DHA) have potent anti-inflammatory properties mediated through incorporation in cell membrane structure and function, suppression of pro-inflammatory transcription factors, and modulation of eicosanoid and cytokine production. These effects may play a significant role in suppressing the generalized inflammatory response and subsequent immunosuppression and capillary leakage after major surgery. Furthermore, resolvins and protectins are novel omega-3 fatty acids products derived from EPA and

DHA following neutrophil-endothelial interactions. These lipid mediators are reported to play a key role in the resolution of inflammation and the promotion of wound healing[1].

Nucleotides

Nucleotides are organic compounds that participate in nearly all biochemical processes as nucleic acid precursors (i.e. DNA, RNA), currency of energy (e.g. ATP), metabolic regulators (e.g. cAMP), coenzymes (i.e. NAD+, FAD, CoA), and activated intermediates in biosynthesis. During metabolic stress, large amounts of nucleotides are required to restore and sustain the immune system and GI mucosal trophism. Since *de novo* synthesis of nucleotides requires considerable energy, endogenous nucleotide production may become insufficient. Therefore, dietary nucleotides may be essential to restore and sustain tissues with rapid cellular turnover[10].

In most of clinical trials, nucleotides have been combined with omega-3 fatty acids and amino acids to form an immune-enhanced diet. It is difficult to assess the effect of nucleotides apart from the other additives.

IMPACT Products

Several immuno-enhancing enteral formulas using a combination of nutrients have been developed. Impact products are an example and are commonly used in clinical trials. Several *Impact* products have been used in clinical trials with slight modifications in the *impact name.* They all containe the active ingredients arginine, nucleotides, and long-chain omega-3 fatty acids. Impact AR® is available in Canada. Other products include Impact®, Oral Impact®, Impact RTD® and they are not available on Canadian market. Although these products all contain arginine, EPA/DHA, and nucleotides, the content varies only slightly. Table 1 illustrates the composition of all Impact products. It is also noted that the content of arginine, nucleotide, and omega-3 fatty acids may vary slightly depending on the location of manufacture, despite the product having the identical name. The biggest differences between Impact AR® and the rest of the products is that Impact AR® provides 1.4 kcal per ml and has a higher osmolarity versus 1.0 kcal per ml in the rest of the products.

Impact® was originally designed to be administered through a feeding tube; however it also has been used orally in pre-op subjects in studies. Oral Impact® is in powder form and designed for oral use with different flavors. Impact AR® can be used orally or administered through a feeding tube. No information is available for Impact RTD®.

Table 1. Summary of nutrition content of Impact products

	Impact AR®	Impact®	Oral Impact® Powder* (Tropical Flavor)	Impact RTD®
Caloric density (Kcal/L)	1.4	1.0	1.0	n/a
Osmolality (mOsm/kg water)	930	298	n/a	n/a
L-arginine (g/L)	17.7	13	13	n/a
EPA+DHA (g/L)	4.6	3.3	3.3	n/a
RNA (g/L)	1.8	1.3	1.5	n/a
Total Carbohydrate (g/L)	190	134	134	n/a
Protein (g/L)	75.6	56	56	n/a
Total Fat (g/L)	39	28	28	n/a

*information of Oral Impact is based on per 1000ml diluted with water (74g Oral Impact +250ml water)

Information of Impact® collected from Nestlé Health Science UK website

Information of Impact AR® collected from Nestlé Health Science CA website

Information of Oral Impact® collected from Nestlé Health Science UK website

Table 2. Major nutrient content per 1000kcal among three products

	Impact AR®	Impact®	Oral Impact® Powder* (Tropical Flavor)
Volume (ml)	714	1000	1000
L-arginine (g/L)	12.6	13	13
EPA+DHA (g/L)	3.29	3.3	3.3
RNA (g/L)	1.29	1.3	1.5
Total Carbohydrate (g/L)	135	134	134
Protein (g/L)	54	56	56
Total Fat (g/L)	28	28	28

Summary of study results

17 studies were found using products from the Impact family. Two studies examined patients with head and neck surgeries. One of them only had 8 subjects and no statistical analysis was performed therefore, it is not included in the summary below. The rest of studies all examined patient with elective GI surgeries. See Appendix 1 for summary of all 17 studies. The products used include Impact®, Oral Impact®, Impact AR®, and

Impact RTD®. Only one study used Impact RTD®. Only one study used Impact AR® which is the product required for review. Although the content of different formulas does vary slightly, they are comparable products, containing about 12.5 g Arginine, 3.3 g EPA+DHA, 1.3g Nucleotides, 134 g carbohydrate, 55 g protein, and 28 g of fat per 1000 calories (except Impact RTD® as no product information can be found). Use of Impact products pre-operatively and post-operatively generally ranged between 5 to 7 days.

Table 3. Studies that show a significant difference using Impact products vs non-significant difference

16 Studies	
Significant	**Not Significant**
Farreras et al. 2004[11] (post-op)	Giger-Pabst et al. 2010[13] (pre-op)
Marano et al. 2013[12] (post-op)	Hubner et al. 2012[14] (pre-op)
Xu et al. 2006[15] (pre-op)	Sakurai et al. 2007[17] (peri-op)
Okamoto et al. 2009[16] (pre-op)	Finco et al. 2007[19] (peri-op)
Braga et al 1999[2] (peri-op)	Helminen et al. 2007[6] (peri-op)
Senkal et al. 1999[5] (peri-op)	Barker et al. 2013[8] (pre-op)
Felekis et al. 2010[18] (peri-op)	Fujitani et al. 2012[20] (pre-op)
Braga et al. 2002[3] (peri-op, pre-op)	
Braga et al. 2002[4] (peri-op, pre-op)	

9 out of 16 studies support the use of Impact products whereas 7 studies fail to find any significant difference. Among the studies that support Impact, 5 out of the 9 studies demonstrated beneficial effects (decreasing LOS and infectious complications) when the Impact product was used peri-operatively. 4 out of 9 studies showed positive effects with the use of Impact products pre-operatively. Of these, two studies compared pre-op use with peri-op use and found that while pre-op use has benefit, it was most effective when delivered peri-operatively. Only 2 out of 9 studies demonstrated positive effects of Impact used only post-operatively.

Among the 7 studies that fail to find significant difference when using the Impact products, 4 studies out 7 showed that Impact products have no beneficial effect on outcomes when Impact products were given pre-op. 3 studies showed peri-op administration had no significant effect on outcomes. No studies in this group looked at post-op use of Impact products.

For the purpose of this review, the literature was reviewed to determine the potential clinical outcomes of Impact products compared to standard enteral formulas:

1. **Does post-op use of Impact products improve clinical outcomes compared to standard enteral formula? (No intervention pre-op)**

   Two studies[11, 12] compared the use of an Impact product to an isocaloric and isonitrogenous standard enteral formula 7 days post-operatively in patients with gastric cancer. They both found the use of Impact significantly reduced LOS (2-3 days) and infectious complications (from 20-30% to about 7%). No difference was found in mortality.

2. **Does pre-op use of Impact products improve clinical outcomes compared to standard oral supplements? (No intervention post-op)**

   Two studies[13, 14] compared the use of an Impact product to an isocaloric and isonitrogenous standard oral supplement 3-5 days pre-op in patients undergoing elective GI surgery. Giger-Pabst and coworkers examined well-nourished patients and Hubner and coworkers examined malnourished patients. Both of these studies reported that Impact product does not reduce LOS, infectious complications, total complications, and 30-day mortality.

3. **Does pre-op Impact + post-op standard EN improve clinical outcomes compared to pre-op + post-op standard nutrition support?**

   Xu et al. studied 60 patients with gastric or colorectal cancer. The study group received Impact® pre-op for 7 days and the control group received an isocaloric and isonitrogenous standard formula. Both groups received the same post-op early standard enteral feeds [15]. Okamoto et al studied 60 patients with gastric cancer. The study group received Impact® while the control group received an isocaloric but not isonitrogenous formula pre-op for 7 days. Both groups received early standard enteral feeds post-op[16]. Both of these two studies show significant reductions in infectious complications[15, 16]. The Xu study also reported significant reductions in LOS (3 days) but that finding was not reported in the Okamoto study.

4. **Does peri-op use of Impact products improve clinical outcomes compared to peri-op use of standard nutrition support? (Impact pre+post vs standard nutrition support pre+post)**

Three studies[2, 5, 17] were found to address this question. Braga and colleagues compared Impact product with an isocaloric and isonitrogenous control formula in colorectal, gastric and pancreatic cancer patients. It is confusing regarding the nutrient content of the Impact product and the control formula in the Senkal study which studied patients with upper GI cancer. They compared Impact with an isocaloric but likely not isonitrogenous formula. Senkal and Braga both reported Impact products reduced LOS and infectious complication[2, 5]. The study by Sakurai et al involving 30 patients with esophageal cancer failed to find any difference in LOS, and surgical site infection[17].

5. **Does peri-op use of Impact product improve clinical outcomes compared to post-op standard nutrition support? (Impact pre+post vs standard EN post-op)**

   Felekis et al. studied 40 patients requiring surgery for head and neck cancer. Impact was compared to an isocaloric but not isonitrogenous formula. This study did report significant reduction in total complications[18].

6. **Does peri-op use of Impact and pre-op use of Impact combined with post-op standard EN provide benefits compared to post-op standard EN? (Impact pre+post vs Impact pre-op+ standard EN post-op vs standard EN post-op)**

   Braga et al studied 150 malnourished patients with GI cancer[4]. An isocaloric and isonitrogenous standard enteral formula was used as the control. There is a trend for lower infectious complications but that was not statistically significant. They concluded that perioperative use of Impact seems to be the best approach to support malnourished patients with cancer[4].

7. **Does peri-op use of Impact products or pre-op Impact provide benefits compared to pre-op standard oral supplement? (Impact pre+ post vs Impact pre-op vs standard oral supplement pre-op)**

   Another Braga study included 200 patients who underwent surgery for colorectal cancer[3]. They compared a different pattern of the use of Impact to an isocaloric and isonitrogenous standard oral supplement. The conclusion is that peri-op use of Impact and pre-op use of Impact both reduce

infectious complication and LOS and that pre-op Impact use is as effective as peri-op use[3].

8. **Does the use of Impact products provide benefits compared to oral diet without standard nutrition oral supplement? (Impact pre+post or pre vs oral diet pre +post)**

Four studies[6, 8, 19, 20] compared the use of Impact product to oral diet without oral supplementation. 28 patients with colon cancer or diverticular disease in the Finco study consumed Impact peri-operatively. The control group was instructed to consume a low fibre diet[19]. Helminen et al compared peri-operative use of Impact to oral diet in 100 patients with GI cancer or benign disease[6]. These two studies failed to found any difference in LOS and infectious complication between peri-op use of Impact with oral diet. No difference was found in mortality.

The Barker study is the only study that used Impact AR. They compared pre-op use of Impact AR to regular diet without nutrition supplement in 95 patients with gastrointestinal surgery[8]. Fujitani et al examined 244 patients with gastric cancer. The study group consumed Impact pre-operatively and the control group was regular diet without nutrition supplement[20]. Both of these also failed to find any difference in terms of LOS, infectious complication[8, 20].

Discussion

Major abdominal surgeries induce post traumatic immune dysregulation which increases the risk of post-operative infection. Post-operative infectious complications add to length of stay and possibly may increase mortality. Causes of post-op infection are multifactorial and dependent on the primary disease, the type and the magnitude of the surgery, length of operation, loss of blood, and malnutrition. The intent for the use of immunonutrition is to minimize patients' immune suppression by providing adequate vital immune modulating substrates thus reducing post-op infection and complication rates.

This review focused on post-operative infectious complications and length of stay as end points. It is noted that the definitions of post-op infectious complications is not universal. For example, Sakurai et al included only pneumonia, surgical site infection and SIRS without clear diagnostic criteria of each of them. Farreras et al., however, included infection of the subcutaneous catheter, surgical wound infection, intra-

abdominal abscess, pneumonia, urinary tract infection, primary bacteremia, and clinical sepsis. Reported infectious complications ranged from 12.5% to 30% in control groups, 6.7% to 28% in the Impact groups. Hence, the post-op infectious complications may not refer to the same definition of "infectious complications" amongst the various studies.

Hospital length of stay is an alternate and perhaps "softer" marker for clinical outcomes. It may vary due to other non-clinical reasons, such as mobility issue or other social reasons. Furthermore, due to the heterogeneous patient populations among the 17 studies reviewed in this summary (oral pharyngeal to upper GI, liver, pancreas to lower GI, from laparoscopic surgery to open surgery) the hospital stay varies significantly. Reported LOS ranged from 6.8 days to 31 days in the control groups. Reported LOS ranged from 7.1 to 26.6 days in the Impact groups.

Compliance to the study products (Impact or standard enteral) also needs to be questioned; Only 5 studies report level of compliance to a prescribed formula. Two Braga studies reported over 82% compliancy[3, 4]. Helminen reported 90% patients consumed 12-15 doses (15 doses in total) pre-operatively, but low post-op compliance with only 30% of patients consuming the 12-15 doses in first five days post-operatively[6]. Hubner study reported 53-60% compliance[14]. Barker study reported 91% of compliance[8].

Common exclusion criteria amongst the studies reviewed included: patients with known organ failure such as heart, liver, lung, and kidney as well as patients with sepsis or pre-existing infections; patients with metabolic disorders or history of immunosuppressive, chemotherapy or radiation therapy; patients with known immunological diseases; patients with evidence of widely spread metastatic disease. Given the extensive conclusion criteria, it is uncertain how the Impact product will benefit to patients with above conditions, especially those with existing infection or sepsis.

Overall based on the results from 16 studies reviewed, there appears to be an almost equal split as to the efficacy of Impact products on decreasing LOS and infectious complications. It is noted that there is no effect on mortality but not every study reported mortality. There is some evidence that peri-operative use of Impact products may have the greatest potential. Two Braga studies[3, 4] suggest peri-op and pre-op use both have benefits. More recent studies have focused on pre-op use of Impact products; however, several of

them[13, 14, 8, 20] fail to confirm the suggested benefits. Whether pre-op use is as good as peri-op use needs further research. The two studies[11,12] reviewed for post-op use of Impact did showed benefits. These seem consistent with the most recent meta-analysis published in January 2014. Osland and coworkers reviewed 20 randomized controlled clinical trials that used arginine-containing formulations in elective GI surgical population. They excluded the studies involving parenteral provision of arginine. Impact products account for 65% of the studied products. They concluded that statistically significant reductions in infectious complications and length of stay were found with perioperative and postoperative administration with no difference in post-op mortality with the provision of immunonutrition irrespective of timing of administration. Meanwhile they do address the high heterogeneity and publication bias present in these data that makes it difficult to draw concrete conclusions[22]. Another meta-analysis was done by Cerantola et al and published in 2011[23]. This was a review addressing exclusively the GI surgical population and the timing of immunonutrition. They concluded that peri-op use of enteral IN decreases morbidity and hospital stay and therefore its routine use can be recommended[23]. However the critique is that they included studies that use nonequivalent controls. This may product outcomes that appear to favor pharmaconutrition independent of the role of immune-enhancing components.

Whether or not malnourished patients may get more benefits compared to well-nourished patients remains uncertain. The primary reason is due to the inconsistence definition of malnutrition. Several studies defined malnutrition as weight loss more than 10%.[4,18] Other studies use Nutrition Risk Screen 2002 or nutritional status assessed according to ESPEN guidelines.[12, 13] Hence without a consistent definition of malnutrition it is difficult to make conclusion about the benefits of Impact on malnourished vs. well-nourished patients. Finally, whether or not Impact studies demonstrate clinical benefits depends on the comparison of the control diet. Several peri-op studies[15, 16, 2, 5] did compare Impact products to standard enteral formulas where all patients received early post-op feeding. All of these studies found benefits of using Impact products. One study compared Impact pre-op with standard oral supplement pre-op and concluded that Impact has a better effect than standard oral supplement pre-op[3]. However, four studies show no difference when Impact products compared to an oral diet.

Conclusion

The results are not consistent within the 16 studies reviewed although there is a favor in the use of Impact peri-operatively in elective GI surgical population. Only one study reviewed Impact AR® that is currently available in Canada. We are unable at this time to determine the best patient population to drive benefit from IN and the timing of optimal administration remains in question. There is too much conflicting evidence to warrant regular use of Impact AR® at this time. Further studies are required.

Including Impact AR® on the WRHA formulary would allow for future research in local clinical trials to further evaluate the potential benefits suggested by the available literatures.

Recommendations:

1. Impact AR® is not recommended for routine use due to inconsistent results from current literatures.
2. Impact AR® is recommended to be included on the WRHA formulary for the purposes of clinical nutrition research

Practice Changes:

- There is no practice change at this point as there is inadequate evidence to recommend routine use of Impact AR®.
- Impact AR® may be investigated in clinical research in one or more of the following settings:
    1. Impact AR® may be trialed in the outpatient/preoperative clinics prior to admission to hospital for elective GI and head and neck surgery in non-immune compromised patients who have not receive chemo and/or radiation therapies.
    2. Impact AR® may be trialed post-operatively in hospital for enteral feeding (oral or tube feeding) in patients without obvious signs of infection.

Anticipated Impact:

It is not suggested at this time that Impact AR® for routine use in GI surgical patients. However, for demonstrative purposes, this is the potential impact of instituting this formula to all (**Health Sciences Centre numbers only**):

Number of patients:

- April 1 2012 – March 31 2013: 234 cases of adult inpatients with GI or Biliary surgery for cancer. The average length of stay was 15.64 days.

Cost ($) of Impact AR:

- $XXX/ml
- Dosage recommendation = 500 ml – 1000 ml / day 5 to 7 days pre operative; 5 to 7 days post operatively
- Therefore, in hospital (post operatively) the cost per patient would range $ XXXX to $XXXX per day, for 5 to 7 days.

Recommendation for implementation:

- Use Impact AR® in a potential future research trial.

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These recommendations are being reviewed by:

Appendix 1: Summary of 17 studies

Author	Year	Population	Intervention	Outcome	Comments
Senkal et al.[5]	1999	N=154 Upper GI cancer (esop, stomach, duodenum, pancrease and other)	-**Impact®** vs control formula (isocaloric, but not isonitrogenous -Pre-op both groups orally drank 1L/d x 5 days, post-op EN started 12 hours post-op x 5 days (goal reached by day 5)	-%pt with complication: Impact group 12.8% vs control 23.7% (P=0.08) After post-op day 3, the number of pt developed complication was lower in Impact group (P=0.04) -significant fewer infectious complication events 14 in Impact group vs 27 in the control group (p=0.05) -LOS: Impact group 22.2 days vs control 25.8 days (P=0.09) -higher EPA/DHA serum level	-confusing composition for the formula Impact and the control. (10 g protein different per liter between pre/post Impact product, Impact group and control group) -CF started in both group on post-op day 5-7
Braga et al.[2]	1999	N=206 Colorectal, gastric, or pancreatic cancer	-**Impact®** vs standard NS (isocaloric and isonitrogenous) -2 groups drank either Impact or standard NS 1 L/d x 7 days pre-op, resume same formula 6 hrs post-op until post-op day 7	-Post-op infection in eligible patients: Impact 11% vs control 24% (P=0.02) -LOS: Impact 11.1 days vs control 12.9 days (P=0.01) -total complication rate Intent-to treat Impact group 14% vs control 30% (P=0.009) -% pt with complication: both malnourished and well-nourished impact group lower than their control (P=0.05) -No difference in post-op non-infectious complications -IL 6 and CRP ↑ post-op, but rose lesser extent in the Impact group	-Malnutrition is defined by ≥10% UBW lost -171 patients were eligible to complete the study -standard formula used in the control group was not commercially available - more patients reported adverse effect in the control group (21% vs Impact 14%)
Braga et al.[3]	2002	N=200 Colorectal Ca	-**Oral Impact®** vs Standard NS(isoenergetic isonitrogenous) vs no NS -4 groups Peri: pre-op drinking Oral Impact 5 days 1L/d, post-op continue Pre-op: pre-op drinking Oral Impact 5 days 1L/d Control: pre-op drinking Standard	-LOS peri-op 9.8 days vs pre-op 9.5 days vs control 12 days vs conventional 12.2 days P<0.0001 vs control and conventional; P<0.0005 vs control and conventional. -Infectious complication: peri-op 10% vs pre-op 12% vs control 32% vs conventional 30% (P<0.02 vs control and conventional; P<0.04 vs control and conventional) -IL6 ↑ less in 2 Oral Impact groups -Intraoperative colon microperfusion significantly higher in Oral Impact groups -Better gut oxygenation associated with 2 Oral Impact groups	-well designed study included more detail information(gut oxygenation, micro perfusion) -mean pre-op intake compliance: 890ml, 905ml, 915ml -82% pt in peri-op group reached the goal 1500ml/d post-op -the mean time to resume oral solid food diet is 4.2,3.9,4.0,4.4 days

			NS 5 days, 1L/d Conventional: no NS		
Braga et al.[4]	2002	N=150 Malnourished Gastrointestinal Ca (esophagus, stomach, pancreas, colorectal)	-**Oral Impact®** vs Standard EN (isoenergetic isonitrogenous) -3 groups Peri-op: pre-op 7 days oral impact 1L/d +post-op oral impact via feeding tube Pre-op:Pre-op 7 days Oral Impact 1L/d+ Std EN formula Control:post-op standard EN +oral diet	- LOS: peri-op 12 days vs pre-op 13.2 days vs control 15.3 days (* P=0.04 vs the pre-op and P=0.001 vs the control; P=0.01 vs the control group) -total complication rate: peri-18% vs pre-op 28% vs control 42% (P=0.02 vs the control group) -Infectious complication: Peri-op 10%, pre-op 16%, control 24% (not significant) -Mean pre-op oral supplement intake 910ml no difference between 2 groups -mean weight loss pre-op 13% -the rate of gastrointestinal adverse effect same among 3 groups -post-op 92%patients reached goal calorie	-heterogeneous patients including gastric, pancreatic, esophageal, and colorectal resection -Malnutrition is defined by ≥10% UBW lost in past 6 months
Farreras et al.[11]	2004	N=66 (60 completed) Gastric cancer	-Impact® vs Isosource Protein -post-op x 7 days Impact group day1 480ml, day2 750ml, day 3 1200ml Isosource P group day1 400ml, day2 625 ml, day3 1000ml	-LOS: Impact group 13 days vs control 15 days (P=0.02) -% pt with infectious complication: Impact group 6.7% vs control 30% (P=0.01) -%pt with complications: Impact group 13.3% vs control 43.3% (P=0.01) -The feeding group was the only significant predictor of the presence of any post-op complication.	-pre-op weight loss, age, gender, surgical time are not associated with the wound complications -both groups received similar amount of calorie and protein per day -Impact group patients younger, weight heavier, had higher caloric intake and higher basal metabolism at base line
Xu et al.[15]	2006	N=60 Gastric or colorectal Ca (gastrectomy 38%)	-**Impact®** vs Standard formula (isoenergetic, isonitrogenous) -Pre-op 7 days of Impact vs Standard enteral formula -Post-op all pts received std enteral formula	-% of total case with complication: Impact group 6.7% vs standard group 26% (P<0.05) -LOS: Impact group 9 days vs standard 12 days (P<0.05) -No significant difference in postop noninfectious complication between 2 groups. -Post-op IgG level and CD4/CD8 ratio was significantly higher in the Impact group -PALB and TRF were significantly higher in the Impact group on post-op day 7	-No clear description on post-op feeding, when feeding start, last for how long. -No information regarding compliance

			-Amount is not clearly		
Finco et al.[19]	2007	N=28 Colon Ca or diverticular disease (50% ca pts)	-**Oral Impact®** vs low fibre diet -Pre-op 6 days of oral Impact 750ml/d x 6 days, post-op day 1 resume Impact x3 days, then conventional diet -Oral diet group post op day 3 resume oral diet	-LOS: Impact group 7.7 days vs control 6.8 days (not significant) -% pt with infection: Impact group 21% vs control 21% (not significant) -Wound infection: Impact group 14% vs control 7% (not significant) -higher CD4 in impact group pre-op and continue high post-op	-Extensive exclusion criteria (DM, current infection, any organ function insufficiency, IBD, etc -small study -all patients received laparoscopic colorectal surgery -more male than female (20 vs 8)
Helminen et al.[6]	2007	N=100 Gastrointestinal Ca or benign diseases (majority colorectal resection)	-**Impact®** vs oral diet -Pre-op oral Impact 900ml/d x 5 days, post-op Impact x 5 days + oral diet -Oral diet group received no OS pre-op and resume oral intake post-op day 3	-LOS: Impact group 10 days vs control 9 days (not significant) -%pt with complications: Impact 28% vs control 24% (not significant) -Infectious complication: Impact 14% vs control 16% (not significant) -no difference in mortality	-exclusion criteria was age younger than 16 and pregnancy -Impact group: higher pre-op compliance 90%patient drank 12-15 doses, the rest drank 5-11 doses, lower post-op compliance 30% patient reached 12-15 doses in first five days, the other drank 0-11 doses, 2 patients could not eat anything in the first 2 post-op days
Sakurai et al.[17]	2007	N=30 Esophageal Ca	-**Impact®** vs Ensure -study groups drank either Impact or Ensure 3 days pre-op plus regular diet -EN using either of the formula started within 24 hours post-op and start with 250kcal/d and progressively increased and last for 14 days with	-no difference in serum total amino acid concentration post-op in 2 groups -Serum ornithine (metabolite of arginine) was significant higher in Impact group -Serum EPA concentration tends to be higher in Impact group and significantly higher in post-op day 7. No difference in DHA concentration between 2 groups -No difference in IL-6 and CRP concentration between 2 groups post-op -IgG significantly higher in Impact post-op day 3 -CD4/CD8 ratio significantly higher in Impact group -No difference in systemic inflammatory	-small study -did not give detail for different complications -shorter pre-op administration and longer post-op administration

			oral intake	response syndrome, the interval of the start of oral intake -LOS: Impact group 26.6 days vs control 31.3 days (not significant) -surgical site infection: Impact group 6.3% vs control 21.4% (not significant)	
Okamoto et al.[16]	2009	N=60 Gastric Ca	-**Impact®** vs MEDIF(isoenergetic formula) -Pre-op 7 days 750ml/d Impact or MEDIF -post-op patients received standard nutrition support(detail unclear)	-LOS: Impact group 23.8 days vs MEDIF group 25 days (P=0.22) -% pt with infectious complication: Impact group 7% vs MEDIF 28% (P=0.039) -the duration of SIRS significantly shorter in Impact group -CD4 in both group significantly decreased post-op, CD4 of Impact group significantly higher than control group on post-op day7	-no details regarding post-op feeding -did not report the nutrient composition of MEDIF and compliance to both formulas
Felekis et al.[18]	2010	N=40 Head and neck Ca	-**Impact®** vs Nutrison -Control: post-op Nutrison, reach goal rate on Day4 -Impact group:pre-op Impact x 5 days. Post-op Impact x8 days	-No significant difference in IL-6, TNF, CRP, fibrogen, alb, pre-alb among groups -Significant ↓ complication rate in total number of patients received Impact (P<0.05) and in particular subgroup with well-nourished patients	-Little detail regarding actual supplement consumption -No clear definition regarding minor complications and major complications -small trial -Malnutrition defined by ≥10% weight loss in the past 6 months, 30 well-nourished and 10 malnourished -majority subjects are male (36/40)
Giger-Pabst et al.[13]	2012	N=108 well-nourished Gastrointestinal Ca (esoph, stomach, pancreas, liver, colorectal, 55% were colorectal)	-**Impact RTD®** vs standard OS (isocaloric, isonitrogenous) - Impact group: pre-op oral Impact RTD 750mlX 3days -Control group: std oral supplement 750mlX 3 days	-No difference in 30-day mortality rate -No difference in post-op non-infectious complications, the type of complication, length of ICU/IMC stay -infectious complication: Impact group 15% vs control 17% (P=0.79) -% pt with any complication: Impact 29% vs control 30% (P=1.00) -LOS: Impact 12 days vs control 11.6 days (P=0.08) -No difference in the type of post-op antibiotic use and the duration of the use -Mean oral supplement intake Impact 640ml vs standard 660ml	-patients heterogeneous including pancreas and liver, over 50% colorectal -Nutrition status was assessed by Nutrition Risk Screen 2002 -No information regarding post-op feeding -No information for the composition of Impact RTD and standard oral supplement -Intervention duration(3days) is shorter than most of other studies

Hubner et al.[14]	2012	N=145 Malnourished gastrointestinal surgery (benign and malignant)	-**Oral Impact®** vs Meritene (isocaloric, isonigrogenous) -Impact group: pre-op Oral Impact tid X 5 days -Control group: pre-op Meritene tid X 5 days -amount not specify	-Intent-to-treat -%pt with complication: Impact 53.4% vs control 45.8% (P=0.408) -Infectious complication: Impact 17.8% vs control 12.5% (P=0.488) -LOS: Impact 19 days vs control 16 days (P=0.345) -Significant increase in serum arginine in Impact group -Post-op IL-6 and IL-10 were prominently increased within 24 hours post-op, no difference after that -No difference in CRP and WBC counts -Compliance with oral supplements: 53% Impact group and 60% control group	-Compliance to oral supplements were low just half of the subjects, subgroup analysis compared patients with adequate intake to the rest showed no difference -Not clear actual intake of the oral supplements -nutritional status was assessed by NRS, Many patients identified may due to older age instead of nutritional status -did not exclude patients with ongoing infection required antibiotics -heterogeneous patient populations, 42.7% hepatobiliary
Fujitani et al.[20]	2012	N=244 well-nourished Gastric Ca	-**Impact®** vs regular diet -Impact group:Pre-op Impact 1L/d x 5 days +regular diet -Control group: regular diet	-No difference in post-op complications: Impact group 30.8% vs control 26.1% -No difference in infectious complication: Impact 25% vs control 24.3%) -LOS: Impact group 18 days vs control 17 days (P=0.395) -Impact favorable to patients with body weight loss ≥5% -Compliance with Impact 94.5%	-Definition of well-nourished: <10%weight loss -extensive list of post-op complications -no post-op feeding information
Marano et al.[12]	2013	N=109 Gastric cancer	-**Impact®** vs Jevity 1.0 -Post-op EN groups (Impact and Jevity 1.0) x 7 days	-Shorter duration of SIRS (P=0.036) -Infectious complications: Impact group 7.4% vs Jevity 20% (P=0.041) -LOS: Impact 12.7 days vs Jevity 15.9 days (P=0.029) -No difference in mortality -No difference in nutrition parameters -reduction of CD4 in Impact group was significantly higher -Nutritional goal was reached in all patient	-no control to pre-op status, post-op diet initiation followed regular process from CF to solids -pt received same calorie and protein -EN reached goal on day 5 -Nutritional status assessed according to ESPEN guidelines, but did not define well-nourished or malnourished patients
Turnock et al.[21]	2013	N=8 Head and neck cancer scheduled for radical resection of the oral cavity, pharynx or larynx	**Oral Impact® + Impact®** vs Isosource standard -2 groups Impact group: pre-op taking Oral Impact 900ml/d X 5 days, post-op EN Impact x 5 days	-No difference in average caloric intake between group, but median daily protein intake in the Impact group was significantly higher than in the Isosource group?? -EPA+DHA/AAratio significantly higher in Impact group post-op -No difference in CRP, TNF - Median LOS was 10 days in Impact group and 21.5 days in Isosource group	-Impact group post-op intake not consistent, mix of Oral Impact and Impact -Isosource standard provides different amount of protein(1.2 concentration with 43 g of protein per L) -patients defined as well-nourished based on total body protein status -pilot study with extremely small sample size

			Control group: post-op Isosource standard via feeding tube X 5 days		
Barker e t al.[8]	2013	N=95 Gastrointestinal surgery (91% lower GI Sx, 21%malnourished defined by SGA)	-**Impact AR®** vs no NS -Pre-op Impact AR 237mlx3/day x 5 days -Control group has no NS	Intent-to-treat -LOS Impact group 7.1 days vs control 8.8 days (P=0.11) -patient categorized by nutrition status, LOS ↓ 4 days in malnourished pts (P=0.21) -%pt with complication Impact group 15.2% vs Control 20.4% (P=0.60) -30-day wound infection Impact group 10.9% vs control 20.4% (P=0.26)	-Compliance with Impact AR use is 91% - No post-op feeding information - Compared malnourished patients and well-nourished patients - Under power trail, required 150 patients instead of 95 - Low total complication rate and low absolute LOS compared to other studies -include hernia repair, ostomy reversal (22% of pts)