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Enhanced Recovery Protocols: An Update

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Introduction
Traditionally, patients following major intestinal resection have remained in hospital for up to two weeks during which time their oral intake was restricted, mobility impaired and analgesia was very reliant on parenteral opioids. In the late 1990s a number of investigators, most notably Kehlet’s group from Denmark, developed the concept of ‘fast track’ surgery. Their philosophy was to employ a combination of epidural or spinal anaesthesia with early mobilisation and oral feeding on the basis that these interventions would reduce the stress response to surgery and aid rapid recovery. The results of many largely observational studies seemed to confirm the benefits of such a ‘fast track’ approach.

These principles were further developed in our unit by adopting the concept of ‘multimodal optimisation’ of perioperative care. Our results were published in two prospective randomised studies which confirmed the benefits of such an approach and demonstrated that such benefit was not simply related to the use of epidural anaesthesia. In the last decade a number of studies have been reported all confirming the benefits of such a multimodal approach to perioperative care. The term ‘Enhanced Recovery after surgery’ is now most commonly used to describe this modern approach to surgical management.

Enhanced Recovery protocols are a combination of evidence-based peri-operative strategies which work synergistically to expedite recovery after surgery. These strategies include, for example, a curtailed pre-operative fast, pre-operative carbohydrate loading, pre-emptive analgesia and early post-operative mobilisation together with expedited re-introduction of diet and fluids. Although each of these individual strategies is beneficial to some extent on its own, to achieve maximum benefit they have to be used together in the form of a package.

Using Enhanced Recovery protocols, post-operative stays following colorectal resection can be safely reduced to around two to four days. This expedited discharge is not achieved by lowering the prerequisites for release from hospital, but rather by fulfilling standard discharge criteria earlier due to an accelerated post-operative phase. The advantages of Enhanced Recovery have been repeatedly borne out in a number of randomised clinical trials and meta-analyses. The underlying mechanism of Enhanced Recovery protocols is thought to be an attenuation of the peri-operative stress response, although there is increasing evidence to suggest that benefits of Enhanced Recovery are actually mediated by return of organ, particularly gut, function. The purpose of this paper is threefold: to present the various components of enhanced recovery along with the rationale behind their inclusion; to suggest strategies to facilitate their implementation and compliance in day-to-day clinical practice, and; to propose directions for future research.

Specific emphasis shall be given to Enhanced Recovery in colorectal surgery as a reflection of the majority of research having been performed in this field. Many of the strategies are, however, transferrable to other branches of surgery. It is also noteworthy that different Enhanced Recovery protocols have been trialled and validated in the literature. They have all been shown to produce similar results, suggesting that protocols can be tailored to take into account local requirements and available resources.

Components of Enhanced Recovery protocols and current recommendations

Components of Enhanced Recovery protocols can be broadly categorised into pre-operative, peri-operative and post-operative interventions.

Pre-operative components

1. Pre-operative counselling and training
Counselling necessitates close collaboration between all members of the surgical team and the imparting of both written and verbal information. Provision of this information to patients may occur in the out-patient clinic, the preassessment clinic or the patient’s home. Patient information leaflets on Enhanced Recovery should be produced to facilitate patient education. Information discussed should include:
   i. What enhanced recovery involves, its core components and envisaged benefits;
   ii. What the patient should expect during the course of the hospital stay. This should include specifics of how Enhanced Recovery is implemented locally and which modalities are employed;
   iii. Specific issues which may delay discharge (such as lack of social support);
   iv. Clear and specific instructions should be given about mobilisation, early introduction of diet and breathing exercises. Active participation of the patients themselves in their recovery should be sought, and daily targets for the patient to achieve should be set up;
   v. Patients who may require a stoma should be identified and appropriately trained such that they are proficient at stoma care, ideally prior to surgery.

Pre-operative information and education has been shown to improve patient satisfaction, allay anxiety and improve pain and other outcomes.
2. Curtailled fasting and preoperative carbohydrate loading

Fasting for a minimum of eight hours before a general anaesthetic has been normal surgical practice for many years. It aims to reduce the volume and acidity of stomach contents, thereby reducing the risk of regurgitation or aspiration. Recent studies, however, have demonstrated that a short (three hour) period of fasting after ingestion of clear fluids is safe and more acceptable to patients. This minimises patient thirst and improves post-operative wellbeing. A short fast in combination with pre-operative carbohydrate loading has been shown to maintain nitrogen balance and reduce post-operative insulin resistance. Any commercially available preparation may be used. However, care should be taken that the formulation used is clear and residue-free.

Special circumstances: Non-insulin dependent diabetics: pre-operative carbohydrate loading has been shown to be safe in non-insulin dependent diabetic patients, and their use is also recommended in this subgroup of patients. In diabetic patients, a pre-operative carbohydrate load has not been shown to result in adverse effects such as hyper-glycaemia or delayed gastric emptying. However, monitoring of blood glucose levels should be carried out at regular intervals.

3. Avoidance of mechanical bowel preparation

Oral mechanical bowel clearing has traditionally been thought to reduce the severity of sepsis in the event of an anastomotic leak. However, a number of meta-analyses have suggested that, in patients undergoing colorectal procedures, the avoidance of mechanical bowel preparation is safe and does not result in increased sepsis in the event of an anastomotic leak. Additionally, the use of mechanical bowel preparation can result in serious adverse events, such as fluid imbalance, in certain patient subgroups, including the elderly. We recognise that the evidence for omitting bowel preparation in patients undergoing rectal surgery alone is equivocal.

4. Deep vein thrombosis prophylaxis

A single daily dose of low molecular weight heparin is recommended for deep vein thrombosis prophylaxis because of its ease of administration and lower risk of bleeding complications. The use of low molecular weight heparin in conjunction with graduated compression stockings was found to be the most effective anti-thrombosis prophylaxis in a recent Cochrane review. There is an increased risk of thrombotic complications up to one month after surgery, due to a hypercoagulable state, and prolonged (up to one month after discharge) antithrombotic prophylaxis with low molecular weight heparin confers significant benefit in terms of reduction of thrombotic complications.

5. Antibiotic prophylaxis

Antibiotic prophylaxis is used to reduce the rates of wound infection after surgery. Multiple doses have not been found to confer any additional advantages and result in increased costs and risk of infections such as Clostridium difficile. For this reason, a single dose of antibiotics covering both aerobic and anaerobic organisms should be administered just prior to incising the skin in all clean procedures which do not involve the insertion of prosthetic materials. When deciding the type of antibiotic used, local resistance patterns should be considered. Increased risk of acquiring a Clostridium difficile infection after using a third generation cephalosporin should also be considered. In those who are known to be carriers of MRSA (Methicillin resistant Staphylococcus aureus), prophylaxis with a glycopeptide antibiotic (Vancomycin, Teicoplanin) should be considered.

Peri-operative components

1. High inspired oxygen concentrations

Molecular oxygen is required by polymorphonuclear cells to produce free radicals which form an important line of defence against pathogens. In addition, it plays an important role in the synthesis of collagen for wound healing and angiogenesis. Higher tissue oxygenation levels in the immediate post-operative period as a result of 80% inspired oxygen have been shown to improve perfusion at the anastomotic site and reduce the risk of surgical site infections. In addition, there is some evidence that it may also reduce post-operative nausea and vomiting (PONV), although this is contentious.

2. Prevention of hypothermia

General anaesthesia can disrupt the normal thermoregulatory processes and result in hypothermia. In addition, exposure of the patient to the cold theatre environment also contributes. Hypothermia (core temperature less than 36°C) can, in turn, lead to an increase in the incidence of surgical site infections, thought to be due to peripheral vasoconstriction induced hypoxia and an altered immune response. Other undesirable effects of hypothermia include coagulopathy, increased cardiac morbidity and increased levels of circulating catecholamines with a resultant exaggerated catabolic response. Active prevention of hypothermia during the peri-operative period has been shown to reduce blood loss and prevent infective and cardiac complications.

For these reasons, hypothermia should be actively prevented using warm-air blankets. Warming should be continued for as long as the patient is in recovery. If the procedure is expected to last for more than an hour, then warmed intravenous fluids should be used. An oesophageal probe should be used during the procedure for measurement of core body temperature.

3. Goal-directed intra-operative fluid therapy

A degree of intra-operative splanchnic hyperfusion may go undetected with conventional monitoring, and this plays an important role in post-operative delay of return of gut function. The administration of excessive amounts of fluid during surgery can also result in delayed return of gut function and cardiac morbidity. An oesophageal Doppler probe is a minimally invasive method of determining the hemodynamic status in the peri-operative period and allows guided fluid management targeted against indicators of cardiac output. The intra-operative use of an oesophageal Doppler probe has been shown to accelerate the return of gut function and expedite discharge after surgery. The haemodynamic status of the patient should first be optimised using an oesophageal Doppler probe such that maximum cardiac output is achieved. Further boluses of colloids (on a background of maintenance fluids) should then be administered against variations in stroke volume (SV) and velocity of blood flow in the descending aorta (FTc). If resources do not permit the universal use of oesophageal Doppler, then its use may be restricted to high risk (ASA 3 and above) and elderly patients. A schema for administering Doppler guided fluid is shown in reference 41. Other minimally invasive methods of optimising the fluid balance include LiDCO plus™ and LiDCO rapid™ and may be used instead of the oesophageal Doppler. These systems depend on a lithium dilution technique to measure changes in haemodynamic parameters, such as cardiac output and stroke volume, and provide continuous real-time measurements.

4. Surgical approach and incisions

Laparoscopic colorectal techniques have been shown to improve outcomes over similar open surgery techniques. These improvements include an earlier return of organ function, reduced post-operative analgesic requirement and an earlier...
discharge from hospital. However, the major trials which have compared laparoscopic to open colorectal surgery have not taken Enhanced Recovery into account and have, instead, compared laparoscopic surgery to conventional open surgery. A recent review which examined the potential added benefits of the laparoscopic approach over and above open surgery with Enhanced Recovery found little evidence of additional benefit.

A large multicentre study which investigated the impact of Enhanced Recovery in both open and laparoscopic surgery (LIFA study) found a marginal benefit, in terms of length of hospital stay for the combination of the laparoscopic approach in the context of an Enhanced Recovery management protocol. When undertaking open procedures, a number of considerations need to be borne in mind. Short transverse incisions are thought to be less painful, impair lung function to a lesser extent, and reduce subsequent post-operative analgesic requirement when compared to vertical wounds. In addition, there is some evidence that the incidence of wound dehiscence may be reduced in transverse incisions. These were the conclusions of a Cochrane review in 2005. However, the results of a recent large randomised trial did not find that transverse incisions were less painful than longitudinal ones.

5. Avoidance of post-operative drains and nasogastric tubes
Nasogastric tubes may be painful and cause considerable discomfort. This can render post-operative mobilisation difficult. There is good evidence that routine use of nasogastric decompression delays the return of gut function, leads to an increase in pulmonary complication and fever and prolongs hospital stay.

These findings are supported by at least two meta-analyses. Abdominal drains have been traditionally placed to evacuate post-operative collections at the site of surgery and drain any possible anastomotic leak. However, similar to nasogastric tubes, they cause considerable discomfort and can hinder mobilisation. Moreover, at least three meta-analyses have revealed that routine prophylactic drainage of the abdominal cavity does not confer any advantages.

6. Short duration of epidural analgesia and local blocks
Epidural analgesia directly attenuates the post-operative stress response and promotes the return of gut function by blocking the sympathetic activity. However, this sympathetic blockade can result in hypotension due to vasodilatation which can prove difficult to manage as it may not respond to intravenous fluids. In these situations, an early decision to transfer the patient to a high dependency unit must be taken and inotropic or vasopressor support initiated. Another disadvantage is that the equipment can interfere with post-operative mobilisation. Whenever epidurals are utilised, these should be initiated at the beginning of the procedure and continued for a maximum of 48 hours. Weaning from epidural analgesia should start 12 hours post-operatively. The role of epidural analgesia in relation to laparoscopic colorectal surgery is not clear. A small number of studies have questioned the use of epidural analgesia in the setting of laparoscopic surgery. However, a small number of trials have produced contradictory results and have shown that additional advantages may be obtained when epidurals and laparoscopic surgery are used together. The current evidence level is weak and insufficient to advocate the universal use of epidural analgesia in laparoscopic colorectal resection.

Alternatives to epidural analgesia include transversus abdominis plane (TAP) blocks and other infusions with local anaesthetic such as the ‘PainBuster’. This latter device has recently been shown to be associated with effective post-operative analgesia.

We have preliminary evidence to suggest that the use of epidural/spinal anaesthesia may be associated with reduced splanchnic flow and are of the view that we are likely to move away from the routine use of this type of regional anaesthesia in the near future.

Post-operative components
1. Avoidance of opiates and the use of Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS)
It is our view that early return of gut function is an important factor in the effectiveness of Enhanced Recovery protocols. Many of the interventions associated with Enhanced Recovery are known to have a direct or indirect effect on gut function. Opiates delay the return of gut function and should be avoided whenever possible. In addition, they can cause considerable post-operative nausea and vomiting (PONV). Opiate minimisation should include the avoidance of Codeine and Tramadol preparations as well as opiate-containing patient-controlled analgesia (PCA) infusions. In their stead, patients should be prescribed paracetamol and NSAIDS, if there are no contraindications to their use. Opiates should be used only for purposes of rescue analgesia. Liberal use of anti-emetics should be employed, but the limitation of these medications in expediting the recovery of post-operative gut function should be recognised.

2. Early post-operative diet
Traditionally, oral diet and fluid has been reintroduced cautiously and gradually after bowel surgery, often rendering the patients nil by mouth or on oral sips only for many days in the post-operative period. This, it was thought, was necessary for adequate healing of bowel anastomoses. However, recently, early introduction of diet and fluids (within 24 hours post-operatively) has been shown to be safe. In addition, there is some evidence that early feeding may be beneficial in reducing the risks of anastomotic dehiscence, infections and reducing the length of stay. Tolerance to early feeding provides a more objective evaluation of gut function than assessment on the basis of bowel sounds or passage of flatus.

3. Early post-operative mobilisation
Even short periods of immobilisation can lead to deleterious consequences such as thromboembolism, loss of muscle strength, pulmonary atelectasis and worsening of pulmonary function. Continuous patient education regarding the benefits of mobilisation is recommended. It was shown in a randomised trial that avoidance of bedside entertainment systems is one pragmatic approach to encourage mobilisation.

4. Restricted amounts of intravenous fluid
During the post-operative phase, intravenous fluids may be required as long as adequate oral fluid intake has not been achieved and/or epidural catheters are still in situ. However, excessive amounts of intravenous fluid should be avoided. A daily regime of 1.5 to 2.5 L should suffice for most patients. The ability of individuals to get rid of accumulated sodium is greatly curtailed in the post-operative period. For this and other reasons, balanced intravenous solutions such as Hartmann’s should be prescribed in preference to Normal Saline (0.9% NaCl) in an attempt to avoid sodium overload, hyperchloremic acidosis and a delayed return of gut function.

5. Audit
A perceived disadvantage of many Enhanced Recovery protocols is that, by discharging patients home sooner, one is simply transferring their responsibility on to primary care providers whilst also predisposing patients to higher re-admission rates. This has not been borne out in trials, where the emphasis was to enhance patients’ recovery in preference to ‘fast tracking’ patients through their hospital stay. Re-admission rates after Enhanced Recovery implementation should not exceed 10%. Additionally, a
Compliance
Enhanced recovery programmes require a multi-disciplinary approach and co-ordination. This can render their initiation and implementation difficult. Compliance to these packages has often been reported to be low, especially in the post-operative period, and outwith the remits of clinical trials. Factors which can facilitate the introduction and implementation of enhanced recovery pathways and improve protocol compliance include:

1. Selected anaesthetic input
Patients should be managed by a selected group of anaesthetists who are committed to the concept of enhanced recovery.

2. Patients should be managed on specific wards
The management of patients by a select group of medical and nursing staff trained in the principles of enhanced recovery may improve compliance. If resources permit, specialised units dedicated to implementing Enhanced Recovery called ‘Enhanced Recovery Units’ should be set up. This may facilitate the organisational aspects of running Enhanced Recovery protocols. Such units can also play a role in patient education, where patients are continuously reminded of the importance of their active participation in the success of enhanced recovery. This may be facilitated by direct staff contact as well as by using appropriate posters and pamphlets.

3. Continuous staff education
The majority of strategies of Enhanced Recovery pathways are simple measures which can be implemented by junior medical and nursing staff. Therefore, whenever junior medical staff rotate into a unit that practices enhanced recovery, targeted teaching sessions should be held to ensure that all staff are familiar with the practices of the unit.

4. A multidisciplinary team approach
An Enhanced Recovery team should be in place and should comprise one or more surgeons, anaesthetists, nurses, dieticians and physiotherapists. These individuals should be ‘signed up’ to the concept of enhanced recovery. In the majority of hospitals, it should not be necessary to expand the workforce to formulate such teams and a reconfiguration and collaboration of existing services should be sufficient. The Enhanced Recovery team may replace and take over the role of other previously existing teams such as the Pain Management Team whose members can, in turn, be trained to be a part of the new Enhanced Recovery team. This would ensure that aspects such as pain control are dealt with in accordance with the principles of Enhanced Recovery.

5. A local champion
Successful implementation of enhanced recovery packages necessitates a local ‘champion’. Such a person is essential to co-ordinate the various aspects of enhanced recovery packages from pre-assessment until discharge. This may be any senior member of the Enhanced Recovery multi-disciplinary team outlined above.

Conclusions and future developments
It is important to emphasise that there is nothing unique to the Enhanced Recovery process. It is merely an amalgam of modern approaches to perioperative care. It is not per se a different approach to caring for surgical patients. This is important because it emphasises that Enhanced Recovery will evolve as our understanding of responses to surgical stress develops and new evidence becomes available about the benefits of nutritional or metabolic interventions.

In this regard it is interesting to note that there is increasing evidence to suggest that pre-operative conditioning with glutamine, gut specific nutrients or antioxidants may be of value. We have preliminary evidence pointing to a benefit from pre-operative iron supplementation. There is no doubt that the Enhanced Recovery of the future will be very different to which we recommend today.

References


Preoperative carbohydrate treatment

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Introduction
For more than a century, dogma and tradition have dictated that patients should be kept “nil per os” for up to 12 hours prior to the induction of anaesthesia in the hope of preventing aspiration of gastric contents. This dogma was based on sparse anecdotes rather than firm evidence and all it achieves is to present the patient to the anaesthetist in a dehydrated state and to make the patient more prone to develop postoperative insulin resistance. Lord Lister recognised the deleterious effects of prolonged fasting prior to surgery when he wrote in 1883: “While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef-tea about two hours previously.” This plea went largely unheeded till recently when a number of national anaesthetic societies have recommended a 6 hour preoperative fast for solids and a 2 hour fast for clear liquids.

Claude Bernard first reported hyperglycaemia as a metabolic reaction to stress in 1877 and from the work of David Cuthbertson in the 1930s, it has been recognised that surgery evokes a metabolic stress response similar to that seen in trauma and starvation. One of the components of the metabolic response to surgery is the development of insulin resistance, which leads to hyperglycaemia, which may be a protective adaptive response if no intervention is instituted. However, in the clinical setting, insulin resistance is generally regarded as deleterious, as chronically elevated glucose concentrations can be responsible for some of the morbidity associated with surgery, such as infections and prolonged length of hospital stay.

Measures to attenuate the development of postoperative insulin resistance may, therefore, be of clinical benefit. Preoperative treatment with complex carbohydrate drinks up to 2 hours prior to the induction of anaesthesia is one such strategy to decrease postoperative insulin resistance. This review describes some of the mechanisms by which starvation and surgical stress lead to insulin resistance and examines the benefits of preoperative carbohydrate treatment on surgical outcome.

Insulin resistance and clinical outcome
Insulin resistance is a state in which there is decreased responsiveness of skeletal muscle, adipose tissue and the liver to the biological actions of insulin. The development of postoperative insulin resistance is clinically significant as it is associated with prolonged hospital stay and greater postoperative morbidity and mortality. A recent prospective study of 273 patients (130 with diabetes) undergoing elective cardiac surgery has shown that for each 1 mg/kg/min decrease in intraoperative insulin sensitivity, there was increased incidence of major complications (odds ratio, OR [95% confidence intervals, CI] 2.23 [1.3-3.85], P<0.004), death (OR 2.33 [0.94-5.78], P=0.067), severe infection (OR 4.95 [1.48-16.8], P=0.01) and minor infection (OR 1.97 [1.27-3.06], P=0.003).

The stress response to injury sets off a series of reactions, including rapid neuroendocrine responses, release of stress hormones, and activation of the cytokine and immune reactions, which lead to mobilization of energy substrates, resulting in a general catabolic state. In elective surgery, these metabolic changes can be reversed by the use of insulin. However, in the postoperative situation, several-fold higher doses of insulin are needed to achieve the same metabolic effects as preoperatively, indicating a state of postoperative insulin resistance. Interestingly, when targeting and achieving normal glucose concentrations with insulin infusion, free fatty acid levels, urea excretion, and substrate oxidation are all normalized, showing that treating postoperative insulin resistance can normalize insulin action and also the main components of metabolism.

Glucose intolerance after surgery was reported by Åärima in 1974 and insulin resistance was first reported after traumatic injury by Black et al in 1982, and later by Henderson et al. Ljunghqvist and co-workers in Stockholm have investigated insulin resistance extensively in the elective surgical setting during the 1990s and showed increasing insulin resistance with greater magnitude of surgery and that the resistance remained for at least a couple of weeks after abdominal surgery of moderate magnitude. They also found that during the early phase of postoperative insulin resistance, the defect was mainly in glucose uptake in the muscle, where the glucose transporters GLUT4 were not activated in a normal way by insulin. More recent work has shown that the intracellular signalling pathways to activate GLUT4, including phosphatidylinositol 3-kinase are down regulated while other signalling systems activating the inflammatory responses are up regulated in muscle and fat tissue during surgery.

While patients with diabetes have a higher risk of complications, recent data have shown that it is seems not be the diabetes per se that represents the risk but rather the glucose levels. Doenst et al showed that the risk of postoperative death was related to the peak glucose level, and it remained the same for both patients with preoperative diabetes and those without diabetes. In another study of over 9000 patients undergoing elective surgery for colorectal cancer peak glucose on the day of surgery and the first postoperative day predicted the risk for complications, in particular cardiovascular events and infectious complications. Again, the degree of the glucose elevation rather than diabetes per se was the risk factor.
Elevated HbA1c as an indicator of disturbed glucose control preoperatively was associated with about 1 mmol/l higher glucose throughout the first five days after colorectal surgery. These patients also suffered a significantly higher rate of complications, mainly infections. Hence, the literature shows a very close association between glucose levels shortly after surgery and outcomes, in particular infectious and cardiovascular complications. With treatment using insulin lowering glucose levels many of these complications are reduced.

**Preoperative carbohydrate treatment**

Overnight fasting leads to thirst, hunger, headaches, and anxiety and preoperative treatment with oral complex carbohydrates can obtund these effects. Most people have breakfast shortly after waking up, leading to the release of insulin, which not only effects the storage of nutrients but also a change in the oxidation from fat to carbohydrates, while also activating glucose transport into muscle and fat and glycogen and fat storage as well as protein anabolism. The most obvious way to change metabolism from the overnight fasted state to the fed state is to give a carbohydrate load. This was initially done using 20% glucose intravenously at a dose of 5 mg/kg/min, and later a mixture of complex carbohydrates as an oral drink. Intake of such drinks completely reverses the setting of overnight fasting while stimulating glucose uptake, shutting down gluconeogenesis, and thus transferring the patient to a much more anabolic state before the onset of the surgical stress. This increase in insulin sensitivity continues in the postoperative period.

It is important to note that the carbohydrate used must be complex such as maltodextrins rather than glucose or sucrose and the minimum dose required is 50 g (in 400 ml). The recommended dose is 100 g (800 ml) on the night before surgery and 50 g (400 ml) 2 hours prior to the induction of anaesthesia. A number of studies have demonstrated the safety and metabolic effects of preoperative carbohydrate treatment. Preoperative ingestion of clear carbohydrate-based drinks is safe (the drinks empty from the stomach in 1.5-2 h), increases liver glycogen reserves, reduces intraoperative plasma non-esterified fatty acid concentrations, and attenuates the development of postoperative insulin resistance by up to 50%, respectively. Recent studies have demonstrated the latter may occur secondary to effects on gene and protein expression, insulin signalling and mitochondrial β-oxidation. Specifically, preoperative treatment with carbohydrate-based drinks in patients undergoing laparoscopic cholecystectomy was associated with a 4-fold reduction in glucose transport into muscle pyruvate dehydrogenase kinase 4 (PDK4) mRNA and PDK4 protein expression, respectively. PDK4 acts to inhibit the mitochondrial enzyme pyruvate dehydrogenase complex resulting in decreased carbohydrate oxidation (COX). As defective glucose disposal (i.e. reduced COX) is a key feature of postoperative insulin resistance, the aforementioned study suggested a possible cellular mechanism by which preoperative carbohydrate treatment attenuates postoperative insulin resistance. Another randomised study of 52 patients undergoing elective colorectal surgery demonstrated that preoperative carbohydrate treatment resulted in enhanced tyrosine kinase activity, phosphorylated-inositol 3-kinase and protein kinase B expression, the cellular pathway responsible for most of the metabolic actions of insulin, the aforementioned changes being associated with decreased postoperative insulin resistance. Finally, preventing excessive or incomplete mitochondrial β-oxidation, which is characterized by perturbed carnitine homeostasis resulting in elevated plasma carnitine concentrations, is suggested to be another mechanism by which preoperative carbohydrate treatment attenuates postoperative insulin resistance. The risk of aspiration is related to the patient’s comorbidity rather than the time of fasting, with the exception of patients with slow gastric emptying.

**Clinical effects of preoperative carbohydrate treatment**

Several studies have examined the effects of preoperative carbohydrate treatment in different elective surgical situations and the results have been conflicting, with some showing benefit and others no benefit. A recent meta-analysis of 21 randomised controlled studies on patients undergoing elective surgery has helped clarify some of these issues. This meta-analysis demonstrated a significant reduction in length of stay amongst patients undergoing major open abdominal surgery. Preoperative carbohydrate treatment was safe (no occurrence of drink-related complications), associated with reduced development of postoperative insulin resistance but the latter was not associated with any effect on surgical complications. The results of this meta-analysis are summarized in Table 1.

The main limitation of this meta-analysis was the relatively weak design of many of the included studies whose quality, as assessed by GRADEpro, was rated as low to moderate. There were small numbers and significant heterogeneity in the design and magnitude of surgery in many studies of preoperative carbohydrate treatment that precluded their inclusion in this meta-analysis. The definitions of outcomes such as complications and reporting of events varied between studies.

Findings from the meta-analysis indicated preoperative carbohydrate treatment was not associated with an increase in drink-related complications; confirming the safety of utilising oral complex carbohydrate drinks of appropriate osmolality preoperatively. Several countries have already updated their preoperative guidelines to recommend preoperative carbohydrate treatment due to its perceived beneficial effects on insulin resistance and wellbeing. This meta-analysis also suggests that, in addition to the aforementioned benefits, faster recovery (decreased length of hospital stay) in patients undergoing open major abdominal surgery may also be expected. Preoperative carbohydrate treatment, as part of a multimodal enhanced recovery protocol, is recommended by the Enhanced Recovery After Surgery (ERAS)® Society. When employing several components of the ERAS recommendations, a recent meta-analysis demonstrated a reduction in length of stay of 2.5 days, in keeping with recent data that suggest the beneficial effects on reduced recovery time and complication rates accrued in an almost stepwise fashion with increased compliance and utilisation of ERAS components. Interestingly, in the latter study the components that affected outcomes were preoperative carbohydrate treatment and avoidance of fluid overload.

**Conclusion**

There are presently limited data on the effects of preoperative carbohydrate treatment in patients who are obese (body mass index >30 kg/m²), ASA grade ≥ III, have diabetes, or are undergoing emergency surgery. Data from non-diabetic patients undergoing elective surgery suggest that although preoperative carbohydrate treatment reduces postoperative insulin resistance, these effects do not uniformly translate into benefit on clinical outcome. However, in patients undergoing major abdominal surgery peroperative carbohydrate treatment may reduce hospital stay by a day. When combined with other interventions incorporated in ERAS protocols, hospital stay may be reduced by as much as 2.5 days.
**Table 1: Effects of preoperative carbohydrate treatment on surgical outcome**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>No. of Studies</th>
<th>Carbohydrate group (No. of patients)</th>
<th>Placebo/fasted group (No. of patients)</th>
<th>Risk Reduction (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>9</td>
<td>355</td>
<td>523</td>
<td>0.88 (0.50, 1.53) – favours CHO</td>
<td>0.64</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
<td>Mean difference (95% CI)*</td>
<td></td>
</tr>
<tr>
<td>All patients (12)</td>
<td>509</td>
<td>689</td>
<td></td>
<td>-0.19 (-0.46, 0.08)</td>
<td>0.16</td>
</tr>
<tr>
<td>Major abdominal</td>
<td>319</td>
<td>443</td>
<td></td>
<td>-1.08 (-1.87, -0.29)</td>
<td>0.007</td>
</tr>
<tr>
<td>surgery</td>
<td>174</td>
<td>232</td>
<td></td>
<td>0.00 (-0.03, 0.03)</td>
<td>0.97</td>
</tr>
<tr>
<td>Surgery w ith expected length of stay ≤ 2 days (3)</td>
<td></td>
<td></td>
<td></td>
<td>0.48 (0.23, 0.73)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>16</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Negative value favours CHO, positive value favours placebo/fasted group

**References**

5. Bernard C., Lecin F. Les fonctions de la glycolyse et la glycolyse animale. 1877; Parvis: Bailliere. 120.
Evidence-based approach to nutrition in upper gastro-intestinal surgery

C Mariette, MD, PhD
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Abstract
Malnutrition is frequently observed in upper gastrointestinal cancer surgical patients, an independent predictor of postoperative morbidity and mortality and leads to both increased length of hospital stay and hospital costs. Evidence-based literature offers high evidence for the implementation of standard nutritional support in malnourished patients and immunonutrition in both well- and malnourished patients in the perioperative setting. The enteral route should be preferred in the postoperative setting and also in the preoperative setting, through a percutaneous ostomy or feeding tube placement. Every effort should be made to include nutritional support as a complementary therapeutic limb in current oncological treatment protocols.

Keywords

Malnutrition in upper gastro-intestinal cancers
Oeso-gastric cancers (OGC) are among the leading causes of cancer-related deaths worldwide due to their late presentation and poor prognosis. Malnutrition is frequently observed in 60-85% of surgical patients with an upper gastrointestinal cancer (UGIC) and is an independent predictor of postoperative morbidity and mortality, leading to increased length of hospital stay and hospital costs. Many factors can affect nutritional status, particularly disease stage and the choice of treatment strategy (surgery, chemotherapy and/or radiotherapy). In curable OGC, a therapeutic strategy encompassing surgery, chemotherapy and/or chemoradiation is frequently mandatory, leading to an increase in the patient’s nutritional risk and treatment toxicity. Nutritional support should therefore be used as a strong therapeutic weapon which may be complementary to standard active oncological therapy.

Nutritional interventions in upper gastro-intestinal cancer surgery

Objectives
Nutritional support in UGIC patients aims to prevent early death, decrease postoperative complications, especially infectious complications, and improve quality of life. It should begin early and be a routine part of the treatment of cancer patients. Depending on the patient’s individual needs, these goals may be achieved by giving patients nutritional recommendations and dietary advice, as well as providing artificial nutrition using oral supplements, enteral nutrition (EN) via a feeding tube, or parenteral nutrition (PN).

Route of administration
Dietary advice may be sufficient when the patient is capable of consuming at least 75% of his/her nutritional requirements to maintain good health and there is no radiotherapy, chemotherapy or surgery scheduled. When dietary advice is insufficient, a higher level of nutritional support must be initiated. Oral supplementation should be used in cases of malnutrition or when the patient is unable to consume more than 50-75% of his/her requirements by means of conventional feeding for a period longer than five consecutive days (Evidence C).

EN is required in moderate or severe malnutrition, or when patients are unable to consume at least 50% of their requirements through conventional feeding for more than 5-7 consecutive days (Evidence A).

EN is recommended when the patient’s gastrointestinal tract is functional, and it appears to have better efficacy, lower cost and cause less iatrogenic complications than PN (Evidence A). In cases where swallowing is affected and/or if serious neoadjuvant treatment-related mucositis is expected, (as is very frequently seen in OGC), preoperative EN should be administered through a nasogastric or nasoenteric tube, if the expected duration is less than 3 to 4 weeks. Alternatively, gastrostomy (in oesophageal cancer) and jejunostomy (in OGC) feeding may be administered when there is an expected period of nutritional supplementation of more than 3 to 4 weeks (Evidence B).

In the postoperative setting, placement of a needle catheter jejunostomy or naso-jejunal tube is recommended for all candidates needing EN (Evidence A). Figures 1 and 2 propose an algorithm for deciding upon the route of EN administration in oesophageal and gastric cancers, respectively.

In a recent review of our experience with percutaneous radiological gastrostomy (PRG) before surgery for oesophageal cancer, we found a PRG complication rate of 3.4%, without any incidence of metastatic inoculation and without any injury of the gastric vascular arcade, showing this to be a technique which doesn’t compromise the feasibility of subsequent gastric pull-up. As a result of enteral feeding, outcomes of malnourished patients were similar to those of non-malnourished patients.

Many scientific societies have established guidelines on perioperative nutritional support in GI cancer surgery.
During the perioperative period, EN is not required in well-nourished patients, those with weight loss <10% or in patients who can have an oral diet providing at least 50-60% of their needs within the week following surgery (Evidence A).

Preoperative nutrition is recommended in severely malnourished patients with weight loss ≥20% who will undergo major surgery (Evidence A). The same approach seems to be beneficial for patients with moderate malnutrition (weight loss between 10% and 19%) (Evidence B).

Postoperative nutrition is recommended:

i. In all patients who benefited from preoperative nutrition (Evidence A).

ii. In all malnourished patients who did not benefit from preoperative nutrition (Evidence A).

iii. In patients who cannot resume oral diet in the postoperative period due to surgical complications (Evidence A); or in cases where oral diet meets <60% of requirements within the week following surgery (Evidence A).

iv. In other patients, no unequivocal recommendation could be drawn (Evidence B).

Duration

If implemented in the preoperative setting, EN is indicated for at least 10-14 days, even in cases where elective surgery must be postponed (Evidence A). In case of neoadjuvant treatment, EN is indicated for malnourished patients or if it is anticipated that the patient will be unable to eat for more than 7 days (Evidence B). If implemented in the postoperative setting, EN should be started progressively during the first 24 hours (Evidence A) and should be continued for at least 7 days or until patients have recovered at least 60% of their required caloric intake (Evidence A).

Immunonutrition

Major surgery leads to a decline in immune status and an increase in postoperative mortality and rates of infectious morbidity. Enhancing immune function could help decrease such complications. In recent years, standard enteral nutrition has been enhanced with nutrients whose specific purpose is to up-regulate the host immune response, control the inflammatory response and improve nitrogen balance and protein synthesis following surgery. The immunonutrients used are glutamine, arginine, poly-unsaturated fatty acids (omega-3), nucleotides, taurine, vitamins A, E, and C, beta-carotene and trace elements.

The use of immunonutrition in the surgical setting has been well studied with over 28 randomised controlled trials showing that immunonutrition is more efficient than a standard isocaloric and isoenergetic formula in significantly decreasing postoperative infectious morbidity, length of hospital stay and healthcare costs. However, there is a great degree of heterogeneity in terms of nutritional status and the type of control used and in some studies samples were quite small. Despite this, the effect of immunonutrition has generally been found to be beneficial, especially in malnourished patients. Numerous meta-analyses have assessed the evidence relating to the use of immunonutrition in the surgical setting. The overall conclusion is that, in surgical patients, a lower rate of infectious complications and shorter hospital stay were associated with peri-operative immunonutrition as compared to standard enteral nutrition (Evidence A). Figure 3 (overleaf) illustrates a decision tree for the nutritional management of patients undergoing UGIC surgery.

Enteral immunonutrition lasting 5-7 days is recommended in the preoperative setting in both malnourished and well-nourished patients who will benefit from UGIC surgery (Evidence A).

In the postoperative period, for all patients who were malnourished in the preoperative period, immunonutrition should be continued for 5 to 7 days in the absence of postoperative complications or until patients can consume an oral diet meeting at least 60% of their requirements (Evidence A).

Perspective

The following facts are established (i) immunonutrition is efficient in the perioperative period in OGC, (ii) OGC patients are frequently malnourished, and (iii) most patients with OGC will receive neoadjuvant chemo(radio)therapy that may compromise both nutritional and immune status. Hence, routine immunonutrition may help to support immune and nutritional status during the neoadjuvant and perioperative treatment periods. To test this hypothesis, an ongoing European randomized controlled trial is assessing the role of long-term administration of immunonutrition in OGC during the neoadjuvant and the surgical phases to improve quality of life, to reduce postoperative morbidity and to reduce neoadjuvant treatment toxicities (NCT01423799).

Conclusion

Knowledge of the nutritional status of patients with UGIC is essential, not only in identifying malnourished and non-malnourished patients, but also in allowing adaptation of treatment along each step of the multimodal oncological treatment pathway. Whether or not the treatment pathway decided upon is surgical, all patients could benefit from nutritional support during oncologic therapy. Dietary counseling should be provided to all patients receiving RT or CT. EN is required in moderate or severe malnutrition, or when patients are unable to consume at least 50% of their requirements through conventional feeding for more than 5-7 consecutive days. Nasogastric or nasojejunal tubes should be placed for short-term support and feeding jejunostomies or gastrostomies for long-term nutritional support. Use of immunonutrition for 5 to 7 days before surgery is recommended for both malnourished and non-malnourished patients with OGC, along with artificial nutrition for at least 7 days for malnourished patients. Surgeons play a key role in the inclusion and administration of nutritional support as a strong therapeutic weapon in the overall oncological treatment strategy for UGIC patients.
**Figure 1:** Artificial nutrition strategy in oesophageal cancer patients according to the percentage of weight loss

### Oesophageal Cancer

**Well nourished patients (weight loss <10%)**
- Oral supplementation during neoadjuvant therapy until 1 week preoperatively
- Orally 1 week preoperatively
- Minimum 8 weeks
- Surgery

**Malnourished patients (weight loss >10%)**
- PEG placement before starting neoadjuvant therapy
- Jejunostomy placement
- Tube feeding during neoadjuvant therapy until 1 week preoperatively
- Enteral IMPACT® 1 week preoperatively
- Enteral IMPACT® 1 week postoperatively
- Minimum 8 weeks TF* (see Product Decision Tree)
- Surgery
- 2 weeks perioperatively IMPACT®
- Tube feeding according to status of patient
- Several months TF* (see Product Decision Tree)

* Tube feeding

**Figure 2:** Artificial nutrition strategy in gastric cancer patients according to the percentage of weight loss

### Gastric Cancer

**Well nourished patients (weight loss <10%)**
- Oral supplementation during neoadjuvant therapy until 1 week preoperatively
- Oral IMPACT® 1 week preoperatively
- Surgery
- Jejunostomy to prevent severe postoperative weight loss to support patients during adjuvant therapy

**Malnourished patients (weight loss >10%)**
- Jejunostomy during explorative laparoscopy or nasojejunal TF* (gastrostomy contraindicated)
- Tube feeding during therapy until 1 week preoperatively
- Enteral IMPACT® 1 week preoperatively
- Enteral IMPACT® 1 week postoperatively
- Minimum 8 weeks TF* (see Product Decision Tree)
- Surgery
- 2 weeks perioperatively IMPACT®
- Tube feeding according to status of patient
- Several months TF* (see Product Decision Tree)

* Tube feeding
Figure 3: Nutritional management of patients undergoing surgery for GI cancer

- **Oral intake possible?**
  - Weight loss <10%
    - Immunonutrition: 1 unit three times per day + oral feeding
  - Weight loss ≥10%
    - Exclusive EN: 1 L immunonutrition: + 500 ml PF 1.5 if weight ≤50 kg or isocaloric if weight 50 kg to ≤60 kg + 1,000 ml PF 1.5 if weight > 60 kg
    - EN: 1 L immunonutrition: + 500 ml PF 1.5 + oral feeding
  - Functional bowel
    - No specific feeding
      - Outdoor if complication
      - Immune feeding: 1,000 ml PF 1.5 + oral feeding

- **Oral intake impossible?**
  - No specific feeding
    - Except if complications or if oral feeding is <60%* of patient needs in the 7 post-op days
    - Continuing standard EN + oral nutrition

*Feeding <50% of the trays EN, enteral nutrition; PF, polymeric formula

Preoperatively: 7 days before surgery
Postoperatively: 7 days before surgery
After postoperative period

References

Nutritional evaluation and morbidity in colorectal cancer surgery

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Introduction
A decline in nutritional status and continuous weight loss may have deleterious consequences for oncology patients. The reported prevalence of protein-energy-malnutrition (PEM) in hospitalized patients up for gastrointestinal surgery shows rates of up to 50%1-6. In those patients nutritional depletion and weight loss are associated with measurable changes in body composition, tissue wasting and impaired organ function which lead to impaired immune and muscle function7. Those changes are related to an increased risk of adverse clinical outcome8-12, poor quality of life, and lower survival rates13-17. Proactive treatment of patients at nutritional risk and intervention are the cornerstones of success in preventing symptoms of PEM. If patients at risk of PEM are identified early, they can be treated, or PEM may even be prevented. Early and adequate provision of nutritional support for those identified as malnourished has been demonstrated to improve outcome18-20. It is therefore essential that nutritional issues be addressed at the time of diagnosis and throughout the course of cancer care.

There is also convincing evidence that nutritional risk is associated with increased postoperative morbidity and mortality following elective surgery21,22,23. The first report demonstrating a connection between nutritional risk, defined as preoperative weight loss, and survival in surgical patients was presented by Studley in 193624. PEM in the perioperative phase is associated with loss of muscle strength, delayed wound healing22,25 and immune system dysfunction leading to impaired complement production and activation. PEM is also linked to bacterial opsonization, and a dysfunction of neutrophils, macrophages, and lymphocytes26-29. Therefore preoperative nutritional depletion may be responsible for an increase in postoperative complications, prolonged hospital stay and higher costs22,30. The importance of nutritional risk as a major factor in the development of postoperative complications has been described by Giner et al.27. Several factors predispose patients undergoing surgery for colorectal cancer to PEM, which include the catabolic effect of cancer as well as the gastrointestinal side effects of nausea, vomiting, loss of appetite, diarrhea and/or malabsorption28-30.

Metabolic changes in major abdominal surgery
Major abdominal surgery induces a systemic inflammatory response syndrome (SIRS) manifested by fever, leukocytosis, negative nitrogen balance, increased synthesis of acute-phase proteins, and altered serum mineral and electrolyte levels. The most important reactions involve the release of stress hormones and cytokines. Several mediators interact, including proinflammatory cytokines, counter regulatory hormones, and sympathetic hyperactivity with increased levels of glucagon and cortisol31. The stress of surgery or trauma additionally increases the protein and energy requirements by creating a hypermetabolic, catabolic state32,33. The rate of development of PEM and the subsequent disabilities in critically ill patients depend on the patients’ preexisting nutritional status and their degree of metabolic stress due to the underlying disease.

Preoperative nutritional status is an indicator of surgical risk
Progress over the last decade has led to reduced morbidity and mortality after general surgery. However, despite these efforts, complication rates are still around 20 to 40% after abdominal surgery34-36. The mainstream of preoperative risk factors related to an increase of postoperative complications cannot always be influenced, however nutritional risk could be potentially abrogated through an adequate preoperative nutritional treatment37. There is substantial evidence that PEM is associated with adverse postoperative clinical outcome in patients with colorectal cancer38,39. Nutritional status is a major risk factor for determining patient outcomes in colorectal cancer surgery. In a review of more than 3,000 cancer patients, Dewys et al. showed that 54% of patients with colon cancer experienced weight loss during a 6 month period. Patients without weight loss compared to those who had lost 6% of their body weight, had significantly improved survival rates40.

Brown et al. showed that in 578 preoperative colorectal cancer patients a weight loss of >3 kg was associated with an increased postoperative morbidity rate41. Preoperative weight loss, low body mass index (BMI), low nutritional intake and hypoalbuminemia have all been associated with worse outcomes after cancer surgery in several studies42,43. In addition, the preoperative nutritional risk in a cancer patient adversely affects outcomes, reflected by increased complications, increased incidence of nosocomial infections, longer duration of hospital stay, reduced quality of life and increased mortality rates44-46. These factors have economic implications for the healthcare system, both in terms of direct costs and costs related to the management of complications47. Therefore, minimizing the risk of potential complications in the preoperative phase is of great importance. The stress of surgery or trauma additionally increases protein and energy requirements by creating a hypermetabolic, catabolic state. As a result, identifying and treating PEM in colorectal cancer patients prior to surgery is critical in achieving favourable patient outcomes.
Careful preoperative nutritional screening is advised

First-line strategies must include routine screening and identification of patients who are malnourished or at risk of becoming malnourished with the use of a simple and standardised screening tool. There is agreement among international nutrition organisations and accredited healthcare organisations that routine nutritional screening should be a standard procedure for every patient admitted to a hospital. It is mandatory to preoperatively identify patients at nutritional risk who can profit from adequate and rapid nutritional support. Several comparisons between different nutritional screening instruments have been published but there is no consensus regarding the best tool to predict outcome. Numerous validated screening tools are available and appropriate. The guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) state that nutritional screening should be able to predict the clinical course based on nutritional status and whether patients could benefit from nutritional treatment. For clinicians it is important to know for which population and care setting a tool was designed, and to decide if a specific tool may be appropriate for their institution.

Careful preoperative nutritional screening should include an evaluation of the nutritional status based on four variables – pathological weight loss, BMI, general health condition and amount of food intake in the preceding week, as well as the determination of the level of stress caused by the underlying disease. For this purpose, a simple, reliable, easily applied and reproducible scoring system, such as the Nutritional Risk Screening 2002 (NRS 2002) tool developed in collaboration with the ESPEN working group, could be used. The NRS 2002 is a reliable, applicable and reproducible tool to easily identify hospitalised patients at nutritional risk. Its predictive value was documented by a retrospective analysis of 128 randomised controlled trials on nutritional support. The clinical benefit of nutritional screening was shown in a prospective, randomised, controlled trial in a heterogeneous group of patients and in a prospective study of a population undergoing surgery. A recent study investigated whether implementation of the NRS 2002 at hospital admission could predict complications and mortality after colorectal cancer surgery. A total of 39% of patients were deemed to be at nutritional risk, based on the NRS 2002. There was a significant difference in the rate of postoperative complications but only a statistical trend for postoperative mortality comparing at-risk with non-risk patients.

**Interpretation of the NRS 2002 and assessment of nutritional risk**

The NRS-2002 is based on four variables – weight loss, BMI, general condition and amount of food intake in the preceding week – in addition to the patient’s age and the severity of the underlying disease. The total score, calculated from the impaired nutritional status section (score 0–3), the score for severity of disease (indicator of stress metabolism and increased nutritional requirements; score 0–3) and age adjustment (score +1 for age over 70 years), ranges from 0 to 7. Patients are classified as being malnourished or at severe nutritional risk (score 3 or more) according to the total score obtained.

In absence of screening tools, severe nutritional risk is defined by the ESPEN working group as the presence of one or more of the following criteria: weight loss >10-15% within 6 months, BMI <18.5 kg/m2 or serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction). In absence of screening tools, severe nutritional risk is defined by the ESPEN working group as the presence of one or more of the following criteria: weight loss >10-15% within 6 months, BMI <18.5 kg/m2 or serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction).

Management of preoperative nutritional support

**General remarks**

The fundamental topics of perioperative nutritional care include: correction of an impaired nutritional status in the preoperative phase, avoidance of long periods of preoperative starvation and re-establishment of oral feeding as early as possible after surgery. It is advisable to inform the patient about the importance of eating normal food up until the night before surgery. Physicians should also provide nutritional supplements during the period before the operation where needed. Accurate treatment of PEM or of nutritional risk preoperatively in surgical patients to decrease postoperative morbidity and mortality is beneficial. As nutritional risk affects both, the treatment and outcomes of surgical patients with colorectal cancer, timely intervention to assess and improve nutritional status is of enormous importance. When nutritional support has been initiated in patients at nutritional risk, positive effects on clinical outcomes, anthropometry and cost effectiveness have been demonstrated.

According to ESPEN working groups’ evidence-based recommendations, the objective is to provide the best preoperative nutritional support for these patients. The summary of the “surgery” statements are listed in Table 1.

A large number of trials have shown improved outcome with nutritional support in appropriate patients in the periperope phase.

**Enhanced patient recovery after surgery (ERAS) protocols**

In recent years, preoperative management has focused on maintaining physiologic function and enhancing postoperative recovery. Individual protocol elements combined optimize perioperative fluid balance, provide dynamic analgesia (thoracic epidural), enforce early mobilisation and encourage timely oral feeding. Evidence for the efficacy of individual protocol elements is often extrapolated from traditional care pathways. The ERAS protocol has become an important focus of perioperative management in colorectal surgery. These changes minimise the catabolic response to the surgery and allow nutrients to be handled in a more normal way than in traditional care where severe stress was prevailing. The ERAS protocol aims for a faster recovery of patients from major surgery. Its goal is to avoid the harms of conventional postoperative care (e.g. decline in nutritional status and fatigue), and reduce the risk of complications as well as health care costs by reducing hospital stay.

The use of immunonutrition in abdominal surgery: what is the current evidence?

Preoperative nutritional support of the patient gained increased attention due to several landmark randomised controlled studies by Braga et al. showing that severe morbidity could be reduced by approximately 50% in patients undergoing major surgery for upper gastrointestinal cancer. This benefit was noted in both the well nourished patients and patients at nutritional risk. Researchers provided oral immunonutrition (IMPACT®) 5 days preoperatively. The formula contained additional arginine, omega-3 fatty acids and nucleic acids (RNA), and resulted in significant decreases in infections rate, length of hospital stay, and hospital-related costs.

A recent meta-analysis of Cerantola et al. included 21 RCTs with 2,730 patients, who underwent elective major surgery for upper or lower gastrointestinal diseases. Around 70% of these patients were well nourished. Control groups in all RCTs received a standard enteral formula (isoeenergetic and isonitrogenous). Postoperative mortality was similar in immunonutrition and control groups. However, immunonutrition significantly
reduced overall morbidity rate, mainly postoperative infection rate. In addition, the immunonutrition groups showed a reduction in length of hospital stay, possibly as a consequence of lower postoperative complications.

A second meta-analysis by Marik and Zaloga combined 21 RCTs, some of which were mentioned in the study by Cerantola et al., with 1,908 patients. This study concentrated on the type of immunonutrition (arginine supplementation alone, omega-3 fatty acids supplementation alone or both together). The best short-term postoperative outcome was shown in both malnourished and well nourished patients, in the combination of both substances. This was probably due to a synergistical effect in the modulation of immune and inflammatory factors.

A third meta-analysis by Drover et al. included 35 RCTs with more than 3,000 patients undergoing major surgery. A statistical analysis of the whole sample showed significant associations between immunonutrition and postoperative infections as well as length of stay, but not with postoperative mortality. The data was also divided into subgroups such as gastrointestinal-surgery versus non-gastrointestinal surgery, then upper versus lower gastrointestinal disease. The next assessment compared the arginine, omega-3 fatty acids and nucleotides (IMPACT®) versus other arginine-supplemented diets. The last subgroup looked at the time point of supplementation such as before surgery only, after surgery only or at both time points.

Significant profit from immunonutrition was found in all types of surgery merely when the diet contained arginine, omega-3 fatty acids and nucleotides: the effect was even stronger when the treatment started before surgery. The superior outcome data through the aforementioned formula might be due to the higher concentration of arginine and the specific combination of nutrients.

A further meta-analysis published a few months ago by Marimuthu et al. assessed 26 RCT with 2,496 patients, 1,252 of whom using immune modulating nutrients perioperatively. Postoperative infection rate and length of stay in patients who underwent major abdominal surgery was significantly reduced. No statistically significant effect was found for non-infectious complications and mortality.

Preoperative metabolic preparation for elective abdominal surgery

In recent years, the traditional practice of overnight fasting before elective surgery has been reconsidered, and a shorter time is recommended. Setting off daytime metabolism with a carbohydrate load up to 2 to 3 hours before anaesthesia initiation, instead of fasting, does not increase the risk of pulmonary aspiration and has been shown to have several positive effects on outcomes after elective surgery. Many of these favourable effects are connected to insulin action and resistance which are due to carbohydrate loading. A 20% glucose infusion given intravenously overnight at a rate of 5mg/kg/min or an intake of 200-400ml of a carbohydrate rich drink at a concentration of around 12% has been used to break the overnight fasted state. This treatment initiates the activation of glucose uptake in the muscle and fat tissue. It reverses the catabolic state before the onset of the operation. This is probably one of the main reasons for the postoperative effect of substantially lower insulin resistance with the use of preoperative carbohydrate loading. Setting metabolism in an anabolic state before surgery using preoperative carbohydrates has several clinically relevant effects. With this procedure protein metabolism is better retained, lean body mass maintained and muscle function (including the heart) in the postoperative phase preserved. Noblett et al. demonstrated that preoperative oral carbohydrate loading in surgical patients with colorectal cancer enhanced recovery and reduced the length of hospital stay.

Conclusion

There is convincing evidence that preoperative risk of becoming malnourished or manifest PEM in surgical patients are associated with increased postoperative morbidity and mortality. Increasing data has been accumulated during recent years, which demonstrate that nutritional screening and an adequate nutritional therapy are essential adjuncts in modern surgical care. Preoperative nutritional support is beneficial in patients at nutritional risk or with PEM, and evidence reveals that preoperative immunonutrition improves outcome in major abdominal surgery, even in patients not at nutritional risk.
Table 1: ESPEN summary of statements: Surgery (preoperative phase)\textsuperscript{52,55}

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recommendations</th>
<th>Grade*</th>
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<tbody>
<tr>
<td><strong>General Indications</strong></td>
<td>Preoperative fasting from midnight is unnecessary in most patients.</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Encourage patients who do not meet their energy needs from normal food to take oral nutritional supplements during the preoperative period.</td>
<td>C</td>
</tr>
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|                       | Initiate nutritional support without delay:  
|                       |   • even in patients without obvious undernutrition, if it is anticipated that the patient will be unable to eat for more than 7 days perioperatively   | C      |
|                       |   • in patients who cannot maintain oral intake above 60% of recommended intake for more than 10 days.                                                                                                      | C      |
|                       | Use nutritional therapy in patients with severe nutritional risk for 10–14 days prior to major surgery even if surgery has to be delayed. Severe nutritional risk refers to at least one:  
|                       |   • NRS 2002 Score ≥3 (severe nutritional risk)   
|                       |   • Weight loss >10–15% within 6 months   
|                       |   • BMI <18.5 kg/m\(^2\)   
|                       |   • Serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction).                                                                                                                                   | A      |
|                       | Consider combination with parenteral nutrition in patients in whom there is an indication for nutritional therapy and in whom energy needs cannot be met (<60% of caloric requirement) via the enteral route. | C      |
|                       | Preoperative parenteral nutrition is indicated in severely undernourished patients who cannot be adequately orally or enterally fed.                                                                       | A      |
|                       | Administer preoperative enteral nutrition preferably before admission to the hospital.                                                                                                                      | C      |
|                       | Preoperative carbohydrate loading using the oral route is recommended in most patients. In the rare patients who cannot eat or are not allowed to drink preoperatively for whatever reasons the intravenous route can be used. | A      |
| **Contraindications** | Prefer the enteral route except for the following contraindications: Intestinal obstructions or ileus, severe shock, intestinal ischemia, gastrointestinal failure.                                                | C      |
| **Type of formula**   | In most patients a standard whole protein formula is appropriate.                                                                                                                                              | C      |
|                       | Use oral or enteral nutritional therapy preferably with immune-modulating substrates (arginine, omega-3 fatty acids and nucleotides) perioperatively independent of the nutritional risk for those patients:  
|                       |   • undergoing major neck surgery for cancer   
|                       |   • undergoing major abdominal cancer surgery  
|                       |   • after severe trauma.                                                                     | A      |
|                       | Whenever possible start these formulae 5–7 days before surgery                                                                               | C      |

*Grade of recommendations


Specialised Nutrition as part of Enhanced Recovery after Surgery

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Introduction
Enhanced Recovery Programmes are quality improvement tools that have been introduced as part of the National Health Service innovation and improvement initiative in the United Kingdom. They are being used to improve patient outcomes, reduce length of stay, allow better use of resources and create better staffing environment. The treatment of oesophageal and gastric cancer is complex and requires a multi-professional approach during diagnosis and treatment. Management of these cancers is audited with a national UK audit being published on an annual basis.

Surgery for oesophago-gastric cancer is a major undertaking. It is only suitable for patients who are relatively fit, and are found to have localised disease on staging investigations. The surgical removal (resection) of the tumour remains the mainstay of curative treatment so it is important that full consideration is given to patients who are suitable. Peri-operative chemotherapy has been demonstrated to improve survival. Recovery from all treatment takes a number of months and in particular surgical patients have a poorer quality of life for approximately 9 months after the surgical procedure.

Overall three year survival rates for patients receiving curative treatment for oesophageal and gastric cancers are 41–49% with 5 year survival being cited as approximately 20% for this group. Any intervention should maximise patient quality of life and minimise morbidity associated with treatment wherever possible.

Improving outcomes in Upper Gastrointestinal surgery
Enhanced recovery after surgery (ERAS) has been used in a number of cancer settings with much of the early work being carried out in colorectal surgery. In addition European guidelines have been published this year for the use of ERAS in pancreatic surgery. Although oesophago-gastric cancer has not been identified as a national priority for ERAS in the United Kingdom, there has been interest in our hospital as to how the principles could be applied to this group of patients with the aim of improving patient outcomes. Oesophago-gastric surgery has now been included in the national priorities for the ERAS in the United Kingdom. All ERAS programmes focus on a multi-dimensional approach and this article describes the nutritional aspects and their implementation in our hospital, a tertiary referral centre for upper gastrointestinal cancer.

There are four elements to the enhanced recovery programme developed in our institution:

1. Pre-operative assessment, planning and preparation before admission.
2. Reducing the physical stress of the operation.
3. A structured approach to immediate post-operative and during (peri-operative) management, including pain relief.
4. Early mobilisation.

When developing the local Upper GI ERAS protocol, multi-professional meetings enabled discussion of the evidence and its implementation. The professions represented at the meetings were Trust Executive – Chief Nurse, Medical – Surgeon and Intensivist, Nursing – Ward, Critical Care, Rehabilitation, Clinical Nurse Specialist, Allied Health Professionals – Dietitian, Physiotherapist.

Integral to its implementation was the development of patient information given at the first clinical appointment and the development of an agreed ERAS careplan which outlined the proposed daily care. Information was disseminated to the relevant clinicians via the multi-professional team.

Nutritional Status at Diagnosis
Nutritional aspects at diagnosis are important for this patient group as they may present with weight loss and difficulty swallowing. Being overweight or obese is a risk factor for adenocarcinoma of the oesophagus and it is likely that weight loss is overlooked in such patients. However some patients experience dysphagia and therefore the provision of an adequate diet, even prior to diagnosis, may be a challenge. Upper gastrointestinal cancer patients are likely to have a high degree of weight loss when compared to other types of cancer diagnosis. Traditionally these patients have been referred to the dietitian via a locally developed pathway either at the local hospital where diagnosis was confirmed or at the cancer centre. Patients without dysphagia are perhaps more likely to be overlooked and not be referred for dietary advice. It is recognised that nationally dietetic support is only available for approximately half of patients.

The maintenance of nutritional status is an important factor for patients during treatment. The majority of the surgical patients will receive chemotherapy prior to surgery. Studies have demonstrated that weight loss is associated with poor tolerance to chemotherapy with increased side effects, longer breaks during treatment to allow the patient to recover and overall a reduction in the quantity of chemotherapy given to patients. Weight loss and malnutrition may also impact on the patient’s performance status and suitability for radical surgery.

A previous local audit in our area identified that half of all upper gastrointestinal patients should trigger a referral to a dietitian at diagnosis due to weight loss and/or dysphagia. For the purposes of ERAS all patients were targeted at diagnosis with a nutritional assessment undertaken by a Registered Dietitian prior to chemotherapy with the specific aim of maintaining or
improving dietary intake and nutritional status. Patients were able to receive specific dietary advice for nutritional problems experienced but also to discuss potential changes to their food intake during their planned neoadjuvant chemotherapy.

Weight maintenance with an adequate balanced dietary intake was the aim for patients of normal or higher body weight. This advice was given in conjunction with advice on exercise from a Registered Physiotherapist with the aim of maintaining muscle bulk and improving aerobic capacity. Advice and implementation of artificial nutrition support was available for those who required more intensive support. This information was provided in conjunction with a comprehensive pre-operative assessment examining co-morbidities, anaesthetic risk and the provision of advice on smoking cessation.

On-going dietary advice and support was given as required through the Dietetic outpatient clinics at the cancer centre. Studies have demonstrated that such regular support is able to help maintain weight and nutritional status during intensive treatment.

**Preparation for surgery**

On completion of chemotherapy it is paramount that the patient is reassessed to ascertain whether their performance status and disease state is amenable to surgical intervention. Various aspects of ERAS are outlined in Figure 1 which describes the relevant interventions as appropriate time points for the patient. At this time the patient was reviewed again by the Registered Dietitian to assess whether the patient had achieved an optimal nutritional status.

In order to optimise surgical outcomes the use of pre-operative immunonutrition has been initiated as part of the ERAS programme. Since the 1980’s a number of studies have looked at the ability of specially formulated enteral preparations containing arginine, omega-3 fatty acids and nucleotides to influence post operative complication and infection rates.

Their action is via modulation of the acute stress response. Early studies included both malnourished and normally nourished patients making it difficult to ascertain which groups would benefit from immunonutrition. Later studies demonstrated that normally nourished individuals benefited from preoperative use of immunonutrition whilst malnourished patients may benefit from both the pre and post operative use of immunonutrition. Some studies, but not all, have shown a beneficial effect on overall post operative complications but the strength of evidence lies mainly in the effect of perioperative use of immunonutrition on reducing post operative rates of infection and length of hospital stay. The European Society of Parenteral and Enteral Nutrition recommend the use of immunonutrition for 5-7 days prior to surgery in all patients undergoing major abdominal surgical cases.

A recent systematic review by Cerantola identified 12 studies of high quality. These studies supported the view of ESPEN in the use of immunonutrition preoperatively with the aim of reducing post operative complications, primarily infection, and reducing length of hospital stay.

The use of other products containing omega-3 fatty acids with glutamine and/or arginine appeared to be less beneficial in influencing clinical outcomes in this patient group. In our hospital pre-operative preparation for ERAS patients included advising patients on the use of 5 days of pre-operative immunonutrition (Oral IMPACT®, Nestlé) to be taken at home. Patients were asked to consume 3 sachets, 750ml, daily. Compliance with taking oral nutritional supplements has been shown to be variable so strategies were employed to ensure that patients were well informed of the potential benefits and that taste preference was taken into consideration. Patients received advice and support from a Registered Dietitian, a prescription of their preferred flavour, a patient information leaflet with details of the date to commence the immunonutrition, tick boxes to help patients track their daily consumption and a shaker to facilitate making the drinks.

The avoidance of long periods of pre-operative fasting and the use of carbohydrate loading has been shown to improve outcome through the ability to influence insulin resistance. The consumption of a carbohydrate containing drink up to 2 hours prior to surgery attenuates insulin resistance, minimises protein losses and may reduce hospital stay. ERAS programmes generally provide carbohydrate in the form of 2 glucose drinks given to patient the night before surgery (100g glucose in 800ml) and the morning of surgery (50g in 400ml). In oesophageal and gastric cases of ERAS the patient receives 130g of glucose per day in the daily amount of Oral IMPACT® so it was decided, for practical reasons, that additional carbohydrate was administered as 50g glucose on the morning of surgery.

**Post operative nutritional support**

Post operative enteral tube feeding is recommended for all patients undergoing major upper gastrointestinal surgery. A jejunostomy tube is placed at the time of surgery and used post-operatively, usually within 48 hours of surgery. Standard polymeric enteral formulations are used although immunonutrition can be considered for malnourished individuals. In practice this has rarely happened as a nutritional focus prior to surgery has enabled nutritional status to be optimised in the majority of patients.

Jejunostomy feeding usually commences within 48 hours of surgery. Some studies and guidelines suggest that feeding can commence within 24 hours of surgery. However, others have expressed concern about early feeding into the jejunum in a haemodynamically unstable patient and the risk of developing non-occlusive small bowel necrosis. The risk appears to be about 1% and therefore enteral feeding is commenced when the patient is deemed to be appropriately stable. The feeding jejunostomy tube is used during the hospital stay and continued at home if additional nutrition support is required. Careful post operative dietetic monitoring with appropriate advice and support ensures that patients return to an appropriate dietary intake as soon as possible with appropriate additional nutritional support in the form of jejunostomy feeding if required.

**Future initiatives**

Implementation of ERAS in oesophageal and gastric cancer has resulted in a reduction in total length of stay by 3 days with no change in stay in critical care. It is recognised, however, that length of stay is influenced by a number of factors and it is difficult to attribute this to any individual part of the ERAS programme. Planned ongoing audit is taking place to examine surgical complications, comparing these with cases prior to the implementation of ERAS. Although this comparison is not without limitations it is important that we consider the overall outcomes for these complex surgical cases.

An audit of the patient’s opinion of the ERAS programme and individual adherence to the pathway has commenced. It is essential that patient’s are involved in the perioperative process and are aware of expectations of their recovery and how they may influence these. From the perspective of staffing it is recognised that this approach is more labour intensive with healthcare professionals concentrating on optimising patients prior to surgery, with the aim of improving patient outcomes. It has also been recognised that adherence to an ERAS pathway may lapse over time and it is therefore important to continually work to ensure that the pathway is embedded in usual practice and is followed by all staff in the upper gastrointestinal team.
**Figure 1:** Enhanced Recovery in Upper Gastrointestinal Cancer

- **2. Pre surgery assessment (usually post chemo)**
  - Assessment of underlying cancer
  - Detailed discussions of surgical procedure
  - Physiotherapy assessment
  - Dietetic assessment
  - Patient information and expectations
  - Date of admission
  - Immunonutrition 5 days prior to surgery

- **Secondary care after MDT. Decision to proceed to surgery**

- **Pre-operative**
  - Admission
  - Intra-operative
  - Post-operative

- **Clinical daily assessments**
  - To determine progress along the pathway according to the protocol

- **Admission day before surgery**
  - Day before surgery patient to drink 750ml of Oral IMPACT® (immunonutrition), 3 drinks to be taken in the morning, late afternoon and evening
  - Carbohydrate loading
  - 1 sachet of Pre Load providing 50g glucose in 400ml
  - Patient to drink glucose drink on the morning of surgery up to 2 hours pre surgery
  - Anti-emetic given as pre med
  - Embolic stockings

- **Optimise fluid management**
  - Individualised goal directed fluid therapy
  - Epidural/regional block
  - Feeding jejunostomy (Minimally invasive surgery)

- **3. Formal pre assessment**
  - Anaesthetic review
  - Cardiopulmonary exercise test
  - Physiotherapy instruction exercise and incentive spirometry
  - Dietetic advice to optimise nutritional status

- **References**

Malnutrition has long been shown to play an important role in the occurrence of post-operative complications, particularly infections and delayed wound healing. It decreases cell-mediated and humoral immune responses. Nutritional support has been associated with a decreased number of postoperative complications. More recently, immunomodulating diets have been developed to specifically address the causal factor of postoperative complications. Several formulas exist, combining in different ratios arginine, omega-3 polyunsaturated long-chain fatty acids (PUFAs), ribonucleic acid and antioxidants (including ascorbic acid and selenium). These different formulas have different physiologic actions, but are all referenced under the name of immunonutrition (IN).

The rationale for using IN in a hospital setting rests on two pillars: firstly, early initiation of enteral nutrition has been shown to decrease infectious complications and hence hospital length of stay (LOS), and secondly, early nutritional deficit alters the efficacy of the immune system, so IN might lead to a further decrease in infectious complications and LOS.

This paper will summarize existing evidence for IN efficacy, available cost data, and factors to consider before IN introduction from a hospital perspective.

**Evidence of IN efficacy**

The available evidence of efficacy of IN rests on three main studies:

- A systematic review of IN in high-risk surgical patients
- A meta-analysis of IN in gastrointestinal surgery
- A systematic review of perioperative arginine

The main findings of these studies will be summarised below.

**Systematic review of IN in high-risk surgical patients**

This review of 21 studies totalling 1,918 patients covers an observation period ranging between 1992 and 2008; fifteen studies included 1,442 patients with gastrointestinal malignancy, 3 studies included 206 patients with a head and neck malignancy, 2 studies included 220 patients admitted for gastrointestinal surgery, and 1 study included 50 patients admitted for cardiac surgery. One study looked at the pre-operative use of IN in 60 patients, 15 studies looked at the postoperative use of IN in 1,249 patients, and 5 studies looked at the perioperative use of IN in 610 patients.

No impact was noted on mortality (risk ratio = 0.90; 95% CI 0.46-1.76) but a statistically significant average protective effect of IN against postoperative infection was noted in all studies (odds ratio 0.49, 95% CI 0.39-0.62). Similarly, in the 15 studies totalling 1,905 patients which addressed the impact of IN on LOS, an average mean reduction of 3.03 days (95% CI -3.43, -2.64) was noted.

**Meta-analysis of IN in gastrointestinal surgery**

This meta-analysis looked at 21 randomised controlled trials totalling 2,730 patients included between January 1985 and September 2009. Twelve studies were considered of high quality.

Again, no impact was noted on mortality. However, IN significantly decreased the average occurrence of overall complications (odds ratio 0.46, 95% CI 0.38-0.56), as well as infectious complications (odds ratio 0.47, 95% CI 0.37-0.59). IN use was associated with a statistically significant average reduction in LOS of 2.12 days (95% CI -2.97, -1.26).

**Systematic review of perioperative arginine**

This review included 54 randomised controlled studies, of which 35 focused only on elective surgery patients. The inclusion period ranged between 1995 and 2009.

Again, the 21 studies looking at IN impact on mortality in 2,207 patients did not show any statistically significant difference (odds ratio 0.8, 95% CI 0.65-1.80). However, perioperative arginine was associated with a statistically significant average reduction in the occurrence of post-operative infection in 28 studies totalling 2,780 patients (odds ratio 0.59, 95% CI 0.50-0.70). Similarly, the 29 studies totalling 2,616 patients looking at perioperative arginine impact on LOS showed a statistically significant mean reduction of 2.38 days (95% CI -3.39, -1.36).

**Cost-effectiveness evidence**

Data about cost-effectiveness of IN come from 2 prospective studies and 3 studies using hospital databases.

A randomised clinical trial comparing pre- and perioperative IN with conventional therapy in 102 well-nourished gastrointestinal-cancer patients in each group showed that the cost of post-operative morbidity consumed a large amount of the DRG reimbursement rate in both groups (93% in the conventional group and 78% in the preoperative group), but that preoperative IN decreased the mean cost per complication from €6,178 to €4,639 (p = 0.05) per patient.

A prospective randomised trial in 144 patients with upper gastrointestinal tract malignant neoplasm, comparing perioperative administration of IN to standard control diet.
showed that treatment costs of complication were lower in the supplemented diet group than in the control group (Deutsche Mark = DM 964 versus DM 2,688 per patient), resulting in savings of DM 1,426 per patient, after accounting for the additional cost of IN.

A US study\(^4\) using a national data base of 126 US hospitals with 1 million patients, and the clinical outcome measures from the 3 major peer review studies described previously\(^4,5\) showed that with an average decrease of 51% in the risk of occurrence of infectious complication and an average decrease of 9.7 days in LOS, assuming a basal infection rate of 5%, IN led to net cost savings per patient, even after accounting for the additional cost of IN. For medical patients, these cost savings amounted to $2,066 per patient, for surgical patients to $688 per patient, and for trauma patients to $300 per patient.

Sensitivity analysis showed a marked variation in the amount of these savings with variation in basal infection rate, and only a slight variation with differences in types of facility or regions of the country. A recently published study\(^6\) applied the US cost data of the Healthcare Cost and Utilization Project 2008 Nationwide Inpatient Sample to the results of a meta-analysis of 6 studies published in 2006 with gastrointestinal cancer patients showing a 56% decrease in infectious complications and a 14% decrease in LOS. Its results showed savings amounting to $3,300 per patient based on the reduction in infectious complication rates, and to $6,000 based on the reduction in LOS. Savings were observed for infection rates as low as 3.5%.

Using the meta-analysis of Cerantola\(^8\) and the hospital costs of 420 patients, of which 64 presented at least 1 postoperative complication, a Swiss study\(^10\) computed the incremental cost of complications from the cost-weight of the corresponding diagnosis related group (DRG). Based on the incremental cost of an infection, IN decreased the cost of hospital stay by a range of Swiss Francs = CHF 1,137 to CHF 2,598 per patient. Based on LOS, the savings ranged from CHF 3,136 to CHF 2,215 per patient. Net hospital savings were observed to occur for a baseline infection rate as low as 5%.

**Decision analysis**

On the basis of these effectiveness and cost data, a rational hospital should consider including IN in its nutritional strategy. However, different interventions can be contemplated and should be assessed separately as well as together to compute the marginal cost-benefit ratio of including IN into the existing strategy.

Alternative nutritional interventions can start during the preoperative period and include in particular screening for high-risk patients, as well as introduction of standard nutritional therapy at home.

During the hospitalization period, available interventions include screening for high-risk patients, inclusion of diet as a medical prescription (to oblige physicians to address this domain which is usually delegated to nurses), as well as introducing a surveillance system of patients’ real nutritional intake. In the intensive care unit, available interventions range from implementing nutritional guidelines, delegating nutritional intake to nurse control, and/or incorporating a specialised nutritionist into the team.\(^6\) Finally, after hospital discharge, nutritional follow-up can be considered.

As a consequence of existing nutritional strategies, the impact of introducing IN will be different in different hospital settings.

**Conclusion**

As IN is a specialised diet which can be added to normal diet, it can be considered as a health care technology as all others, and assessed with the same methods. The finding that IN can be a cost-saving strategy in high-risk patients, despite the additional cost of IN is another proof that nutrition is an undervalued treatment modality. Increased attention to this simple way of taking care of patients can have a tremendous effect on hospital outcome results and quality of care. It can avoid suffering to patients and save hospitals valuable resources.

At the time of high technology and expensive medicine, better consideration for nutrition can bring clinicians back to basic medical knowledge and wisdom, already known at the time of Hippocrates, who said "Let food be your medicine". This example is an interesting additional case for the ongoing strategy that, selecting wisely, less can be more.\(^7\)

**References**
