Nutritional Support to Prevent and Treat Multiple Organ Failure

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Abstract. Enteral nutrition (EN) has several advantages over parenteral nutrition (PN) for postoperative/posttrauma patients. Modern technologies for tube-feeding have made early EN possible. Jejunal tube-feeding has advantages over gastric tube-feeding: faster metabolic recovery, less vomiting, and less risk of regurgitation and aspiration. Immediate or early EN stimulates the splanchnic and hepatic circulations, improves mucosal blood flow, prevents intramucosal acidosis and permeability disturbances, and eliminates the need for stress ulcer prophylaxis. Saliva containing important antimicrobial substances and gastric acidity are important in sepsis prevention. Chewing, saliva, and gastric acidity support gastric nitric oxide (NO) release, important for mucosal blood flow, gastrointestinal (GI) motility, mucus formation, and bacteriostasis. An oral supply of NO-donating substances and chewing of nitrate-rich food, such as lettuce or spinach, can be useful. Oral and mucosa-protective lipids are recommended. H_2 blockers and saliva-inhibiting drugs are avoided. Immediate EN should be given, starting with 25 ml/hr and increasing to 100 ml/hr over 24 to 48 hours. For the immunocompromised patient special attention should be given to the purity of water. Bottled water can contain bacteria such as *Pseudomonas*. Food antioxidants such as glutathione, vitamin E, and β-carotenes are important. Ingredients for the colonic mucosa are important. Approximately 10% of caloric need is satisfied by so-called colonic food (prebiotics), fermented at the level of the colonic mucosa to produce colonic mucosa nutrients and to prevent gut origin sepsis. More than 10 g of fiber per day is recommended. The fermenting flora (probiotic flora) is deranged owing to disease or antibiotic treatment, and resupply of flora is important. A new concept of ecoimmune nutrition is presented for enteral supply of mucosa-reconditioning ingredients: new surfactants, pseudomucus, fiber, amino acids such as arginine, and mucosa-adhering *Lactobacillus plantarum* 299.

During the early days of surgery, enteral nutrition (EN) produced problems such as vomiting or diarrhea. The gastrointestinal (GI) tract was regarded as paralytic and often nonfunctioning after operation or injury. Early parenteral nutrition (PN) solutions were deficient with < 10% sugar and < 500 kcal/day. Total parenteral nutrition (TPN) eliminated the problems of vomiting or diarrhea and was a major advance at the time. Now it is recognized that GI paralysis is mainly present in the stomach and colon, whereas the small intestine nearly always is functioning. Even with some ileus there is enough absorptive capacity at 25 to 60 ml/hr infused into the upper jejunum.

Early studies comparing EN and PN dealt with nutritional and

metabolic aspects, most often nitrogen metabolism [1]. As the problems of postoperative/posttrauma (POT) patients came into focus, and the etiologic relation of POTS to the gut was recognized, there was increased interest in the use of EN. Today there have been great advances in nutritional support by enteral means.

Problems of Patients with POT

Today it is accepted that many of the septic complications after injury are due to colonization of the oropharynx, the tracheobronchial tree, and the upper GI tract or to translocation of potentially pathogenic microorganisms (PPMs) in the lower GI tract. Many believe that translocation is an important etiologic factor in POT patients. Among organ donors with a median hospital stay of only 1.9 days (range 6 hours to 8 days) bacterial cultures were positive in 67%, most often in mesenteric lymph nodes, lung, liver, and spleen [2]. Endotoxin was found in abdominal fluids in approximately 50% of the cases, in peripheral blood in 20%, and in portal blood in 10% [2]—before any changes were evident in the bowel wall. Increased intestinal permeability as early as 16 to 24 hours after moderate burns was described by McDonald et al. [3]. A single dose of endotoxin given to healthy humans significantly increased permeability [4]. The first peak of endotoxin occurred in the serum of patients about 12 hours after burns [5]. It is likely that there was increased intestinal permeability at that time as well. The presence or absence of gastric intramucosal acidosis during the first 12 hours after trauma is predictive of outcome [6]; a low intramucosal pH on admission, remaining low at 12 hours, was associated with 87% mortality, compared to 36% when intramucosal pH had returned to normal after 12 hours and 27% if it was normal on admission and remained normal at 12 hours. Deranged intramucosal pH reflects poor mucosal oxygenation, and splanchnic ischemia contributes to multiple organ failure (MOF). Such tonometric measurements in the stomach may reflect the status of oxygenation of the entire GI mucosa. EN counteracts intestinal ischemia via several mechanisms and probably should be instituted in trauma cases immediately on arrival at the hospital and in postsurgical patients immediately on arrival in the recovery room to overcome the traditionally long preoperative period of intestinal starvation.

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Mucosal Function during Starvation

It was shown in experimental animals by the mid-1970s that with starvation the intestinal mucosa loses a large proportion of its structure and function [7] by 7 days. There are reasons to suspect that functional down-regulation occurs within 12 to 18 hours of intestinal starvation (e.g., the usual time of no eating before elective operations). Patients may be "metabolically handicapped" and susceptible to splanchnic ischemia and translocation on arrival in the operating room. The liver at that time is devoid of glycogen. The capacity of the liver to store calories as glycogen is only 500 kcal, which is consumed before surgery even begins. The hepatocyte has no capacity to build and store glycogen during and immediately following anesthesia. Glycogen deficiency can be eliminated only by a supply of carbohydrates immediately before operation, which considerably increases insulin sensitivity. Fasting for 24 hours increases translocation after hemorrhagic stress [8], which cannot be inhibited by TPN; early EN is needed.

Four observations reported in 1980 had a great influence on the development of EN in POT patients. Roediger found that intestinal mucosa was unable to nourish itself completely from blood [9]. Half of the nutritional needs of the small intestine and > 80% of that of the large intestine must come from luminal nutrition. Mucosal atrophy develops during early intestinal starvation, even when complete TPN is given. Hoover et al. [10] described positive nitrogen balance (+ 12%) in patients given EN (by jejunostomy) compared to a negative balance (− 45%) in TPN-treated patients. Alexander and coworkers [11] found that raising the amount of protein in EN from 15% to 23% increased survival from 56% to 100% in children with severe burns. Finally, Shephard described an increase in mesenteric and hepatic circulation [12] after early institution of EN.

Role of Saliva and Gastric Acidity in Infection Prevention

Colonization of the oropharynx, tracheobronchial tree, and esophagus, often with gram-negative aerobic bacteria, occurs early in both intubated and nonintubated sick and critically ill patients [13]. It is promoted by endotracheal tubes, tubes in the GI tract and urinary bladder, and intravascular catheters. Some antibiotics, anticholinergics, other mucus-inhibiting drugs, H_2 blockers, and antacids may promote microbial translocation by facilitating intestinal colonization with PPMs. It also explains why many of these drugs, particularly H_2 blockers, produce diarrhea.

It is well known among dentists that "the saliva possesses a multiplicity of defense systems for antibacterial warfare that the Pentagon can envy" [14]. In addition to the protective role of oral bacteria such as lactobacilli, specific antimicrobial proteins such as lysozyme, lactoferrin, and lactoperoxidase are produced in saliva. Other important colonization-preventive ingredients are mucin and immunoglobulin A (IgA). Salivary mucins concentrate on mucosal surfaces and provide a barrier against environmental insults [15]. Mucus produced in the mouth follows and covers ingested food as a protective layer from the oral cavity and probably down to the colon. Extirpation of salivary glands in experimental animals reduces the content of mucus in the lower esophagus by 80%. The loss in salivary mucus can only partly be compensated for by local mucus production: A strong epidermal growth factor stimulation increased it by 50% [16]. Mucus-producing cells, or goblet cells, increase in density with distance from the oral cavity. Dietary fiber stimulates production of intestinal mucus, thereby preventing PPMs from getting a foothold on the mucosal surfaces and initiating translocation [17]. Saliva in amounts up to 300 ml/hr is produced with stimulation, and when resting it is approximately 25 ml/hr. Drugs used in intensive care units (ICUs) inhibit saliva; among them are anticholinergics, antispasmodics, antidiarrheals, analgesics, antidepressants, antihistamines, antihypertensives, antiparkinsonian agents, antipsychotics, and diuretics. Pilocarpine best stimulates and effectively increases the salivary output [18], an important factor in patients with xerostomia and associated salivary gland dysfunction. Low pH in the stomach is one of the most important barriers against invading PPMs. Gastric pH < 3.5 is usually bactericidal for most species. This barrier may be broken by stress ulcer prophylaxis, decreased acid production, H_2 blockers, or alkalinization of gastric contents by continuous gastric feeding, allowing GI overgrowth of PPMs, retrograde colonization of the pharynx, and increased risk of pneumonia and other infections [19]. Instead of H_2 blockers, mucosa-protecting drugs such as sucralfate have been recommended [19]. In experimental animals, sucralfate mixed with water, when aspirated, causes lung edema and when mixed with HCl causes severe lung edema [20]. McDonald et al., in more than 100 patients after burns [3] demonstrated that immediate (within 6 hours) nasogastric tube-feeding prevents stress ulcer bleeding and eliminates the need for prophylactic antacids for H_2 blockers. Similarly, good protection can be obtained by substances such as pectin and phospholipids [21]. If the feeding is used, it should be administered intermittently to allow the gastric pH to decrease between feedings to prevent gastric colonization [22]. This step is not necessary if enteral tube-feeding is used instead. There are several reasons to avoid H_2 blockers, especially omeprazole. Oral administration of glutathione eliminates the gastric pH-elevating effect of omeprazole [23]; most likely omeprazole also reduces glutathione, at least in the stomach. Omeprazole degrades vitamin C and eliminates the gastric production of nitric oxide (NO), which is essential for bactericidal effects in the stomach, hemodynamic normalization, and mucosal oxygenation [24].

To overcome microbial overgrowth, selective decontamination with nonabsorbable antibiotics has been used extensively during the last 10 years. A recent meta-analysis [25], based on 11 studies and about 1500 patients, failed to show any major benefits of selective decontamination. It is more likely that antimicrobial proteins alone or in combination with immediate EN can successfully prevent problems in POT patients. Such a protein could be the bactericidal/permeability-increasing protein reported to be successful in experimental animals [26]. A single bolus injection (10 mg/kg) protected 15 of 16 mice from lethal endotoxin challenge compared with none of 16 in the control group. Another interesting approach is to supply the GI mucosa with new surfactants, pseudomucus, fiber, and protective lactobacilli [21]. Whatever measure is chosen, it must be applied at an early stage. Fast progression of disease necessitates immediate actions to prevent and counteract MOF. Many adult patients have MOF on arrival to the ICU. In children, 50% of deaths occur during the first ICU day and most within 7 days [27].

Colonic Food

Food must contain nutrients for colonic mucosa that cannot be broken down and absorbed in the small intestine. Normally, about 10% of human caloric need is met by colonic feeding. Fiber and protein substances for the colon are called *prebiotics* or *colonic foods*. Sloughed endothelium, pancreatic enzymes, mucus, and so on are recycled after bacterial fermentation in the colon [28]. Sloughed epithelium in the entire GI tract measures about 287 g/day and more with some diseases [29]. Thus 80 g of protein and 12 to 30 g of lipids are recycled every day. When colonic food and other substrates reach the colon, the endogenous microbial flora (probiotic flora) metabolize it and produce nutrients for colonic mucosa. These nutrients are short-chain fatty acids (SCFAs), amino acids, peptides, and polyamines [21]. Some substrates for colonic food can be met by recycling epithelium and enzymes of 10 to 30 g/day, but fiber must be supplied. If the probiotic flora is reduced or eliminated by disease or antibiotic treatment, a resupply of human-specific probiotic bacteria is needed, especially in potential or established MOF patients, including patients with subacute or subchronic forms of MOF, such as those with human immunodeficiency virus or acquired immunodeficiency syndrome (HIV/AIDS). Colonic mucosal starvation induced by TPN or elemental/fiber-free EN leads to a deficient colonic microflora. Cosmonauts develop a deranged intestinal microflora, an increase in enteropathogens, and almost total elimination of lactobacilli [21], most likely due to emotional stress and a fiber-free diet.

Probiotic Bacteria

Probiotic bacteria have several important functions in the colon: (1) production of nutrients for the mucosa: acetate, butyrate, propionate, other SCFAs, pyruvate, lactate, and amino acids (arginine, cysteine, glutamine); (2) production of micronutrients (β group and folic acid, antioxidants, and polyamines), histamine, 5-hydroxytryptamine, piperidine, tyramine, cadaverine, pyrrolidine, agmatine, putrescine; (3) prevention of overgrowth of PPMs; (4) stimulation of the immune system, especially the gut-associated lymphoid tissue (GALT) system: NO is produced by these bacteria in the mouth and GI tract; (5) elimination of toxins from the lumen; (6) participation in intestinal regulation, mucus utilization, nutrient absorption, GI motility, and blood flow through signaling substances such as NO.

To study the effectiveness of various bacteria, a library of hundreds of lactobacilli was collected from healthy humans [30]. Studies of abilities of lactobacilli to ferment fiber in vitro, to survive the acidity of stomach and the bile acid contents of the small intestine, to adhere to the colonic mucosa, and to remain and function there after the supply stopped led us to identify a few human lactobacilli with great capability. In the past, lactobacilli for treatment were most often yogurt lactobacilli. They do not survive the acidity of the stomach; or, if so, they do not adhere and function on the mucosa. The first lactobacillus with therapeutic benefits [31] was *Lactobacillus rhamnosus* GG, isolated from human feces. In vitro it adheres to human mucosal cells (0.5–2.0 bacteria/cell). We then identified *Lactobacillus plantarum* strain 299, which has an adherence of 15 bacteria/cell, e.g. the level of E. Coli [I. Adleberth and A. Wold, unpublished data]; *lactobacillus plantarum* produces lactate and acetate, deaminates serine to pyruvate and arginine to ornithine (produces NO at the mucosal surface), and produces hydrogen peroxide and probiotics called

Table 1. Nutrient content in 100 ml of nutrition solution.

Nutrient	Standard solutions with fiber ($n = 8$)	Immune nutrition IMPACT	Ecoimmune nutrition
Energy (KJ)	429	420	325
Protein (g)	4.0	5.6	2.8
Fat (g)	3.6	2.8	1.1
Linoleic acid (g)	1.7	0.22	0.5
Carbohydrate (g)	13.9	13.2	13.8
Fiber (g)	> 1.0		0.57
Vitamin E (mg)	2.0	6.0 IU	0.23
Thiamine (mg)	0.13	0.20	0.09
Riboflavin (mg)	0.14	0.17	0.02
Vitamin B_6 (mg)	0.16	0.15	0.07
Vitamin B_{12} (g)	0.4	0.0008	< 0.1
Folic acid (μg)	29	0.04	12
Pantothemic acid (mg)	0.7	0.67	0.09
Sodium (mg)	78.5	110	2.0
Chloride (mg)	126	130	11.3
Potassium (mg)	137	130	55
Calcium (mg)	71	80	10.7
Phosphorus (mg)	70	80	64
Magnesium (mg)	23	27	18.5
Iron (mg)	1.1	1.20	0.72
Zinc (mg)	1.1	1.50	0.62
Iodine (mg)	9.0	0.010	0.13
Copper (mg)	0.12	0.17	0.14
Manganese (mg)	0.3	0.20	0.55
Chromium (μg)	5.0	0.001	0.37
Selenium (μg)	5.0	0.001	0.003
Molybdenum (μg)	10	0.002	20
Arginine (mg)	160	1358 (added)	2500 (added)
Yeast RNA (mg)	0	135	0
Lactobacillus plantarum			1.5×10^9
Viscosity			0.02 m PaS

plantaricins. We have used *L. plantarum* 299 to produce a new *Lactobacillus*-containing enteral feeding formula by in vitro fermentation of a fiber-rich substrate. Oats were chosen, as they are one of the most complete foods. They have a favorable amino acid pattern, are rich in glutamine/glutamic acid, and are rich in fiber, especially water-soluble β-glucans. A unique feature is its high content of membrane lipids—phospholipids—which is 100 times higher in oats than in any other known food [32]. Strong synergistic effects with arginine suggested supplementing 2.5 g of L-arginine per 100 ml (Table 1). The original formula (without arginine supplementation) was extensively studied in animals. The supplemented formula is presently undergoing clinical trials for several indications including POT nutrition. Excellent reviews have been published on the roles of arginine [33], glutamine [34], SCFAs [35], lipids such as omega-3 fats [36], and RNA [37].

Membrane Lipids

The alveolar surfactant system may be involved in the acute respiratory distress syndrome (ARDS). Similarities exist between ARDS and preterm babies with respiratory distress, where deficient surfactants are the primary cause [38]. In the traumatized patient, total bronchoalveolar phospholipid content is unchanged, but a progressive decrease in the relative amounts of phosphatidylcholine and phosphatidylglycerol parallel a progressive increase in other membrane ingredients, including surfactant proteins [39]. The extent of changes relates to the severity of ARDS.

Similar changes seem to occur in the GI mucosa. In experimental animals with subtotal liver resection, we could prevent microbial translocation by an enteral supply of phosphatidylcholine [40]. Gangliosides such as GM_1 or GM_3 may be more potent glycolipids. GM_1 has an ulcer-healing effect on gastric mucosa [41] similar to that of H_2 blockers but without inhibition of gastric acidity. Intestinal mucosa is rich in GM_3, which changes in concentration and composition with age and disease and results in low fluidity in the brush border membranes. Gangliosides are incorporated into cell membranes [42] and influence membrane function and cellular response. In rats, oral administration of GM (300 μg/day) prevents rejection after rat heart–lung transplantation [43]. Lymphocytic infiltration was not observed in the transplanted organs. GM_3-rich food may increase GM_3 content in intestinal mucosa and reduce the load on the GALT. This assumption is supported by preliminary data from our laboratory. Milk is rich in GM_3, especially colostrum.

Antioxidants

An antioxidant is any substance that "when present at low concentrations compared to those of an oxidizable substance, significantly delays or inhibits oxidation of that substrate [44]. Destruction of membrane lipids by lipid peroxidation is paralleled by destruction of deoxyribonucleic acid (DNA). Human plasma contains several water-soluble antioxidants, such as ascorbate, glutathione, urate and bilirubin, and many lipid-soluble antioxidants such as tocopherols, carotenes, lycomene, lutein, zeaxanthine, and ubiquinol-10 [45]. Tocopherols are collectively referred to as *vitamin E*, the major lipid-soluble antioxidant in plasma and red blood cells. The effect of vitamin E depends on interaction with vitamin C and β-carotenes and sulfhydryls in membrane proteins. Vitamin C is the most important antioxidant in extracellular fluids. Glutathione (GSH), a tripeptide of glutamate, cysteine, and glycine, is present in most cells and is an important antioxidant in intestinal mucosa and the liver. It is estimated that GSH in the amount of 150 mg/day is consumed with a normal diet of fresh fruits, vegetables, and meat. The intake of GSH in sick patients has been neglected. GSH deficiency contributes to organ dysfunction after hemorrhagic shock [46] and sepsis [47]. It is a strong immune modulator, required for T cell activation [48]. Oxidant-induced liver peroxidation occurs with endotoxemia and bacterial peritonitis and with severe shock and reperfusion [49]; it is preventable in part by GSA.

Pectin, present in many fruits, is a strong antioxidant against all three main types of oxidation damage: peroxide, superoxide, and hydroxyl radicals [50]. It adheres to mucosal surfaces, especially at a low pH, and serves as an artificial protection layer, or pseudomucus. It delays gastric emptying and intestinal transit time and thus modifies absorption of glucose, cholesterol, bile acids, metals, and vitamins [51]. It also increases intestinal barrier function and prevents microbial translocation and disruption of intestinal microflora. Pectin increases colonic production of SCFAs. Pectin has strong mucosal protection when administered alone or together with various membrane lipids in models of gastritis, colitis, GI ulceration, and translocation with sepsis. Good clinical effects have been reported in patients with HIV/AIDS [52] after administration of a pectin-rich diet called the BRAT diet (banana, rice, apple, tea/toast). This diet is effective if there is a potent colonic endogenous flora to ferment the pectin. When a large amount of pectin is supplied (36 g/day), most of it (85%) is metabolized [53].

Pectin increases the thickness of the "unstirred water layer" on the mucosal surface [54], which explains its therapeutic effects, especially when used in combination with membrane lipids. To provide the most effective mucus-adhesive gel, pectins with the lowest molecular weights should be used.

Nutrition and Immune Function

More than 35 years ago Scrimshaw et al. suggested a bidirectional interaction between nutrition, immune response, and infectious diseases [55]. Almost all nutrient deficiencies can impair the host defense [56]. Thus many nutrients also have the ability to enhance the immune defense. Patients with protein deficiency have impaired production of interleukin 1 (IL-1), which can be corrected by diet [57]. The acute-phase response seen after injection of IL-1 is impaired in protein-deficient rabbits [58]. Reduced ability to produce IL-2 or to respond to IL-2 administration is implicated in the aging process, as well as in disease. Supply of vitamin E doubles IL-2 production in aged mice [59]. MOF secondary to sepsis is associated with higher IL-8 concentrations than the MOF of noninfectious shock [60]. IL-6 in septic patients has a late peak that correlates with a fatal outcome. TNF alters surfactant composition, which may in turn contribute to the development of ARDS [61]. TNF may also affect the GI surfactants and promote increased permeability and translocation. TNF-∂ mediates a decrease in tissue glutathione and increases the sensitivity of pulmonary vascular endothelium cells to H_2O_2 [62], which can be prevented by supplying N-acetylcysteine (NAC). TNF-∂ induces early systemic hypotension after trauma, which is inhibited by N^G-monomethyl-L-arginine [63]. Inhibition of both inducible and constitutive forms of NO increases mortality in rabbit models given endotoxin, but inhibition of only the inducible form is preventive [64]. Thus NO released by inducible enzymes may exert a protective role in septic shock, favoring vasodilator tone and maintaining blood flow to visceral organs. Clinically in trauma patients and experimentally after administration of endotoxin, methylene blue is a safe option to counteract malignant NO production and to obtain benefit from the positive NO effects, including scavenging of oxygen-free radicals, and the important microbicidal effects [64, 65]. This action is nutrition-dependent, and the response to trauma and sepsis is often limited by lack of substrates for NO production; for example, vasodilation is improved by previous administration of L-arginine. The decrease in gut blood flow after burns is modified by nitroprusside infusion, which also prevents translocation [66]. In a double-blind study patients responded well to the treatment and showed an increase in gastric intramucosal pH, oxygen delivery, and cardiac index and decreased systemic vascular resistance [67]. Responders showed a higher survival (69%) than nonresponders (19%). A higher dose or repeated doses could give even better results, as observed with fulminant hepatic failure [68].

Ingested nitrate is absorbed in the GI tract, extracted from plasma, secreted by saliva, and converted to nitrite by facultative anaerobic bacteria on the tongue. After ingestion of 200 mg potassium nitrate, the nitrite level rose from 111 μM to 1030 μM [70] Nitrite, when acidified in the stomach to approximately pH 2, produces NO at a concentration of about 600 nl. NO has a high affinity for iron/sulfur-containing respiratory enzymes, and it damages bacterial DNA [69] by a mechanism similar to that of leukocytes using NO to kill gut pathogens. It was suggested by Benjamin et al. [69] that acidified nitrite is not only effective on

Candida albicans and *Eschirechia coli*, but also on various gut pathogens, including *Helicobacter pylori*, amebae, and chronic intestinal parasites. Some food contains nitrate, especially such green vegetables as lettuce or spinach. NO also stabilizes gastric mucus by increasing its viscosity [71].

Neutrophils are involved in the induction of septic shock [72], and various neutrophilic functions are impaired in the presence of sepsis. Neutrophil respiratory burst function in critically ill patients is significantly depressed during early septic shock but not in nonseptic patients; the function recovers as the patient improves clinically [73]. It is assumed that this deficiency can be prevented by dietary manipulations.

Parenteral Nutrition

Parenteral nutrition is accompanied by decreased secretion of saliva, gastric and intestinal juices, and bile—all important for GI function and for antimicrobial defense. Bile acids are bacteriostatic, and bile contributes IgA to the intestine, an important factor in luminal control of microbial colonization. The inability of TPN to reverse catabolic states and prevent sepsis is now widely accepted. Energy requirements in critically ill and septic ICU patients are not as increased as previously thought. It should almost always be possible to meet nutritional needs by EN. A group of sick ICU patients were given aggressive TPN of 2750 kcal and 127 g amino acid intake per day. After 10 days of treatment they had lost an average of 12.5% of the body protein despite a mean gain of 2.2 kg in body fat [74]. A recent meta-analysis on perioperative TPN shows minimal effects on complication rates, varying from 12.8% better to 2.3% worse [75].

Jejunal Tube-Feeding

The development of devices for tube-feeding has made it possible to use enteral feeding before, during, and immediately after surgery. Feeding directly into the upper jejunum has the potential not only to eliminate the problem of vomiting and diarrhea but also to prevent microbial translocation and gut origin sepsis. Early jejunal EN should, if possible, be complemented with immediate, but minimal, oral/gastric feeding to increase acidity and stimulate gastric NO production. Such gastric feeding should contain NO precursors (lettuce or spinach) if possible, which should be carefully chewed.

Simultaneous intragastric pectin with phospholipids should provide gastric mucosal protection: A natural product such as the unripe banana is rich in pectin and surfactants. Pectin should never be given through a feeding tube because of the risk of clogging.

Jejunal tube-feeding should start at about 25 ml/hr and then be increased to about 10 ml/hr over the next 24 to 48 hours. Studies comparing intragastric and intrajejunal feeding have shown that metabolic recovery is considerably faster when the intrajejunal route is used [76]. The risk of aspiration is 600% greater with intragastric feeding [76]. Should one decide to use the intragastric route, it is advisable to feed intermittently [22], allowing acidity to increase between feedings to prevent microbial colonization of the stomach. Intrajejunal tube-feeding, in most cases, can be provided by preoperatively placed feeding tubes. If this maneuver is not possible, a jejunal feeding tube is placed either as a percutaneous endoscopic gastrostomy (PEG) tube or as a needle jejunostomy during surgery. Routine jejunal tube-feeding has

been hampered by poor performance of the feeding tubes presently available. The rate of spontaneous transpyloric passage of these tubes is unacceptably low, approximately 35% after 24 hours and approximately 70% [77] after 72 hours, which often necessitates additional use of endoscopy or radiography to place the tip of the tube in the upper jejunum. This fact and the high costs for extra hospital days and for the additional procedures (endoscopy or radiography) has discouraged many from routine use of tube-feeding. Hence one of us (S.B.) [78] developed a self-propelling feeding tube, which when introduced into the stomach propels itself into the upper jejunum within 4 hours. This tube has never and can never be regurgitated. It will be available in America and Europe within a year.

Content of Nutrition Formulas

Diets rich in fat, particularly omega-6-rich vegetable oils, produce diarrhea and enhance loss of fluids and electrolytes [79]. They seem also to interfere with absorption and other nutrients. Thus restriction of fats other than the omega-3 variety is recommended. High quality water is important. Immunocompromised patients should be given only boiled, filtered water. Bottled waters can contain bacteria; *Pseudomonas* organisms were identified in 6 of 8 American [80] and 39 of 87 European brands [81]. Outbreaks of infections from bottled water are rare, but the risk is important in sick patients.

Enteral Nutrition and Clinical Outcomes

A meta-analysis based on eight prospective randomized trials, published before 1991 [82] concluded that septic complications occur half as often (18%) in EN-fed patients when instituted after 6 to 72 hours than in TPN-fed patients (35%). The most significant differences were seen in trauma patients. Two randomized studies published in 1992 comparing EN and TPN in patients after abdominal trauma [83] and general trauma [84] showed as much as 65% and 76% fewer infections, respectively, in the EN-treated patients. These results were obtained with standard formulas without fiber or other specific ingredients. One could expect even better results using EN formulas to which immune-modulating ingredients, other substances, and probiotic bacteria are added.

Immune Nutrition and Clinical Outcomes

The first immune nutrition formula—enteral diet supplemented with arginine, omega-3 fatty acids, and RNA (IMPACT)—is regarded as a pharmaceutical agent. It is a supplement to standard nutritional formulas, containing ingredients documented to modulate the host's immune response and influence gut barrier function. It is based on many experimental studies that have shown protective effects in POT patients via components such as arginine, omega-3 fatty acids, RNA, vitamin C, and glutamine.

Gottschlich et al. [79] reported a significant reduction of nosocomial infectious complications and wound sepsis in burned patients with a diet enriched with arginine and omega-3 fatty acids. Daly and coworkers [84], randomized 85 patients to receive IMPACT or a standard formula after upper abdominal surgery for GI malignancies. The group receiving IMPACT had fewer complications (11% versus 37%), improved lymphocyte mitogenesis, and a shorter hospital stay (15.8 days versus 20.2 days). These results were confirmed in a recent report [85]. Braga and colleagues [86] showed a significant reduction of the severity (but not

the frequency) of postoperative infections and a shorter hospital stay among IMPACT-fed patients. The immune nutrients improve the phagocytic function of monocytes; the release of IL-2, IL-2 receptors, IL-1β, interferon γ (IFN-γ), IgM, and πgG; the number of CD3$^+$, CD4$^+$, and β lymphocytes; the response of skin delayed hypersensitivity; and reduced the circulating levels of TNF∂ and IL-6 [86, 87].

Bowers et al. [88] reported a large prospective, randomized multicenter clinical trial in ICU patients. Nutrition with IMPACT significantly reduced the length of stay, but only in patients classified as septic, and decreased the rate of acquired bacteremia and urinary tract infections. These differences were most evident in the subgroup receiving an adequate amount of the experimental diet (821 ml/day). No advantages were observed in the group having the systemic inflammatory response syndrome. The results of this study were modest but better than those reported for selective decontamination and without side effects.

Ecoimmune Nutrition—A New Generation of Nutrition

Most of the ingredients provided in EN solutions (simple carbohydrates, glutamine, arginine, omega-3 fats, RNA, and amino acids) are absorbed by the small intestine, often in the jejunum; only minimal amounts, if any, reach the colon. The diet/formula should contain substances that are substrates for fermentation and production of specific substances vital for colonic mucosa. There must also be probiotic bacteria available in the colon to ferment the various substrates and to produce sufficient nutrients in quantity. In most ICU patients such bacteria are absent owing to disease or antibiotic treatment and must be supplied along with nutrition.

The need for such bacterial supplementation was described by Eiseman et al. [89] and Wilmore [90], which was why we developed a new enteral feeding formula based on in vitro fermentation of oats and containing large quantities of live *Lactobacillus plantarum* 299. The results of treatment with this formula, without arginine supplementation, were as good as or better than those achieved by broad-spectrum antibiotics in animals with induced peritoneal sepsis [21]. It was tried, without arginine supplementation, in a small group of patients judged to be dying of MOF. In these patients, all antibiotics were discontinued, and lactobacilli and oat fiber were infused into the intestine. All five patients recovered dramatically and could leave the ICU. Their APACHE II score fell from an average of 18.4 before to 12.2 on day 5 and 8.8 on day 10. This treatment has the potential of being the next generation of immune nutrition. It is under clinical trial in the United States and Europe in posttrauma patients; after large operations; after transplantation, especially of bone marrow and liver; and in patients with acute pancreatitis, HIV/AIDS (chronic MOF), or advanced cancer, especially with heavy irradiation and cystostatic treatment. So far the results are encouraging. The product will most likely be available within 2 to 3 years.

Résumé

L'alimentation entérale présente plusieurs avantages par rapport à l'alimentation parentérale chez le patient polytraumatisé ou opéré. Les technique modernes d'alimentation par sonde ont fait de l'alimentation entérale précoce une réalité. L'apport alimentaire dans le jéjunum a plusieurs avantages sur l'apport alimentaire dans l'estomac: meilleur rendement métabolique, moins de problèmes de régurgitation et d'inhalation. L'alimentation entérale précoce ou immédiate est suivie d'une stimulation de la circulation splanchnique et hépatique, d'une augmentation de la vascularisation muqueuse intestinale, évite l'acidosc et les perturbations de la perméabilité de la muqueuse intestinale et élimine la nécessité d'une prophylaxie antistress. La salive, contenant d'importantes substances antimicrobiennes et l'acidité gastrique sont des éléments importants dans la prévention du sepsis. Mastication, et sécrétion de salive et d'acidité gastrique, stimulent le largage d'oxyde nitreux (ON), si important pour le débit sanguin de la muqueuse, la motricité gastro-intestinale, la formation de mucus et la bactériostase. Donner oralement les substances qui augmentent la production d'ON et mâcher des aliments riches en ON tel que la laitue ou les épinards peut être utile. On recommande également les lipides pris par la bouche et ceux qui sont sensés protéger la muqueuse. Il faut éviter les anti II$_2$ et les médicaments qui inhibent la production du salive. L'alimentation entérale immédiate, en commençant par 25 ml/hr, doit être augmentée à 100 ml/hr en 24–48 heures. Une attention particulière doit être apporté à la pureté de l'eau chez le patient immunodéficient. L'eau en bouteille peut contenir des bactéries telle le *pseudomonas*. Il faut préconiser les antioxydants alimentaires comme la glutathion, la vitamine E et les β-carotènes. Les aliments destinés au côlon sont très importants. Environ 10% des besoins caloriques sont fournis par les aliments coliques dits «prébiotiques», fermentés au niveau de la lumière colique dans le but de nourrir la muqueuse colique et prévenir le sepsis d'origine intestinale. La flore de fermentation (flore prébiotique) est perturbée en raison de la maladie ou d'un traitement antibiotique: restaurer la flore est donc aussi important. On recommande des fibres en raison de 10 gr/jour. Une nouvelle conception d'«éco-immunonutrition» est présentée ici pour donner une alimentation entérale comprenant l'apport de surfactants nouveaux, de pseudo-mucus, de fibres, d'acides aminés comme l'arginine et du *lactobacillus plantarum* 299.

Resumen

La nutriciòn enteral (NE) posee diversas ventajas sobre la nutriciòn parenteral (NP) en pacientes postoperatorios/post-trauma (POTS). Las modernas tecnologìas de alimentaciòn por tubo han hecho posible la NE precoz. La alimentaciòn yeyunal tiene ventajas sobre la alimentaciòn por tubo gàstrico: màs ràpida recuperaciòn metabòlica, menos vòmito y menor riesgo de regurgitaciòn y aspiraciòn. La NE inmediata o precoz estimula la circulaciòn esplàcnica y hepàtica, mejora el flujo mucoso, previene la acidosis in tramucosa y las alteraciones de permeabilidad y eliminan la necesidad de profilaxis de ulceraciòn de estrès. La saliva, que contiene importantes sustancias antimicrobianas, y la acidez gàstrica son de importancia en la prevenciòn de la sepsis. La masticac iòn, la saliva y la acidez gàstrica favorecen la liberaciòn de òxido nìtrico (NO) gàstrico, de importancia para el flujo mucoso, la motilidad gastrointestinal, la formaciòn de moco y la bacteriostasis. Una provisiòn oral de sustancias donantes de NO y la masticaciòn de alimentos ricos en nitratos, tales como la lechuga y la espinaca, pueden ser de utilidad. Se recomiendan lìpidos orales y protectores de la mucosa, y se deben evitar los bloqueadores H-2 y las drogas inhibidoras de la saliva. Se debe provee r NE inmediata, comenzando con 25 ml/hora e incrementando a 100 ml/hora en el curso de 24–48 horas. En el paciente inmunocomprometido se debe prestar especial atenciòn a la

pureza del agua. El agua embotellada puede contener bacterias tales como pseudomon as. Antioxidantes alimentarios como la glutamina, la vitamina E y el (caroteno son importantes. Los ingredientes para la mucosa colònica son importantes. Aproximadamente el 10% del requerimiento calòrico es satisfecho por los denominados alimentos colòni cos (prebiòticos), que se fermentan a nivel de la mucosa colònica para producir nutrientes de la mucosa colònica y para prevenir la sepsis de origen intestinal. Se recomienda fibra por encima de 10 gramos/dìa. La flora de fermentaciòn (flora prebiòtica) s e altera debido a enfermedad o tratamiento antibiòtico, por lo cual la replecciòn de la flora es importante. Un nuevo concepto de eco-inmunonutriciòn es presentado para la provisiòn enteral de ingredientes recondicionadoras de la mucosa: nuevos surfactante s, pseudomocos, fibra, aminoàcidos tales como arginina y el Lactobacillus plantarum 299.

Acknowledgment

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