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Nutritional Support and Infection: Does the Route Matter?

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Abstract. Questions regarding the effects of the route of nutrition began to surface shortly after the introduction of total parenteral nutrition (TPN). Although TPN has become a life-saving therapy for patients who cannot tolerate enteral nutrition, it is not the panacea it was hoped to be. It appears that the enteral route of nutrition decreases rates of infectious complications compared with parenteral feeding. Reasons for this phenomenon are not clear, but it seems that enteral nutrition supports the gut barrier and gut-associated lymphoid tissue, which may have effects on infections at distant sites such as the lung. These effects do not appear to be due solely to prevention of malnutrition, as the infectious complications develop early after injury or illness. However, the lack of understanding of the mechanisms does not negate the fact that in many clinical studies the enteral route of nutrition is superior to the parenteral route in terms of reducing infectious complications in critically ill or injured patients.

Beliefs about the optimal quantity and composition of adequate nutrition for the hospitalized or sick patient have changed radically over the last 30 years. How nutrients affect the immune system, particularly in times of stress, is currently being studied aggressively. For thousands of years the only route available for feeding was enteral; however, the whole area of nutritional support was revolutionized by Dudrick et al. when total parenteral nutrition (TPN) was introduced in 1968 [1]. With improvements in catheters, catheter care, formulas, and monitoring, the use of TPN skyrocketed. Because the use of enteral nutrition was perceived to be labor-intensive and associated with multiple complications, TPN became the preferred route of nutritional support for many patients. It has been life-saving for those with severe inflammatory bowel disease, short gut syndrome, and other diseases. Today, however, a growing body of evidence has demonstrated that in many patient populations the enteral route of nutrition has significant advantages over TPN, including cost, safety, and support of the gut and immune system. Specifically, enteral compared with parenteral nutrition has been shown to decrease infectious complications in critically ill and injured patients. This paper reviews the evidence for and against this concept and presents current hypotheses that attempt to explain these effects.

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Enteral versus Parenteral Nutrition: The Beginnings

The first major clinical study to suggest the benefit of enteral nutrition on immune function was of patients in a pediatric burn unit [2]. Subjects were allowed oral feeds ad libitum and received supplemental tube feeding or TPN as necessary. They were randomized into two groups: one received a standard enteral formula, and the other received a high-protein enteral formula. The control group received more calories, but only about half of their calories and protein were delivered enterally. Patients receiving the high-protein formula received slightly more protein, but approximately three-fourths of their calories and protein were delivered via the enteral route. Patients receiving the high-protein diet had significantly higher values of serum protein, transferrin, complement C3, and immunoglobulin G (IgG), and their leukocytes had a higher opsonic index than those from patients receiving the control diet. Patients in the control group had more days of bacteremia and days on systemic antibiotics. The survival rate was lower in the control group (56% vs. 100%; $p < 0.03$), and all mortality was attributed to infection. Results of this study could be interpreted in a number of ways. The additional protein or the quality of protein might have been responsible for the improvements seen in the study group compared with the control group. Alternatively, the fact that most of the nutrition in the study patients was provided via the enteral rather than the parenteral route may have played a significant role. Although this study did not answer the question of whether route of nutrition had an effect on the incidence of infection in burn patients, it certainly raised many intriguing questions.

At the same time, work from Sheldon's laboratory explored the roles of malnutrition and the route of nutrition on survival following sepsis [3–5]. Using a highly lethal model of intraperitoneal injection of *Escherichia coli* suspended in hemoglobin, animals were divided into two groups [3]. One group was fed rat chow ad libitum, and the other was fed a protein-depleted diet. After 2 weeks, the *E. coli*-hemoglobin adjuvant solution was injected intraperitoneally. Survival rates in the normal and protein-depleted rats were 66% and 15%, respectively ($p < 0.01$). Next, a group of animals were protein-depleted for 2 weeks and then refed with chow, TPN, or TPN plus lipid. Survival after *E. coli*-hemoglobin adjuvant injection was 53% in chow-fed animals, 0% in the TPN group, and 4% in the TPN plus lipid group [3]. Subsequently, protein-depleted animals were pair-fed a TPN

Table 1. Results of studies comparing early enteral versus early parenteral feeding for patients with abdominal trauma.

Study	Inclusion criteria	No. of patients	Patients with major septic complications (no.)[a]			Comments
			Enteral	TPN	*p*	
Feliciano [9]	ATI = 15–40, penetrating trauma	22	1/11 (9%) (1 IAA)	3/11 (27%) (3 IAA, 1 pneumonia)	NS[b]	Hospital stay longer with TPN (26.9 ± 22.2 days vs. ENT 13.7 ± 5.2 days; $p = 0.03$)
Moore [10]	ATI = 16–39, blunt and penetrating trauma	59	1/29 (3%) (1 IAA)	6/30 (20%) (2 IAA, 6 pneumonia)	0.03	Route of nutrition primary risk factor for pneumonia
Kudsk [11]	ATI > 15, blunt and penetrating trauma	96	8/51 (16%) (6 pneumonia, 1 IAA, 1 empyema)	17/45 (38%) (14 pneumonia, 6 IAA, 4 empyema)	<0.02	Route of nutrition important only if ATI > 24 or ISS > 20; one obstruction at jejunostomy site; 13.3% line sepsis with TPN
Adams [12]	Injuries to two or more body systems	46	12/23 (52%) (11 pneumonia, 1 IAA)	10/23 (43%) (8 pneumonia, 2 IAA)	NS	Two life-threatening TPN complications; one obstruction at jejunostomy site

ATI: Abdominal Trauma Index; TPN: total parenteral nutrition; ENT: enteral nutrition; ISS: Injury Severity Score.
[a]Intraabdominal abscess (IAA), empyema, and pneumonia.
[b]Insufficient study population.

solution orally or via a central line and compared with chow-fed controls [4]. Using the same peritonitis model, survival at 48 hours was approximately 65% in the oral TPN group, 55% in the chow group, and 35% in the IV-TPN group, demonstrating a benefit of the enteral compared with the parenteral route of nutrition in response to sepsis after protein depletion.

To determine whether route of nutrition was important in experimental conditions other than after recovery from a protein-depleted state, well nourished rats were entered into a similar protocol [5]. Prior to intraperitoneal *E. coli*-hemoglobin adjuvant injection, rats were fed the same solution either via gastrostomy or central catheter for 12 days. The 48-hour survival was 60% in the enteral group and 20% in the parenteral group. These studies implicated the route of nutrition and not the formula itself as the reason for the differences between groups.

Clinical Studies of the Effect of Enteral versus Parenteral Nutrition on Infection

Initial investigations of the effect of the route of nutrition on infection in trauma patients compared early enteral feeding with delayed feeding (enteral or TPN). In a small study from Italy, 18 patients were randomized to receive early (within 12 hours) postoperative jejunostomy feeding or to have their nutrition delayed for 7 days (control) [6]. By day 7, the sepsis rate (including pneumonia and intraabdominal abscesses) was 25% in the control group compared with 10% in the fed group. In a larger, well designed study, Moore and Jones randomized trauma patients who had an Abdominal Trauma Index (ATI) of >15 to receive jejunal feedings within 12 to 18 hours postoperatively or to receive no nutrition for the first 5 days followed by either an oral diet or TPN [7]. The ATI provides a risk analysis for the development of septic complications. By using the number of organs injured and their severity of injury, scores can be rapidly calculated. The rate of infectious complications gradually increases as the ATI climbs to between 15 and 25 but increases more rapidly as the ATI increases >25 [8]. The enteral group had a significantly lower rate of infection (including pneumonia and intraabdominal abscess) compared with those in the control group (9% vs. 29%; $p < 0.05$).

Most clinical evidence comparing early enteral feeding versus parenteral nutrition has come from studies of patients requiring celiotomy for abdominal trauma (Table 1) [9–12]. In general, most of these studies have found a decrease in infectious complications with the use of early enteral nutrition. In three of four of these studies, investigators used the ATI to determine eligibility for entry into the clinical studies [9–11]. In addition to the ATI, the Injury Severity Score (ISS) was used to stratify patients. The ISS is a more global measure of body injury and reflects a score of the three most severely injured body systems. An ISS > 20 is considered severe. In the Tennessee study, most of the benefit of enteral nutrition seemed to occur in the most severely injured patients (i.e., patients most likely to become infected and require intensive resource utilization) [11]. Patients with an ISS ≤ 20 or ATI < 25 had low rates of infection and no differences between enteral and parenteral feeding. In patients with an ISS > 20, an ATI ≥ 25, or both, randomization to TPN increased the risk of infection by 6.7, 7.3, and 11.3 times, respectively. Feliciano et al. found a sepsis rate of 27% with TPN compared with a 9% rate with enteral feeding, which was comparable to the other reports; however, there was insufficient patient accrual to achieve statistical significance [9]. Data from several of these studies [7, 9, 10] were included in a meta-analysis of trauma and general surgery patients and confirmed the benefit of enteral nutrition in many critically ill patients [13].

One notable exception to these observations was documented in a study by Adams et al., who found no differences in infectious complications between patients with abdominal trauma randomized to TPN or jejunal feeding [12]. Patients were eligible if they sustained major injuries to two or more body systems regardless of the magnitude of intraabdominal injury. Several problems exist with this study, however. The surgical team randomized patients during celiotomy, creating a potential bias. The groups did not appear to be well matched; for example, the enteral group had three times as many patients with chest injuries and almost twice as many head-injured patients as the TPN group. The difference in the incidence of infectious complications may have been affected by these injuries: (1) severe chest trauma is a major risk factor for prolonged ventilator dependence and pneumonia; and

(2) radiologic changes associated with atelectasis or pulmonary contusion from chest trauma could easily be misinterpreted as pneumonia. Finally, the type of enteral nutrition and the method for calculating nutrient needs were not consistent throughout the study.

Enteral feeding studies of patients with severe head injury have produced inconsistent results. In a study of head-injury patients randomized to receive TPN within 8 hours of injury or intragastric feedings when tolerated, mortality was higher in the enteral group, although almost all of the deaths were attributed to head injury [14]. At least one-third of the patients in the enteral group developed sepsis, although the septic rate in the TPN group was not reported. However, enteral nutrition was greatly delayed as judged by a mean caloric intake of 500 cal/day in the enteral group at 7 days compared with almost 2000 cal/day in the TPN group. In addition, none of the patients in the enteral group received more than 600 kcal/day for the first week or 1000 kcal/day for the first 10 days. Because of the apparent delay in enteral feeding due to gastric atony, no conclusion regarding early enteral nutrition can be reached from this study. It did suggest benefits of early TPN rather than delayed enteral feeding in head-injured patients, although these results were not confirmed by the same group in a subsequent study [15]. On the other hand, Grahm et al. showed a significant reduction in infectious complications with early jejunal feeding following severe head injury [16]. In this study, 32 patients with severe head trauma were randomized to receive either a nasojejunal tube placed within 36 hours of injury or direct intragastric feeding after gastric atony resolved. Patients given the early enteral feeding had significantly fewer episodes of septic complications, including bronchitis, pneumonia, and ventriculitis. Although this study was promising, a subsequent study by Borzotta et al. [17] randomizing 57 patients to either TPN or early enteral feeding within 72 hours of injury failed to find any significant difference. Both routes were effective in meeting nutritional goals, but there were no differences in infectious complications.

The effect of enteral versus parenteral feeding has been studied for several disease processes other than trauma. A recently released study of pediatric patients with short bowel syndrome (SBS) showed a higher incidence of "sepsis" when patients received enteral feeds rather than TPN, compared with that in children of similar age and diagnoses who required surgery but did not have SBS [18]. Unfortunately, "sepsis" and "bacteremia" were used interchangeably in the report, and all cases were attributed to line sepsis, although no lines were removed or cultured. In addition, the number of infectious episodes were not correlated with the number of days of enteral or parenteral feeding. The latter study clearly has a different patient population, and it is difficult to extrapolate these findings to critically ill or injured patients.

On the other hand, enteral nutrition compared with parenteral feeding has been shown to reduce infectious complications in patients with inflammatory bowel disease [19]. In a study of 42 patients with moderate to severe attacks of ulcerative colitis, patients were randomized to receive either intragastric feeding or TPN if they did not respond to 48 hours of intravenous steroids. Although the groups were well matched, they were somewhat malnourished as evidenced by a mean ideal body weight of 83% to 85%. There were significantly more infections in the TPN group than the enteral group, demonstrating a benefit of the enteral route of nutrition in this moderately to severely ill patient population.

A recent area of investigation has been the importance of enteral diet composition. Various "immune-enhancing" components, such as glutamine, arginine, omega-3 fatty acids, nucleotides, and β-carotene, have shown significant promise in laboratory experiments and recently in several clinical studies. Burned pediatric patients administered a diet supplemented with arginine and omega-3 fatty acids sustained fewer infections and a shorter length of stay per percent body burn than patients fed unsupplemented enteral diets [20]. In a multiinstitutional study of general surgical patients randomized to a diet supplemented with arginine, nucleotides, and fish oil, the hospital stay was significantly shortened for patients tolerating at least 800 ml/day of the immune-enhancing diet [21]. In the subset of patients with sepsis, those fed the study diet had a significant reduction in hospital stay and a major reduction in the development of nosocomial infections. Patients undergoing surgery for upper gastrointestinal malignancy had an improvement in T cell function along with fewer infections and shorter length of stay if they were fed an immune-enhancing diet compared with those fed a standard formula [22]. In another study of patients undergoing resection for upper gastrointestinal malignancy, patients randomized to an immune-enhancing diet sustained significantly fewer infections and a shorter length of stay than patients randomized to an isonitrogenous and isocaloric standard enteral diet [23]. Likewise, in two prospective studies of patients sustaining blunt or penetrating trauma, patients randomized to an immune-enhancing diet containing glutamine, arginine, omega-3 fatty acids, nucleotides, and branched-chain amino acids sustained significantly fewer abscesses and a significantly reduced infectious complication rate than patients randomized to standard enteral diets [24, 25]. In the second of these studies, the control diet was isonitrogenous; patients randomized to the immune-enhancing diet had a significantly shorter length of hospital stay and required significantly fewer days of therapeutic antibiotics than patients randomized to the isonitrogenous control diet [25]. Unfortunately, because formulation of these diets contain several "immune-enhancing" components, it is unclear which component or combination of components is responsible for the improved outcome.

Rationale for the Benefit of Enteral versus Parenteral Route of Nutrition

The mechanisms explaining the reduced septic complications with the use of enteral nutrition compared with parenteral nutrition are currently unknown. Specifically, in trauma patients it does not appear to be related to malnutrition because most of these patients are well nourished. It is difficult to implicate protein-calorie malnutrition as an etiologic factor in the development of the pneumonias and intraabdominal abscesses that occur within 4 to 10 days of injury. One hypothesis to explain the increased rate of infection in parenterally fed patients is that intravenous nutrition induces immunosuppression.

Support of this concept comes from the U.S. Veterans Administration (VA) Cooperative Study of perioperative TPN in general surgical patients [26]. Altogether 395 malnourished patients were randomly assigned to receive either TPN for 7 to 15 days at 85% of their nutrient goals or no perioperative TPN but allowed ad

libitum oral intake. There were significantly more infectious complications noted in the patients randomized to TPN than in the control group, but there was a decrease in noninfectious complications (e.g., anastomotic or wound dehiscence) in the TPN group, although the difference failed to reach statistical significance. Closer examination of the data showed that most of the increase in infectious complications occurred in patients who were borderline or minimally malnourished (i.e., patients likely to recover without the need for aggressive nutritional support after surgery). In patients with severe malnutrition documented by significant hypoalbuminemia and weight loss, noninfectious complications were significantly higher in the unfed group. Despite the obvious benefit of TPN in the severely malnourished patients, the increased risk of septic complications in minimally malnourished patients suggested that TPN had an immunosuppressive effect.

Subsequently, a study from Memorial Sloan–Kettering Cancer Center appeared to substantiate these findings [27]. Patients undergoing major pancreatic resection for malignancy were randomized to perioperative nutrition support or to standard dextrose-containing salt solutions postoperatively. Abscesses were significantly more frequent in the group randomized to TPN. Neither group was severely malnourished as evidenced by an average perioperative weight loss of 5.8% and 6.8% and serum albumin levels of 3.1 and 3.3 g/dl in the TPN and control groups, respectively. These studies suggest that patients who are undergoing major surgical procedures and who are given TPN are at increased risk of infectious complications.

The finding of increased septic complications with TPN has not been substantiated in all studies. In a study of 124 patients undergoing resection of hepatocellular carcinoma [28] patients randomized to perioperative intravenous nutritional support in addition to their oral diet had fewer septic complications and sustained a significant reduction in overall postoperative morbidity. Most of the clinical advantage occurred in patients who had underlying cirrhosis and were undergoing major hepatectomy. In particular, the incidence of pulmonary infections was higher in the unsupplemented group with no significant difference in intraabdominal abscess formation between the two groups. In those patients there was no obvious immunosuppressive effect of TPN.

More important than whether TPN is immunosuppressive are the mechanisms through which patients are rendered at risk for pneumonia and intraabdominal abscess following trauma or elective surgical procedures. Impaired gut-barrier function has been implicated as a significant causative factor. In health, the normal gastrointestinal tract effectively allows absorption of nutrients yet maintains an effective barrier against intestinal toxins and bacteria. The enterally fed intestine is a metabolically active organ that actively and passively maintains this barrier through peristalsis, secretory IgA, mucin, numerous inhibitory factors within the mucin layer, and intact cell–cell junctions lining the villi. Multiple immunologic mechanisms support this barrier, with Kupffer cells serving as an important secondary barrier to increased permeability. Starvation, infection, chemotherapy, irradiation, hemorrhagic shock, TPN, and other insults allow subsequent metabolic and immunologic deterioration of the gut barrier [29–35]. In these situations, the gut is thought to become a driving organ of progressive multiple organ dysfunction by releasing proinflammatory cytokines from the mucosa and other immunologic cells lining the gastrointestinal tract [36–40]. Such cytokines include interleukin-6 (IL-6), which induces hepatic protein reprioritization in order to produce acute-phase proteins [41]. In addition, the gastrointestinal tract serves as a priming site for neutrophils that subsequently relocate to pulmonary tissues and other nonintestinal sites [42]. It may also be a window for bacterial invasion into the systemic and splanchnic circulation. Bacterial translocation has been demonstrated in animal models and in humans under certain clinical conditions, such as bowel obstruction, inflammatory states, shock, and the use of vasopressors [31, 43]. Sampling of portal vein blood after trauma has not documented the presence of enteric bacteria, nor has bacterial translocation been shown to be a culprit in the development of intraabdominal, respiratory, or extraintestinal infections [44].

Although the human gut may not become permeable to bacteria during critical illness, it has been well documented that it becomes more permeable to intraluminal macromolecules such as lactulose. Interestingly, the route of nutrition has also been shown to affect this barrier function. Experimental models have shown increased permeability to lactulose in enterally fed animals compared with those fed parenterally [45]. Hadfield et al. examined the gastrointestinal tract permeability to 3-*O*-methyl-D-glucose, D-xylose, L-rhamnose, and lactulose in critically ill patients and found more rapid improvement of permeability in those fed enterally than in those given TPN [46]. On the other hand, our work has demonstrated that the gastrointestinal tract becomes increasing permeable to lactulose in approximately one-third of severely [47] injured patients regardless of the route of feeding, and that this permeability positively correlates with serum IL-6 levels measured 24 to 36 hours after injury [48]. In other work, we demonstrated that serum levels of IL-6 at 24 to 36 hours after injury are significantly higher in patients who develop subsequent infections on days 4 through 10 compared with patients who have uneventful—nonseptic—recovery [49]. These seemingly disparate results might be explained by the hypothesis that the increased IL-6 is a marker of increased gut permeability. This breakdown of the gut barrier leads to infection. If the use of enteral versus parenteral nutrition decreases the permeability of the gut, it would be expected that these patients fed enterally would have decreased IL-6 serum levels and therefore decreased rates of infectious complications. However, a definite link between this permeability and the development of infections has yet to be made.

Another method by which enteral nutrition may have an impact on the immune system is by affecting intestinal immunoglobulin. Approximately 50% of the body's total cellular immunity lines the upper and lower respiratory and gastrointestinal tracts, producing 70% to 80% of all the immunoglobulin produced by the body [50]. This immunoglobulin—secretary IgA—serves as a protective barrier within the mucin layer by blocking adherence of bacteria, viruses, and other toxic products to the mucosal cells [51]. In animal models, clinical conditions that reduce IgA levels within the intestine are associated with bacterial overgrowth and the development of bacterial translocation to mesenteric lymph nodes [30, 33, 34, 52, 53]. IgA does not work by creating an inflammatory process via stimulating complement formation but by agglutinating foreign material. Infectious organisms are thus neutralized by trapping them within the mucin layer to be subsequently extruded by normal body processes. Intravenous TPN and even enterally administered TPN solution (administered as a model of an

elemental-type diet) leads to reductions in IgA, bacterial overgrowth, and increased bacterial translocation [33, 53, 54].

Although some species have separate bronchial-associated lymphoid tissue, the source of most mucosal immunity in humans is from the gut-associated lymphoid tissue (GALT) in the Peyer's patches of the small intestine. Neonates are born without any significant GALT, but it slowly increases to normal levels over the first 2 years of life; initial protection is provided by colostrum from mother's milk [55, 56]. The cells in mucosal and glandular tissue, such as mammary ducts, which generate secretions that are released onto the mucosal surfaces, originate from Peyer's patches. Naive B cells circulate through the bloodstream and exit into the Peyer's patches at the high epithelial venule [57]. If an antigenic challenge is processed by the Peyer's patches as the cells migrate into these sites, and if there are appropriate T cell cytokine signals, the up-regulated, stimulated B cells then migrate to the mesenteric lymph nodes. Here they proliferate, releasing myriad cells into the thoracic duct and vascular tree, where they are subsequently distributed to various mucosal sites, especially the lamina propria of the small intestine. At these affector sites, the B cells become plasma cells producing significant quantities of IgA against the antigen to which they have been sensitized. This system of mucosal protection appears exquisitely sensitive to both the route and type of nutritional support in animal models. In animals fed intravenous or enteral TPN solutions, there is a significant reduction in the total number of lymphocytes, B cells, and T cells, as well as intraepithelial lymphocytes obtained from the small intestine of mice [58]. Within the primary site of IgA production—the lamina propria—there is a significant reduction in the CD4/CD8 ratio in animals fed these two diets. The administration of chow maintains the GALT and intestinal IgA levels. Feeding the animals a liquid enteral diet that is more complex than TPN solution has the same effect on the GALT except in the lamina propria. Although a significant reduction in T and B cells occurs there, the normal CD4/CD8 ratio is maintained, presumably providing an adequate stimulus to B cell production of IgA. This reduction in total GALT mass and deviation in the CD4/CD8 ratio within the lamina propria can be entirely avoided in TPN-fed animals if they are administered subcutaneous doses of bombesin, a tetradecapeptide that stimulates secretion of hormones by the gastrointestinal tract [59]. In addition, if glutamine—a lymphocyte and mucosa-specific fuel—is added to the TPN solution, GALT cell mass and function is also preserved to a large extent [60].

These changes within the intestinal GALT, however, appear to have significant extraintestinal effects. Because cells produced by the Peyer's patches are distributed to the submucosa of the respiratory tract, upper respiratory tract mucosal immunity has also been shown to be affected by intravenous nutrition. When animals that have been sensitized to IgA-mediated H1N1 influenza virus are fed intravenous TPN, mucosal immunity is impaired and susceptibility to infection is increased; that is, immune animals have become nonimmune [61]. Interestingly, although both chow and a complex diet maintain this barrier, intragastric TPN fails to preserve enteral GALT but maintains normal respiratory tract immunity. The simultaneous administration of bombesin [59] during intravenous TPN or the addition of glutamine to the TPN solution [60] also improves mucosal immunity compared with animals fed intravenous nutrition alone. The clinical implications of this are significant because many bacteria, including *Klebsiella*, *Haemophilus influenzae*, *E. coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and others have been shown to be IgA-mediated [62] and the use standard of intravenous nutrition may be failing to provide normal mucosal immunity against these common respiratory pathogens.

Similar findings have been found within the peritoneal cavity [63, 64]. When rats were randomized to enteral or intravenous nutrition and given a subsequent intraperitoneal bacterial challenge, animals fed via the gastrointestinal tract had significantly reduced intraperitoneal bacterial counts in association with a much greater burst of cytokine activity within the peritoneal cavity and less systemic translocation of bacteria or inflammatory cytokines than animals fed intravenously [63]. The intravenously fed animals had higher levels of bacteria within the peritoneal cavity, a blunted intraperitoneal cytokine response, increased spillover of bacteria into the systemic circulation, and an increased proinflammatory systemic cytokine response. In another study by the same investigators, rats given intraperitoneal *Escherichia coli* also demonstrated increased bacterial counts, fewer exudative cells and lower tumor necrosis factor (TNF) and IL-1α levels in the peritoneum of intravenously fed animals compared with those fed enterally [64]. Animals fed via the gut had lower numbers of bronchoalveolar cells and lower levels of TNF but higher amounts of interferon-γ (IFNγ) in bronchoalveolar lavage fluid than those fed TPN. Systemic levels of TNF were higher and IFNγ were lower in the TPN group. This finding can be interpreted that intravenous nutrition decreases the release of peritoneal cytokines, which in turn negatively affects the migration of inflammatory cells to the peritoneum, allowing increased translocation of bacteria. Because of this reduced response, more bacteria may have been released to the systemic circulation, and the animals respond with higher systemic TNF levels. The authors postulated that the decreased numbers of cells in the bronchoalveolar fluid in enterally fed animals was due to migration of these cells to the peritoneum induced by higher levels of IFNγ.

In a clinical study of normal volunteers, there were increased levels of serum TNF, IL-6, and soluble TNF receptor type II following endotoxin infusion in those who had been fed intravenous TPN for 7 days compared with those maintained on a liquid enteral diet for 4 days [65]. Conversely, membrane-bound TNF receptors and soluble TNF receptor type I were lower in TPN-fed patients compared with the enteral group. The changes in TNF receptors is interesting, but at this time its implications are unknown. Santos et al. performed a similar study, giving intravenous endotoxin to normal volunteers who were randomized to enteral versus parenteral feeding. They found no difference in symptomatic response and a decrease in serum TNF and IL-6 in those fed TPN, which contradicts the results of the above studies [66].

Although the cellular mechanisms that explain these effects are still being unraveled, intravenous nutrition appears to blunt the immunologic response within the intraperitoneal cavity. It is interesting that many of the cells that lie within the gastrointestinal tract originate from intraperitoneal sites, suggesting a close relation between the GALT and intraperitoneal protection.

Although it has yet to be determined whether the mechanisms described above are the driving force in the improved clinical outcome and reduced septic susceptibility in patients fed via the gastrointestinal tract, it is clear that enteral feeding improves the clinical outcome of critically ill and injured patients. Delivery of

nutrients via the gastrointestinal tract improves recovery in patients likely to become infected (i.e., those with the highest ATI or ISS whose systemic and mucosal defenses are likely to be the most severely impaired). Whether it is the amino acids, protein, glucose, and trace elements that are being processed by the gastrointestinal tract or some stimulatory effect of these nutrients on the gastrointestinal tract has yet to be determined. Clearly, however, it is more than just the prevention of malnutrition that produces these beneficial effects considering the short time frame between injury and the development of these infectious processes.

Résumé

On a commencé à s'interroger sur la valeur des différentes voies d'administration de la nutrition artificielle dès l'apparition de l'alimentation parentêrale totale (APT). Blen que l'APT soit une thêrapeutique qui augmente la survie lorsque l'alimentation entêrale est impossible, elle ne représente pas la panacée imaginée au départ. Il semble que la voie entérale diminue l'incidence des complications infectieuses par rapport à l'alimentation parentérale. Les raisons pour cela ne sont pas claires. Cependant, il semble que la trophicité de la barrière muqueuse intestinale et le développement du tissu lymphoïde intestinal sont améliorés après alimentation entérale. Ces effets ne sont pas dus simplement au rôle nutritif car les complications infectieuses se voient assez tôt après les agressions chirurgicales ou traumatiques. On ne connaît pas encore les mécanismes d'action exacts de la nutrition artificielle mais il n'en reste pas moins vrai que la plupart des études cliniques montrent que l'alimentation entérale est supérieure à l'alimentation parentérale pour réduire les infections chez les patients gravement malades ou victimes de traumatisme.

Resumen

Tan pronto como se introdujo la nutrición parenteral total (NPT) surgieron los primeros interrogantes pertinentes a la mejor ruta para administrar nutrición. Aunque la NPT ha demostrado ser una terapia capaz de salvar la vida en los pacientes que no toleran la nutrición enteral, no es la panacea que una vez se pensó. Hoy aparece evidente que la vía enteral disminuye las tasas de complicaciones infecciosas en comparación con la nutrición parenteral. No son claras las razones; sin embargo, parece que la nutrición enteral dá soporte a la barrera intestinal y al tejido linfoide intestinal, lo cual puede significar efectos sobre el desarrollo de infecciones en lugares distantes, tales como el pulmón. Estos efectos no parecen deberse exclusivamente a la prevención de la malnutrición, por cuanto las complicaciones infecciosas aparecen temprano una vez ocurrida la lesión o en el curso de la enfermedad. Pero la carencia de suficiente conocimiento sobre los mecanismos involucrados, no niega el hecho de que en muchos estudios clínicos la ruta enteral se demuestra superior a la vía parenteral en cuanto a la reducción de las complicaciones infecciosas en los pacientes traumatizados y en estado crítico.

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