Enteral versus Parenteral Nutrition: Alterations in Mechanisms of Function in Mucosal Host Defenses

Nicholas A. Meyer and Kenneth A. Kudsk

Department of Surgery, University of Wisconsin – Madison, Madison, Wisc., USA

Parenteral nutrition has significantly advanced the survival of patients who sustain major loss to the GI tract or prolonged delayed ability to take oral or tube feedings. However, there is accumulating evidence that the processing of nutrients via the gastrointestinal (GI) tract maintains an important immunologic defense mechanism, the mucosal associated lymphoid tissue (MALT), which functions as the primary source of specific immunity at all mucosal surfaces. Investigation of trauma patients reveals that parenteral nutrition is associated with a significantly higher incidence of pneumonia, intra-abdominal abscess, and possibly multiple organ dysfunction, than enteral nutrition [1–4]. This chapter describes the mounting evidence supporting the current clinical trend to aggressively pursue nutritional delivery via the GI tract.

Parenteral Nutrition

Parenteral versus Enteral Nutrition: Clinical Data

Total parenteral nutrition (TPN) is extremely concentrated in order to deliver the necessary amount of nutrients within a volume that is tolerated by patients. The high osmolar load requires delivery into a large, central vein where the high flux of blood rapidly dilutes the concentrated nutrient solution. Although the use of central venous catheters themselves present a source of infectious complications, clinical evidence shows an increase in both intra-abdominal abscess formation and pneumonia in studies comparing parenteral feeding to enteral feeding or to starvation.

Supported by National Institutes of Health grant R01 GM53439.
In early studies of this phenomenon, Moore and Jones [1] randomized moderately to severely injured patients to either enteral feeding or intravenous dextrose. Parenteral feeding was instituted in the patients who did not tolerate a diet by day 5. The enterally fed group had a significantly lower incidence of infectious complications, primarily intra-abdominal abscess formation. In a follow-up study, patients with similar injuries were randomized to either parenteral formula or protein- and calorie-matched enteral formula advanced to goal rate within 72 h of injury [2]. Patients fed enterally had a significantly lower incidence of infectious complications, primarily pneumonia, with a trend toward a reduction in intra-abdominal abscess. Subsequent research at the University of Tennessee randomized 98 patients to either enteral feeding or to a nitrogen- and calorie-matched parenteral formula including more severely injured patients with extremely high abdominal trauma indices (ATI) and high injury severity scores (ISS) [3]. In this study, patients receiving parenteral feeding had a significantly higher incidence of pneumonia, intra-abdominal abscess formulation and line sepsis. In addition, infected patients fed parenterally sustained significantly more infections. Most of the differences between enterally and parenterally fed patients occurred in the more severely injured patients (ATI ≥25 or ISS ≥20).

Specific nutrients in the enteral formula appear to provide additional protection. Moore et al. [4] demonstrated a significant reduction in intra-abdominal abscess and a lower rate of multiple organ dysfunction syndrome (MODS) in patients randomized to a diet enriched in glutamine (GLN), arginine, n-3 fatty acids, and nucleotides [4]. In a subsequent study of high-risk trauma patients (ATI ≥25 and ISS ≥20), Kudsk et al. [5] found a significant reduction in intra-abdominal abscess formation in patients receiving the immune-enhancing diet compared to an isonitrogenous, isocaloric standard enteral formula and a markedly reduced incidence of infection compared to patients receiving no feeding at all.

Mechanisms for the Reduced Incidence of Pneumonia and Intra-Abdominal Abscess Formation

Many investigators have studied the potential mechanisms underlying the septic complications associated with TPN and a lack of enteral stimulation. One hypothesis involves bacterial translocation (BT) where lack of intraluminal stimulation leads to a loss of integrity of intestinal mucosal defenses, which in turn allows BT from the intestinal lumen into the gut lymphatic and blood stream to seed distant sites. Most of this work has been done in rats which are extremely sensitive to a lack of enteral feeding where ‘gut starvation’ produces rapid atrophy in the proximal gut mucosal to approximately to 50–60% of normal. Simultaneously, biliary immunoglobulin A (IgA) levels decrease associated with an overgrowth of aerobic bacteria in
the cecum. While protein calorie malnutrition by itself does not increase BT, addition of an extra-intestinal inflammatory focus such as a sterile abscess or zymosan dramatically increases BT to the mesenteric lymph nodes (MLNs), liver, spleen and lung. BT, however, has never been linked to MODS or extra-intestinal infectious complications clinically. Moore et al. [6] sampled portal vein blood in the early post-trauma period and noted no translocation. Positive blood cultures are not uncommon following trauma, but they do not correlate with subsequent infectious complications. Interestingly, laboratory conditions which increase BT are also associated with a reduction in the primary specific immunologic mucosal defense, IgA. Because of the inconsistent findings associated with BT, an alternative mechanism based on the mucosal immune hypothesis provides a better supported explanation for the increases in pneumonia and intra-abdominal abscess associated with lack of enteral feeding.

**Mucosal Immunity**

Gut-associated lymphoid tissue (GALT) is an integral part of the body’s immune system both by providing immunological control of resident intraluminal flora and, as part of the larger MALT, provides protection of distant sites such as the lungs, nasopharynx, mammary glands and genitourinary tract. The afferent limb of GALT consists of Peyer’s patches (PP) and MLNs. Intraluminal antigen is taken up by M cells overlying the PP, processed by antigen-presenting cells that then interact with naïve T and B lymphocytes which enter the PP via interaction with mucosal addressin adhesion molecule-1 (MAdCAM-1). These sensitized cells are distributed via thoracic duct drainage and the vascular system to various submucosal locations where they contribute to the efferent limb of GALT. The lamina propria (LP) of the intestine is one effector site where activated T and B lymphocytes accumulate and produce IgA after conversion of B cells to plasma cells. Polymeric IgA manufactured in the submucosa is transported into the lumen by the overlying epithelial cells which are enriched with the polymeric immunoglobulin receptor, secretory component (SC) [7]. The IgA prevents adherence of bacteria, viruses, and other toxic molecules to the mucosal surface. Multiple animal models demonstrate that IgA levels correlate inversely with bacterial overgrowth, translocation and changes in intestinal permeability. Activated T and B lymphocytes also distribute themselves to other mucosal effector sites where they contribute to local IgA production in a similar fashion. In this manner continued intraluminal antigenic stimulation maintains an immunologic barrier to microbial invasion.

In the mouse, the lack of enteral stimulation quickly leads to a dramatic reduction in PP, LP, and intraepithelial lymphocytes. Within 72h of stopping enteral feeding, the PP and LP sustain a 55–66% reduction in B and 40%
reduction in T lymphocytes [8]. MAdCAM-1 is partly responsible for this change since MAdCAM-1 direct unsensitized lymphocytes to the PP and sensitized lymphocytes to the LP. Within hours of parenteral nutrition alone, PP MAdCAM-1 expression drops but recovers rapidly with enteral refeeding [9].

The lack of enteral stimulation also affects the balance of cytokines controlling lymphocyte maturation. T-cell subpopulations change with a decrease in the CD4:CD8 ratio. CD4 cells produce interleukin (IL)-4 and IL-10, both of which upregulate IgA production [10]. In mice, parenteral nutrition decreases intestinal IL-4 and IL-10 levels creating an imbalance in favor of the IgA-inhibiting cytokine interferon-γ (INFγ) which is unaffected thereby decreasing IgA production by plasma cells [11]. Since CD4 cells stimulate B cell proliferation, colony expansion, and immunoglobulin secretion, the relative depression in CD4 cells, IL-4 and IL-10 appears to reduce the stimulatory effects on B cells since levels of IL-4 and IL-10 correlate positively with IgA levels.

The lack of enteral stimulation also decreases epithelial transport of IgA. IgA produced in the LP is normally transported across the epithelium by binding to SC, a protein receptor on the basolateral surface of the mucosal epithelial cell [7]. The IgA-SC receptor complex is transported to the apical surface where the IgA and part of the receptor are cleaved off the cell. TPN depresses the selective transport of IgA into the lumen but does not completely abolish it [12]. Cytokine changes can at least partially explain this effect. SC expression is regulated by IFNγ and IL-4 in a synergistic fashion [13]. Although TPN does not appear to affect intestinal levels of IFNγ, TPN reduces intestinal IL-4. The effect on MALT is lowered IgA production and epithelial transport due to reduced lymphocytes and cytokine alterations. Laboratory studies using the mouse have consistently shown decreases in both intestinal and nasotracheal IgA levels within 3 days of ‘gut starvation’ with TPN [8, 11, 14].

The decreases in intraluminal IgA induced by a lack of gut feeding and parenteral nutrition may explain the increased incidence of pneumonia seen with parenteral feeding. Mice intranasally immunized against Pseudomonas aeruginosa accumulate antigen-specific respiratory mucosal IgA in their respiratory tracts which reduces mortality to an otherwise lethal dose of P. aeruginosa. When successfully immunized animals are challenged with a lethal bacterial load 5 days after initiating a parenteral diet, their mortality rate is over 70% higher than chow-fed animals, comparable to the mortality rate of nonimmunized animals [15], reflecting a loss in established antibacterial immunity. A similarly increased susceptibility to viral upper respiratory tract infections has been found. An influenza virus infection well documented to be IgA-mediated, A/PR8, was studied in the mouse model. Previously immunized mice which normally sterilize a second viral dose within hours were fed TPN for 5 days and then challenged with an intranasal virus load. Two days later 50% of the animals receiving TPN continued to shed virus in the respiratory tract compared to none in groups receiving an enteral diet [16].
Peritoneal Protection

Several laboratories have reported differences in the peritoneal response of animals fed parenterally following intraperitoneal sepsis. Lin et al. [17] noted that the number of peritoneal exudative cells (PECs) was significantly reduced in parenterally fed compared to enterally fed mice tract. This reduction in PECs was associated with a blunted intraperitoneal tumor necrosis factor response, an increase in bacterial proliferation, and an augmented vascular inflammatory cytokine response. Recently, our laboratory investigated the response to a sterile peritonitis model using a 1% glycogen solution [18]. A lack of enteral stimulation and TPN significantly reduced the number of polymorphonuclear cells (PMNs), macrophages, and lymphocytes within the peritoneal cavity 4 h after glycogen injection. Interestingly, supplementation of TPN with 2% GLN reversed the TPN-induced peritoneal effects to glycogen peritonitis.

Vascular Inflammatory Responses

The alterations in the mucosa-associated immune system associated with a lack of enteral nutrition may also contribute to noninfectious-mediated multiple organ failure by augmenting inflammatory responses to subsequent stressors. Polymorphonuclear neutrophils are the major effector of the nonspecific immune inflammatory response and their role in organ failure after injury is becoming well established. The vascular bed of the GI tract has the capacity to prime PMNs which, once activated, respond to subsequent insults by causing further tissue destruction. This has been especially well documented in the lungs [19]. PMNs are intrinsically involved in the acute, nonspecific inflammatory response where they adhere to the capillary endothelium, migrate across the endothelial wall and can cause destruction of both invasive microbes and body tissues by releasing destructive enzymes and toxic oxygen radicals. Such nonspecific tissue destruction can contribute to eventual organ failure.

TPN induces priming of PMNs compared to enteral nutrition by recruiting PMNs to the GI tract. Intercellular adhesion molecule-1 (ICAM-1) is the endothelial ligand counterpart of CD11/18 integrins expressed on PMNs. The binding of CD11/18 integrins to ICAM-1 is the basis for PMN margination and triggers the maturation process for PMNs enabling them to pass through the endothelial cell lining and begin the activation process [20]. IFN$\gamma$ is an important stimulator of ICAM-1 expression while IL-4 and IL-10 are important inhibitors of ICAM-1 expression. Lack of enteral feeding does not alter IFN$\gamma$ levels, but it reduces gut IL-4 and IL-10 levels [21]. The observed induction of intestinal ICAM-1 expression is consistent with this change in cytokines [22]. P- and E-selectin also influence the PMN-endothelial cell interaction.
These adhesion molecules expressed on the surface of endothelial cells trigger leukocyte rolling along the endothelium of postcapillary venules as a precursor to firm adhesion through CD11/18-ICAM-1 interaction. TPN increases expression of P-selectin in the GI tract and E-selectin in the lungs [23]. The detection of elevated myeloperoxidase (MPO) levels in the GI tract confirm an accumulation of PMNs associated with increased adhesion molecule expression [22]. Both intestinal ICAM-1 and MPO levels return to normal 4 days after reinstitution of an oral diet. Therefore the lack of enteral feeding induces a transient, nonspecific response, with endothelial changes in the intestine and subsequent PMN priming.

This priming is evident when TPN-fed mice are exposed to a second insult. Similar to classic models of hemorrhagic shock with splanchnic hypoperfusion, mice fed parenterally for 5 days were exposed to either 15 min of superior mesenteric artery occlusion and compared to animals fed chow, a complex enteral diet, or TPN formula delivered intragastrically. Within 72 h of this ischemic event, mortality was significantly higher in the parenterally fed group (40%) than in animals fed via the GI tract (mortality 5–10%). When studied 3 h after this ischemic event, there was a significant increase in vascular permeability in the lung and liver of parenterally fed animals compared to the enterally fed groups. Expression of CD11a or CD11b (markers of PMN activation) did not increase any of the groups prior to the ischemic event but, CD11b expression was significantly increased 3 h following ischemia only in circulating PMNs isolated from the parenterally fed group. Using immunohistochemistry, only the lung of animals fed parenterally had elevated levels of activated myeloid cells reflected in increased CD18 expression.

**Complexity of the Enteral Diet**

Not only the route of nutrition (oral vs. parenteral) but also the complexity of oral nutrition affects the integrity of the mucosal immune system and alters the inflammatory response of intestinal and extra-intestinal organs to a nonseptic insult. In many experiments the above effects were investigated in mice by comparing TPN to standard mouse chow taken ad libitum, a complex (intact protein, carbohydrate and fat) enteral diet which could be delivered isonitrogenously and isocalorically to the parenteral group to control for variable nutritional intake values, and the parenteral formula delivered through a gastric feeding tube instead of intravascularly. In most of the experiments, similar differences were observed between parenterally fed mice and mice fed either chow ad libitum or a complex enteral diet. Therefore it is safe to dismiss a possible difference in calories or protein as driving the immunoregulatory changes that have been associated with parenteral nutrition. The elemental diet (intragastric parenteral formula), completely devoid of complex nutrients and roughage, induced a partial
suppression of the MALT when compared to chow but not as severely as seen with complete lack of enteral stimulation.

However, some important differences have been noted when the same formula was used intravenously and intragastrically. Mortality in immunized mice after a bacterial pneumonia challenge was less in mice fed an elemental intragastric diet (57%) than in mice fed parentally (88%), yet significantly greater than in mice fed a complex enteral diet (10%) [24]. However, in the model of viral upper respiratory infection, the elemental diet resulted in intact defenses and no viral shedding [25]. An intragastric, elemental diet decreases lymphocyte mass in the PP, LP, and intraepithelial sites, lowers intraluminal IgA, and depresses levels of intestinal IL-4 but not IL-10 [11, 25, 26]. An intragastric, elemental diet also partially upregulates ICAM-1 expression in the intestine but not to as great an extent as TPN [27]. After an intragastric elemental diet, survival to 15 min of mesenteric ischemia is similar to chow-fed mice, but it decreases survival rates to that of mice given parenteral nutrition when ischemia is extended to 30 min.

The Enteric Nervous System

A complex enteral diet or chow preserves the immune system better than a simple elemental diet. It is likely that complex molecules within the diet stimulate the GALT via neurological and hormonal mediators. Strong evidence supports an interaction between intraluminal stimulation, GALT and the enteric nervous system (ENS). The ENS is densely incorporated in the gut with approximately 2 m of nervous tissue/cm³ of intestinal tissue [28]. Neuropeptides released by this network regulate gut motility, secretions, growth, immune function and mucosal defenses.

Gastrin-releasing peptide is a neuropeptide produced by the human ENS. Exogenous bombesin (BBS), an analogus peptide obtained from frogs, reverses the TPN-associated GALT atrophy and impairment in respiratory defenses to pneumonia and viral infections. BBS given concurrently with TPN prevented decreases in total lymphocyte yield from PP, LP, and intraepithelial spaces, maintained the CD4/CD8 ratio of T cells in the LP, and returned depressed intraluminal IgA levels to normal [29]. BBS also reversed TPN-associated impairment of IgA-mediated defenses to an upper respiratory tract viral challenge [30] and also improved the drop high mortality rate (21%) of the Pseudomonas pneumonia to levels comparable to the chow-fed group (15%) [31]. The reversal of detrimental TPN effects with BBS is not complete, however. ICAM-1 levels elevated by TPN in the small intestine are not affected by BBS nor are IL-10 levels returned to normal [32].

BBS may function directly to stimulate GALT or may act by releasing other GI hormones. Gastrin, cholecystokinin and neurotensin are released in response to BBS and may be involved in preserving GALT. When given
concomitantly with TPN in the mouse model, each neuropeptide influenced GALT positively but to varying extent [33]. All three preserved lymphoid cell mass in the PP comparable to chow, but the site of activity was different. Gastrin and cholecystokinin had less effect on the distal small bowel while neurotensin was more effective distally. Intestinal IgA levels associated with each neuropeptide were significantly higher than in animals given TPN alone but not as high as in animals given chow. Immunity to bacterial pneumonia was maintained with cholecystokinin and gastrin but neurotensin appeared to have no effect. Although all three neuropeptides help to preserve GALT when enteral stimulation is lacking, none acting singly reflects the nearly complete resolution of GALT depression seen with BBS administration.

Glutamine

Supplementation of TPN with GLN attenuates many of the detrimental GALT effects. GLN is an important respiratory fuel for the intestinal tract but is not routinely added to TPN because of its instability over time in solution especially with heat sterilization. Addition of GLN to TPN increases cellularity and attenuates atrophy of the intestinal mucosa [34], decreases BT [35] and abrogates alterations in mucosal permeability [36]. Replacing 2% of the amino acids in TPN with GLN improved total lymphocyte yield in the PP and LP, normalized the CD4/CD8 ratio in the LP and normalized IgA concentrations in the small intestine, nasal tract and lungs [37, 38]. GLN partially preserves upper respiratory immunity both to a viral challenge (A/PR8 virus) [37] and to *Pseudomonas* pneumonia [39]. Intestinal IL-4 levels are maintained comparable to chow diet but not IL-10 levels [32, 38]. As with BBS, GLN reverses some but not all of the effects on nonspecific PMN activation. Elevated ICAM-1 expression associated with TPN is returned to normal when TPN is supplemented with GLN [32]. Survival of mice after intestinal ischemia/reperfusion injury is improved with GLN as well, but is still significantly lower than in animals fed chow [40].

Conclusion

Clinical differences clearly occur in response to the route and type of nutrition. A complex enteral diet maintains mucosal immunity whereas a lack of enteral stimulation quickly leads to impairment of the GALT and common mucosal immune system and predisposes patients to remote infections, pneumonia, and noninfectious multisystem organ failure. Complex enteral nutrition is beneficial and should be pursued orally or by nasoenteric, gastric or jejunostomy tube unless absolutely contraindicated. In those situations where TPN must be used, stimulation of mucosal immunity with hormones such as BBS or GLN may overcome some of the detrimental effects of TPN.
References


**Discussion**

*Dr. Peeters:* We have heard a lot of people talk about the fact that you can postpone feeding in an acute insult for, let’s say, 2 days when a patient comes to the intensive care unit (ICU) with major burn for instance. But what about those effects that happen in the first 24 h?

*Dr. Kudsk:* We have looked at this. There are only a couple of areas that you can get into the body to test. I can’t take out the intestines of my patients to look and see what their mucosal addressin adhesion molecule expression is or what their IgA level is;
however, I can do a bronchoalveolar lavage (BAL) and look at the levels of IgA within their airways which gives an insight into this system. I studied a group of patients with head injury, they were not fed via the gastrointestinal tract, and they were intubated. We quantitated how much of the fluid we got back was epithelial fluid by performing a microurea technique and then corrected for that. Between 24 and 36 h after injury there are approximately 100,000 units of IgA/cm² of epithelial fluid. After another 36 h, this value plummets to about 20% of normal. If we wait another 72 h, the results stay the same. I have data from 2 patients who we then started to feed. In these 2 patients I saw IgA levels gradually increase. It does not prove the concept but there is nothing inconsistent between these findings and the data that I showed you in the animals.

Dr. Cynober: Your hypothesis is that the route of administration makes the difference. We have another interpretation, that the content of total parenteral nutrition (TPN) products is imbalanced and inappropriate and as a matter of fact you showed that when you add glutamine to TPN you have the same effect as enteral nutrition on IL-4 expression, on intracellular adhesion molecule (ICAM) expression which mice develop after gut ischemia. I believe that certainly we have to improve the content of the TPN solution and then to discuss the route of administration.

Dr. Kudsk: I might agree with you except that I have given animals intragastric TPN, which is the same solution they were fed intravenously. When that same solution is fed via the gut it preserves a lot of the mechanisms. There may be an effect of nutrients, but it can’t only be the nutrients. We have shown [1] that cholecystokinin, gastrin and bombesin (or gastrin-releasing peptide) are all able to bring this immunity back to normal. So that would argue against it just being a component of the TPN.

Dr. Cynober: But we can discuss your argument that providing TPN intragastrically mimics the effect of the chow diet simply for one reason, most of the TPN products, and probably you use standard products, mimic the content of regular diet given by the enteral route, and the major issue with TPN is that you have a shortage of splanchnic metabolization and rebuilding of a new profile. I am absolutely not surprised that the TPN product is working very well when given by enteral route.

Dr. Kudsk: I think that TPN can be improved. There are products available on the market, at least in Europe now, which show some benefits. I am not saying that this is the only product that can work but I think that there are novel things that can be done to improve immunity. And whatever that defect is, our laboratory has been very successful in showing where the immunologic vulnerability is. It is that the bacteria get into the airway in our intubated patients and are not bound by IgA. This is an explanation which has to be disproved before I am going to give it up.

Dr. McClave: I am still struggling to understand the TH1 and TH2 subset because I think they set a tone in the environment at the level of the gut and, in inflammatory Enteral versus Parenteral

Dr. McClave: I am still struggling to understand the TH1 and TH2 subset because I think they set a tone in the environment at the level of the gut and, in inflammatory

Dr. Moore: I will address it in my talk but I think that you really have to ascertain that resuscitation is complete before you feed somebody, and what we know is that after shock you have a disproportion of vasoconstriction in the gut and once you resuscitate, gut perfusion does not come back to normal. We have used the gastric tonometry as a monitor in shock resuscitation and found it not to be that helpful as an endpoint for resuscitation. However, it is helpful when you start feeding patients after shock resuscitation. If PrCO₂ goes up the patient is not going to tolerate enteral nutrition. So that is my fast answer of how we currently could monitor gut perfusion.

Dr. Moore: I will address it in my talk but I think that you really have to ascertain that resuscitation is complete before you feed somebody, and what we know is that after shock you have a disproportion of vasoconstriction in the gut and once you resuscitate, gut perfusion does not come back to normal. We have used the gastric tonometry as a monitor in shock resuscitation and found it not to be that helpful as an endpoint for resuscitation. However, it is helpful when you start feeding patients after shock resuscitation. If PrCO₂ goes up the patient is not going to tolerate enteral nutrition. So that is my fast answer of how we currently could monitor gut perfusion.

Dr. Moore: I will address it in my talk but I think that you really have to ascertain that resuscitation is complete before you feed somebody, and what we know is that after shock you have a disproportion of vasoconstriction in the gut and once you resuscitate, gut perfusion does not come back to normal. We have used the gastric tonometry as a monitor in shock resuscitation and found it not to be that helpful as an endpoint for resuscitation. However, it is helpful when you start feeding patients after shock resuscitation. If PrCO₂ goes up the patient is not going to tolerate enteral nutrition. So that is my fast answer of how we currently could monitor gut perfusion.
bowel disease, chronic parasitic infection generates a TH2 response that
downregulates the inflammatory response and you are less likely to get invasive
pneumococcal disease. If you have bacterial and viral infection it is a TH1 response, it
is more inflammatory, and you are more likely to get invasive pneumococcal disease.
I wonder in the discussion we have had about compensatory anti-inflammatory
response syndrome (CARS) if this is the difference between a TH1-predominant or a
TH2-predominant environment? You just made the comment that the difference in
TH1-inflammatory TH2 downregulates, though systemically it is reversed at the level
of the gut. Could you clarify that? And the second point is have you interpreted that
correctly?

Dr. Kudsk: We have just now started to add injury in our models. We have tried to
define the system and all the permutations caused by diet. As I have looked at some
of those slides with the CARS, when IL-4 and IL-10 go up, I am wondering whether
that is the period of time when there is a reduction in IgA. There are bacteria present
because the IgA levels are dropping. The bacteria become more virulent. There is work
done by Alverdy et al. [2] on the nonfed gut and bacteria. While we see a reduction in
IgA in my models, they see these bacteria becoming stressed and responding by
producing adhesins which make them more attachable to the mucosa. I speculate that
the increase in serum IL-4 and IL-10 is a spillover from the gut which is trying to
defend against the bacteria.

Dr. McClave: You don't interpret the drop in IgA as an effect of the downregulated
response by IL-4?

Dr. Kudsk: There are two things that I believe are affecting the IgA. One is the
reduction in cell mass and the second is the change in cytokines. So both issues play
a role prior to the bacterial infection. I haven't studied how the mucosa responds once
bacteria have attached.

Dr. McClave: Some of the immunology that you are talking about really is similar
to the immunology of Crohn’s disease, especially when you increase the endocrine
levels you increase neutrophils and myeloperoxidase activity. Do you think that maybe
what you are seeing with TPN versus enteral nutrition is merely a rapid alteration in
gut flora that is causing this inflammatory response in TPN, and certainly in
inflammatory bolus where you see probiotics now attenuate that response? That can
also explain why, when you give the TPN fluid orally, you get less of an inflammatory
response because you don't change the gut bacteria.

Dr. Kudsk: There are several things happening simultaneously, downregulation of
cytokines and a downregulation of the basic immunity, IgA, which keeps bacteria out
of our system. It has been shown in animal models that starved animals maintain a
barrier there to keep the bacteria out. If an inflammatory focus occurs, however, the
whole system breaks down. But as the gut is starved while TPN is given to prevent
malnutrition, the bacteria become more virulent. We plan to inject exogenous IgA to
determine whether we can keep the bacteria, from becoming more virulent. That will
tell me whether these bacteria are responding to a weaker host or whether they are
trying to survive.

Dr. Heyland: I just want to understand your perspective on TPN a bit more. You
as well as several others in other populations have demonstrated in clinical trials that
there is a consistent that enteral nutrition is associated with a reduction in infectious
morbidity in critical illness. You also say that TPN is more deficient than being actually
a toxin or doing harm to the patient. What about the association of parenteral nutrition
and hyperglycemia and its subsequently increased infectious morbidity, and what
about the discussion we had yesterday related to lipids and the lipid component of the
TPN, its immunosuppression, and the trials that actually would hold the lipid part of
the TPN and they demonstrate a reduction of infectious morbidity? So I guess when I
look at it that way I think maybe there are toxicities associated with particular kinds of TPN or at least a misuse of TPN that may explain these clinical trials. Do you want to comment on that?

Dr. Kudsk: I am glad you raised that point. Let’s talk about lipid first. I haven’t done studies with lipids. One of the reasons we use a TPN solution that is glucose-based is because of the controversy whether the lipid itself is an immnosuppressor. If these experiments were performed with lipid, one could argue that it is the lipid that caused the immunologic deficiency. With regard to glucose, I am surprised at how people have accepted these data on hyperglycemia, and been so willing to accept it. You know as soon as the article came out in the *New England Journal of Medicine* [3], we had more insulin drips going in our ICU than ever before, and some of these patients had blood sugars as low as 47. There is going to be a price to be paid for that. Pomposelli et al. [4] wrote that the reason for the increased infections in the VA Cooperative Study and in the Moore et al. [5] study is that the patients had high blood sugars. But what is not known is when those blood sugars were drawn. Were they drawn before the infection or during infection? All we know is the peak glucose. As patients become infected, their blood sugars go up. We went back then to our study population and looked at 95 of the 98 randomized patients in our enteral/parenteral trial [6]. We had drawn blood sugars sequentially over the first 5 days in 86 of them. I analyzed them and found that blood sugar had nothing to do with the outcome and published this about a year ago [7], but it is never brought up that the study shows that glucose did not play a significant role in our population. There was a difference of about 15 mg% over the course of the experiment between the enterally and parenterally fed patients but nowhere near the 180–190 mg/dl associated with infection. The incidence of blood sugars over 200 mg/dl was far higher in the enteral group than in the parenteral group. The people who had the highest blood sugars were not the ones who got infected. So the difference between enteral and parenteral feeding on infection cannot be explained by hyperglycemia from my data. 63% of those patients in the Van Den Berghe et al. [3] study were cardiac patients. A recent study that just came out in the *American Journal of Surgery* [8] showed no impact of diabetes on the postoperative outcome in patients having cardiac surgery. It seems to me that glucose may be working through some other mechanisms such as inotropic effects. I think it is amazing what people have accepted without question. I suspect that there will be publications that show that insulin did not have an effect on outcome.

Dr. Déchelotte: In your studies in animals did you also try to correlate your observations with IgA and IL-10 to the glutathione status in the gut or in the lung and also the production of chemokines?

Dr. Kudsk: Yes I do have those data. With intravenous TPN glutathione drops significantly.

Dr. Déchelotte: On the clinical point of view, in the clinical settings, what would you suggest to be the best way of assessing the effects of enteral nutrient supply on lung immunity? Does it make sense to determinate the aurine tricarboxylic acid concentration in BAL fluids or in the saliva for instance. What is your experience?

Dr. Kudsk: Salivary IgA can be used but it is very difficult to collect it in ICU patients. But BAL is a technique which is useful in the clinical population. I would love to get a piece of small gut from these people but that is impossible. You can get a nip of the mucosa but that is not what we are talking about, we are talking about mass along the whole gastrointestinal tract.

Dr. Schultz: Thinking about the intraepithelial lymphocytes and the context of your experiments, do you think there is any correlation between the gut and the nasal mucosa in terms of the concentrations of the γδ T cells, especially because these cells are producing α in a very high concentration?
**Dr. Kudsk:** The γδ cells are in the intraepithelial space much more than within the lamina propria. The person who is the expert on that is Dr. Teitelbaum at the University of Michigan. Those cells make IFN-γ, and they are important in controlling tight junctions between the epithelial cells. They also may provide another signal to the underlying gut-associated lymphoid tissue (GALT) cells, but he is working on what the intraepithelial lymphocytes do.

**Dr. Nitenberg:** In your experimental data you always get better results with a chow diet than with commercial diets and than with intravenous administration supplemented either with bombesin or with glutamine. Could you comment on that?

**Dr. Kudsk:** I think there are two things. The complex enteral diet (CED) produces similar results but is less stimulating than chow. This is one thing that chow provides that the CED does not. The CED animals are continuously infused and the animals that get chow have intermittent feeding. I looked at the gastrointestinal tract of animals that got intravenous TPN, intragastric TPN as a perfusion, and others that drank the TPN solution. Clearly intermittence of feeding plays a role [9]. Now I believe that it is an effect of the neuropeptides.

**Dr. Nitenberg:** Do you think it is important to have gastric feeding instead of jejunal feeding?

**Dr. Kudsk:** To try to put a jejunal catheter in mice would be difficult. The stomach does, however, generate a stronger hormonal response.

**Dr. Chioléro:** In patients difficult to feed by the enteral route, septic patients for example, would you add parenteral nutrition, practically?

**Dr. Kudsk:** Yes, when they are frankly septic and hyperglycemic and unstable I don’t really feed them anything. If they are being fed into the small intestine and they become septic and unstable, we stop small bowel feeding at that time.

**Dr. Chioléro:** Yes, but if the evolution is prolonged, sepsis can last days and days, so then comes a day where you should feed these patients and when the enteral route does not work well, what would you do practically?

**Dr. Kudsk:** It depends upon the severity of the sepsis. If you are talking about severe sepsis with catecholamines in high levels that should resolve within a day or 2 or the patient dies, but if you are talking about very sick patients who respond to resuscitation and are better the next day, that is when we feed them intravenously and switch them to enteral feeding as soon as possible.

**Dr. Bozzetti:** What is the minimal dose that you expect to be beneficial in clinical practice, the minimal dose of enteral feeding?

**Dr. Kudsk:** There are very little data on that. We only have a study by Alexander [10] in which he gave animals 100% TPN, 75% TPN and 25% enteral, 50–50, 25–75, and 100% enteral. In that particular experiment when he went from 25% enteral to 50% enteral was when the big reduction in translocation occurred. That was using a burn model.

**Dr. McClave:** A lot of the stimulation for GALT are ubiquitous organism and so I would expect those same organisms to be in the nasal cavity and colonizing an endotracheal tube and stimulating mucosa-associated lymphoid tissue (MALT) in the lungs. So I would expect these same systems, the nasopharyngeal-associated lymphoid tissue (NALT) and the MALT, in the lungs to have exposure, process the lymphocytes and have them home back to those areas, and yet you have shown in your experiments, when you don’t feed the gut the IgA levels fall off as if those systems atrophy. So my question is when you look at NALT and MALT how much of their mass is due to their own processing and homing mechanisms versus immune tissue being processed at the level of gut and coming up these sites? Is that something you can answer?

**Dr. Kudsk:** We did the second experiment to generate immunity because patients who get put in the ICU and have to generate resistance and defenses against new
bacteria are generally resistant to gram-negative bacteria. As they get challenged with bacterial overgrowth, they need to respond to them. I think that the defect occurs because this whole system is being downregulated and also there is an impairment to a new challenge.

Dr. McClave: Let me clarify it. How much of these distant site MALT in the lungs, not in the nasal cavities, are dependent on their own antigen processing versus antigen processing in immune tissue, come from the gut to these distant sites?

Dr. Kudsk: An experiment we have never done is to divide the esophagus of these animals and immunize via the nasal passages so the antigen can’t go into the stomach and see if protection develops in the gut. Then immunize another group of mice into the stomach to see how much protection there is in the airway. In human studies, a type-specific *Escherichia coli* was given to the mothers towards the later part of the pregnancies [11]. Whereas the colostrum had no specific IgA before immunization, after the subjects had been immunized then suddenly the colostrum provided IgA against that particular *E. coli*. So clearly a distribution does occur in humans. How much of the antigen is processed within the nasal passages, I don’t think anybody knows.

Dr. Baracos: I am sitting back here cogitating on amino acid requirements for gut-associated immunity and starting to understand some of the things that were said by Dr. Cynober. There is group of people who spend their time and energy studying first the path metabolism of amino acids in the gut. So they are looking at what disperses from the lumen and what appears on import blood, and they spend their time fantasizing about what the amino acids might have been utilized for in the first path. I wonder if you know what the respective culture of that profile of amino acids might be in the gut-associated immune cells as opposed to the enterocytes? Then, if I understood Dr. Cynober correctly, was he suggesting that if you knew what that culture in your amino acid solution was to optimize gut-associated immunity if delivered parenterally, would it be based on that first path culture?

Dr. Kudsk: I haven’t studied that very much but I think back to an article in 1969 by Hirschfield and Kern [12]. They looked at animals that were given amino acids both in the well-fed state and animals that had been fasted, and then during recovery. What they found was that in the animals that had a fed gut, the amino acids basically passed across the mucosa. When the animals had been fasted and had gastrointestinal tract atrophy, then almost none of the amino acids passed through into the vascular system until the mucosa had regained its thickness, or nearly regained it. Then it allowed the amino acids to go into the systemic circulation.

Dr. Allison: If you put some non-absorbed thing into the gut just like bulk, would that have the same effect? I mean have you got to put substrates that are metabolized bulk substrates in?

Dr. Kudsk: Spaeth et al. [13] did that and studied bacterial translocation. They gave animals just bulk and found that bacterial translocation was reduced by it. I believe that as the bulk moves it stimulates neuropeptide release which stimulates normal levels of IgA and there is less bacterial translocation.

Dr. Déchelotte: I have an additional comment on the point made by Dr. Baracos about absorption and splanchnic extraction because there have been several studies performed in humans, in healthy humans, by Dr. Mathews and myself, demonstrating the kinetics of glutamine absorption with this quite saturable uptake process in humans. Splanchnic extraction strongly depends of course on the nutritional status and the quantity of glutamine supplied: the highest glutamine supply, the lowest splanchnic extraction.

Dr. Kudsk: Is there a difference in absorption between someone who has been fasted for 5 or 6 days and someone who is just postprandial?
Dr. Déchelotte: To this specific point I don’t have any answer.

Dr. Cynober: There are classic studies which support this idea and what you mentioned before.

Dr. Rosenfeld: How much is the minimal amount to have these results in patients with enteral nutrition because sometimes it is very difficult to feed them?

Dr. Kudsk: Again I go back to the only study we have, the one with the burned guinea pigs [10] which took between 25 and 50% of the calculated nutrient goal for guinea pigs to maintain integrity with no bacterial translocation.

Dr. Peeters: Thank you very much. Maybe you will allow me to summarize. We heard quite a lot of proof for the statement we all made 25 years ago, if we want to feed a patient, feed him through the gut, and if you can’t give him parenteral nutrition, it all depends on the energy you want to put in, the way you want to try to feed into the gut. Thank you very much for your presentation.

References


