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Intestine, immunity and parenteral nutrition in an era of preferred enteral feeding

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Abstract

PURPOSE OF REVIEW—To review the benefits of enteral nutrition (EN) in contrast to the inflammatory consequences of administration of parenteral nutrition (PN) and enteral deprivation. To present the most recent evidence for the mechanisms of these immunologic changes and discuss potential areas for modification to decrease infectious complications of its administration.

RECENT FINDINGS—There is significant data supporting the early initiation of EN in both medical and surgical patients unable to meet their caloric goals via oral intake alone. Despite the preference for EN, some patients are unable to utilize their gut for nutritious gain and therefore require PN administration, along with its infectious complications. The mechanisms behind these complications are multifactorial and have yet to be fully elucidated. Recent study utilizing both animal and human models has provided further information regarding PN's deleterious effect on intestinal epithelial barrier function along with the complications associated with enterocyte deprivation.

SUMMARY—Changes associated with PN administration and enteral deprivation are complex with multiple potential areas for modification to allow for safer administration. Recent discovery of the mechanisms behind these changes present exciting areas for future study as to make PN administration in the enterally deprived patient safer.

INTRODUCTION

Parenteral nutrition (PN) is a life preserving therapy for patients unable to utilize their intestinal tract for nutritional gain. PN, wherein all nutrition is supplied via the parenteral route, is used by over 350,000 patients annually in the United States, with 40,000 patients receiving home-based PN [1]. Despite its nutritional benefits, PN administration is associated with significant complications, primarily infectious in nature. While these adverse effects have been well documented, the etiology of PN-associated septic complications is an area of ongoing investigation. The following review will discuss the inflammatory and infectious complications of PN administration in the setting of enteral nutrient deprivation as well as potential approaches to limit the impact of these complications for those who require the life preserving treatment of PN.

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THE CASE FOR EARLY ENTERAL BUT DELAYED PARENTAL NUTRITION

The importance of adequate nutrition is well documented, both for the medical and surgical patient. Perioperative malnourishment is associated with poor healing and decreased immunologic function [2]. The most advantageous mode of nutrition administration, enteral vs. parenteral, has been studied extensively. Practically, both enteral and parenteral nutrition are associated with unique risks and complications. PN is easier to administer and is well tolerated by most patients. In contrast, EN is cheaper but more challenging to deliver and is associated with an increased percentage of patient intolerance. GI upset, diarrhea, and distention often lead to discontinuation of enteral feeds which in turn leads to periods of undernourishment. In the setting of these practical considerations; morbidity and mortality data overwhelmingly supports enteral nutrition. Many early studies focused on the infectious complications with data revealing decreased infection in those receiving enteral nutrition compared to matched patients placed on parenteral nutrition. Current recommendations advise early initiation of enteral nutrition. Studies of initiation of feeds within hours of their operative interventions have shown positive outcomes; mortality is reduced when enteral feeds are initiated within 48 hours of ICU admission [3]. In their recommendations regarding enteral feeds, the American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines cite multiple studies in which feeds were started within 24 hours postoperatively. These patients displayed improved clinical outcomes compared to similar patients in which diet was introduced more slowly, including decreased infectious complications and decreased mortality. These results support their recommendations for early initiation of enteral nutrition, particularly in the critical care setting where a significant amount of the study and benefit of early enteral feeds has been displayed.

With the known complications of perioperative malnourishment and benefits of early enteral feeds in the surgical patients, the question remained of when to initiate PN for ill patients who cannot meet caloric goals enterally [4]. A recent systematic review by Bost et al reviewed studies of early initiation vs. late initiation of PN. Those in the early group were started on supplemental PN within 48 hours of ICU admission, whereas the latter group was initiated on the 8th day after admission (if their caloric goals were not met in the interim). There was no significant difference in mortality, time on mechanical ventilation, time required for renal replacement therapy, days in the ICU, and a hospital stay. Given the equivocal findings and the higher infectious associations of PN administration, later administration of PN is recommended. Current recommendations continue to emphasize a preference for enteral feeding, with delayed administration of PN in adults until 7 days postoperatively with continued reassessment for PN need once initiated [2].

Despite the known advantages of enteral nutrition, a clinical population unable to tolerate enteral feeds exists. For these patients, PN is a life sustaining treatment despite its risks. The complications associated with PN are multiple and include hepatic dysfunction, bacterial translocation, metabolic problems, and electrolyte derangements [5]. The etiology of these findings is multifactorial in nature, but several contributing factors have been identified: a shift in the mucosa-associated intestinal microbiome, an increased mucosal pro-inflammatory state, and a subsequent loss of epithelial barrier function (EBF).

ENTERAL DEPRIVATION AND THE INTESTINAL MICROBIOME

The connection between PN-associated sepsis and the gut microbiome was initially suggested by the finding that cultured organisms from the blood of PN-dependent patients are predominantly intestinal microbiota. This has been supported by animal models, and suggests a loss of intestinal epithelial barrier function (EBF) and subsequent translocation of gut microbes and bacteria-derived toxins. While a gut origin of sepsis has been suggested in diverse scenarios of critical illness, this phenomenon has been increasingly observed in the setting of TPN, with convincing data based on animal models and emerging data from human studies.

First, the deleterious effects of enteral nutrient deprivation on EBF has been shown to occur independently of systemic nutrient delivery. A mouse model in which PN is administered while prohibiting enteral nutrition has demonstrated decreased EBF, as measured by reduced transepithelial resistance, loss of tight junction protein localization, and translocation of intestinally-derived bacteria [6].[7]. These changes are in contrast to animals that have undergone identical central venous cannulation with saline administration and oral feeding.

As total nutrient delivery remains unchanged between the fed and PN-dependent states, the means by which the nutrition is delivered must drive the changes seen with PN. Increasing evidence suggests a role for altered intestinal microbiota in mediating the proinflammatory effects of enteral nutrient deprivation. The human intestinal microbial population is diverse and plays a profound role in organism homeostasis. Among other roles, gut microbiota allow for the utilization of complex carbohydrates otherwise indigestible by human enterocytes and are necessary for the production of mucosa-maintaining nutrients such as short chain fatty acids. They also help modulate and bolster the host's immune system via cell interaction-primarily with cells of the lamina propria[8]. Through this interaction bacteria can activate toll like receptors (TLRs) which in turn modulate mucosal inflammation. PN-dependence has been shown to lead to a marked shift in mucosa-associated microbiota after six days of enteral deprivation [9]. At the phylum level, this is notable for a reduction in Firmicutes and increased representation of Proteobacteria, Bacteroidetes, and Verrucomicrobia.

The mechanism by which enteral deprivation leads to these changes in the microbiome are currently under investigation. Clearly, in the unfed state, the availability of luminal nutrients for bacterial metabolism is dramatically decreased. This alone might contribute to the survival of more resilient, and potentially more pathogenic, species. Host factors may also drive this microbial shift. Enteral nutrients stimulate the secretion of Paneth cell-derived antimicrobial peptides, and PN-dependence has been shown to reduce Paneth cell function [10]. An increase in goblet cells, which secrete microbe-regulating mucin, has been observed with PN-dependence, and may reflect a compensatory mechanism of the host in response to the altered microbial community.

Though a causal relationship between shifts in the microbiome and PN-associated inflammatory changes has yet to be demonstrated, animal studies have demonstrated a potential mechanism for luminal bacteria to initiate an inflammatory response. Host-

microbiome interactions are mediated in part by myeloid cells of the host lamina propria (LP)[11]. This interaction takes place via TLR signaling utilizing the membrane-associated protein, MyD88[11]. Interaction with luminal microbiota and the MyD88 receptor leads to increased expression of pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ). Along with increased inflammatory cytokines, this LP interaction down regulates the T-regulatory cells normally present in the LP, leaving the inflammatory cascade is left unregulated [9]. The role of this bacterial sensing mechanism in the development of PN-associated inflammatory changes has been demonstrated using MyD88 knockout mice, where changes in mucosal inflammation and epithelial barrier function were prevented, despite similar changes in the gut microbiome.

INFLAMMATION AND LOSS OF EPITHELIAL BARRIER FUNCTION

To further understand this phenomenon, multiple inflammatory cytokines have been studied using the aforementioned PN mouse model. Two cytokines which are increased in the circulation of PN dependent mice are TNF- α and IFN- γ . These cytokines are associated with epithelial cell apoptosis and loss of EBF integrity[12]. To further study whether the increase of circulating cytokines leads to the loss of barrier function, experimental knock out models have been established. These knockout mice, which are unable to produce and release specific cytokines, allow for study of the individual inflammatory markers in the setting of PN administration. Based on these findings the following mechanisms have been proposed.

An intact EBF is dependent on a multitude of factors and signaling cascades. A careful balance of growth factors and cell cycle regulators are necessary to promote both EBF integrity and prevent cellular overgrowth. As previously mentioned, PN delivery results in an increase in TNF- α expression. TNF- α is commonly associated with cell death but is also key in the regulation of epithelial cell growth, primarily via its interaction with epidermal growth factor (EGF). EGF acts to promote EBF integrity and cell growth, it requires intact TNF- α and Erb-1 signaling pathways. Erb-1 is reduced in PN administration, leading to a shift in the ratio of TNF and Erb-1 so that TNF- α 's primary role is that of cell destruction as opposed to cell growth[13]. Potentiating the intestinal atrophy, TPN administration leads to decreases in both keratinocyte growth factor and glucagon like peptide. Like EGF, these cellular mediators are associated with an intact epithelial cell barrier and their diminished presence in PN delivery contributes to decreased epithelial integrity.

TNF- α incurs further EBF injury activation of downstream cellular mediators, myosin light chain kinase (MLCK) and nuclear factor-kB (NF-kB)[7]. Briefly, TNF receptors lead to activation of myosin light chain kinase (MLCK) which when activated causes actin and myosin contractions on the surface of intestinal epithelial cells. This allows for dissociation of tight junction proteins, proteins necessary for an intact EBF. Further loss of function occurs with TNF- α downstream activation of NF-kB. NF-kB initiates an inflammatory amplification cascade with potentiates unregulated inflammation and EBF deterioration.

In addition to upregulation of proinflammatory cytokines, there is a decrease in anti-inflammatory interleukin-10 (IL-10) in the setting of PN dependence. IL-10 is one of the most important regulators of the mucosal immune system and in its absence, the

inflammatory cascade is left unchecked. IL-10 knockout mice display increased epithelial permeability and PN dependent mice supplemented with exogenous IL-10 have increase in EBF function[14]. Loss of EGF leads to further EBF injury through its association with phosphatidylinositol 3-kinase/p-Akt signaling. EGF is important for P13k/p-Akt signaling and in PN dependency its decreased expression leads to diminished P13k/p-Akt signaling and resulting epithelial cell apoptosis. This finding has been corroborated through study of TPN-dependent mice inoculated with Akt-activating peptide who do not display the same epithelial cell loss[13].

LIVER DISEASE

The pro-inflammatory state associated with PN has disparate physiologic consequence. For example, another well-known complication associated with PN is cholestasis and liver injury, known as PN-associated liver disease, or PNALD . The etiology of PNALD is incompletely understood, but the overall proinflammatory state displayed by patients receiving PN is one possible source. Pathologic findings in PNALD are notable for Kupffer cell hyperplasia and inflammation [5]. One mechanism for this inflammation is increased lipopolysaccharide (LPS) toll-like receptor-4 (TLR 4) activation in the context of EBF dysfunction and subsequent activation of Kupffer cells. In a study by El. Kasmi et. al, small bowel permeability along with PN administration led to increased activation of Kupffer cells and liver injury. Both administration of PN and small bowel permeability were tested in isolation and neither resulted in PNALD in isolation. More recently, this model revealed an expansion of the gut microbial family *Erysipelotrichaceae* [15], with attenuation of PNALD after antibiotic treatment and reduction of this bacterial strain. This demonstrates a parallel role of PN-associated changes in the gut microbiome, intestinal inflammation, and altered gut immunity in the pathogenesis of both septic complications and liver injury.

The previously described findings have all been displayed in mouse but human data is less abundant. Utilizing healthy volunteers, Buchman et al reported loss of EBF in maintained on PN for only two weeks but the results were to a lesser extent than mice. In this human study group, PN dependency led to decreased mucosal thickness, increased villus cell count, and increased intestinal permeability[16]. Recent work by our lab has revealed promising findings in human gut deprived of enteral nutrition[17]. Using small bowel harvested during loop ileostomy reversals, fed and unfed intestinal segments from the same patients were studied. Epithelial barrier function first was assessed by comparing transepithelial resistance (TER) in fed and unfed bowel. In unfed bowel, TER was decreased, indicating higher intestinal permeability. To confirm this phenomenon, tracer molecules were introduced to the gut lumen and found to be more likely to translocate in unfed bowel. Immunofluorescence was also used by staining tight junction proteins. Unfed samples showed decreased adherens proteins along with villus atrophy.

SUMMARY and FUTURE STUDY

PN administration is a life preserving therapy for many patients, but it is not without risk. Infectious complications of PN have been well described but the exact pathophysiology of such complications is not fully elucidated. Increased inflammation and marked microbial

changes are likely associated with the adverse effects seen. Areas of future study are vast. Environmental modifications which allow for persistence of a benign microbial population in the setting of PN administration would likely decrease the natural inflammatory response. Prevention of inflammation via blockade of different signaling cascades is another potential therapeutic option. Bolstering the EBF via EGF administration or direct enterocyte nutrition is another research pursuit we hope to take on in the near future.

Great gains in the understanding of the complications of PN have been made since its relatively recent introduction to the medical field. With continued utilization of both animal in human models of therapy, new treatment techniques will be founded and create a safer TPN for those who require its life sustaining nutrition.

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