Chapter

Parenteral Nutrition Modeling and Research Advances

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Abstract

Parenteral nutrition (PN) provides nutritional support intravenously to individuals who have gastrointestinal (GI) failure or contraindication to enteral feeding. Since the initial development of PN, researchers have developed specialized formulas with complete macronutrients, micronutrients, vitamins, minerals, and electrolytes to support patients' metabolic needs. These formulas prevent malnutrition and optimize patient health, especially under long-term feeding circumstances. Although PN is commonly used and essential in preterm and malnourished patients, complications associated with PN feeding include gastrointestinal defects, infection, and other metabolic abnormalities such as liver injury and brain related disorders. In this chapter, we highlight an overview of PN and its association with abnormalities of microbiome composition as well as with gastrointestinal (GI), immune, hepatic, and neuronal disfunction. Within the gut, PN influences the number and composition of gut-associated lymphoid tissue (GALT) cells, altering adaptive immune responses. PN also modulates intestinal epithelium cell turnover, secretions, and gut barrier function, as well as the composition of the intestinal microbiome leading to changes in gut permeability. Collectively, these changes result in increased susceptibility to infection and injury. Here, we highlight animal models used to examine parenteral nutrition, changes that occur to the major organ systems, and recent advancement in using enteric nervous system (ENS) neuropeptides or microbially derived products during PN, which may improve GI, immune cell, hepatic, and neuronal function.

Keywords: parenteral nutrition, animal models, gastrointestinal immunity, Paneth cells, microbiome, mucosal immunity, parenteral nutrition associated liver disease (PNALD), neurodevelopmental disorder

1. Introduction

Parenteral nutrition (PN) is a clinical nutrition strategy that provides patients with essential calories, macronutrients, and micronutrients needed for metabolic function through vascular access. PN is necessary in preterm babies and malnourished adult patients who are unable to feed, such as following gut trauma or general surgery, or in instances where the bowel requires rest under chronic inflammatory conditions. 'Parenteral' derives from the English *para* (beside) and ancient Greek *enteron* (intestine) and is usually administered via the central vein (jugular or subclavian vein). The formulation typically contains vital nutrients such as dextrose (D-glucose), amino acid cocktails, electrolytes, vitamins, tracer elements, and usually emulsified lipids in a hypertonic solution that is added just before

administration. When lipids are added, the term total parenteral nutrition (TPN) is applied. PN helps preserve lean body mass, supports immune functions, and reduces metabolic complications and oxidative stress in patients who are otherwise unable to consume and digest food by GI [1]. In the United States today, approximately 40,000 patients remain permanently dependent upon TPN and another 350,000 require transient PN for the treatment of or to prevent malnutrition [2]. Prior to the clinical use of PN, thousands of individuals developed severe malnutrition and while others starved when faced with GI failure.

2. History of parenteral nutrition development

The complexity of PN technique proved challenging and successful long-term administration was not performed until 1968, even though PN is now considered an essential clinical strategy in modern medicine [3]. Interestingly, NASA accelerated the field by attempting to formulate standardized elemental nutrition solutions during the Mercury space program. For almost 400 years prior, clinicians attempted to administer numerous solutions intravenously, including salt water, milk, and wine, with limited success [4]. The first successful use of PN in humans was performed by *Dudrick and Wilmore* when they intravenously supported an infant with PN for 6 weeks [3]. This development led to the rapid use of PN in clinical settings. Early on, PN was administered prophylactically to many patients in pre- and post-surgical settings regardless of their nutrition status. In today's practice, patients are first assessed for whether the risks outweigh the benefits of either short-term or long-term PN feeding. The decision to use PN has become more selective because long-term PN confers certain clinical risks related to vascular access, inflammatory bowel disease, catheter site infections, improper brain development (in neonatal settings), and other metabolic complications such as hepatic steatosis and cholestasis related to the continuous hypertonic glucose solution entering circulation compared with intermittent enteral feeding. When PN is used in otherwise healthy and well-nourished patients, these individuals are exposed to these risks without room for significant nutritional benefit [5–8].

Several clinical trials supported the shift to reserving PN for those with GI failure or malnutrition. In one trial, 400 general surgery patients were preoperatively randomized to receive either PN alongside *ad lib* oral feeding or *ad lib* oral intake alone [9]. The results demonstrated that PN elevated the risk of major infections and did not reduce non-infectious complications between treatment groups. However, further analysis demonstrated that subjects with existing malnutrition in the cohort did benefit from PN by exhibiting improved wound healing compared with the control group [9]. These results showed that PN provides the greatest benefit in malnourished patients, and that nutritionally replete patients could be exposed to harm from PN complications with minimal benefit. Clinicians are still faced with challenges, since definitions of nutrient status and malnutrition vary across the life span, clinical settings, and between disease states, making exact categorization of patient nutritional status and risk-benefit balance difficult [10]. With these challenges in mind, PN is generally targeted to surgery patients with existing malnutrition or individuals who are not expected to feed enterally for 7–10 days, since loss of lean muscle begins within 2 weeks following lack of enteral intake.

In addition to general surgery settings, another common setting of nutritional deficiency occurs in patients with hypermetabolic states following acute infection or those with traumatic injuries where rapid proliferation of immune and organ cells is required [1]. The average human typically maintains 1200 kcals in hepatic glycogen storage, before lean muscle mass and peripheral fat are utilized to support

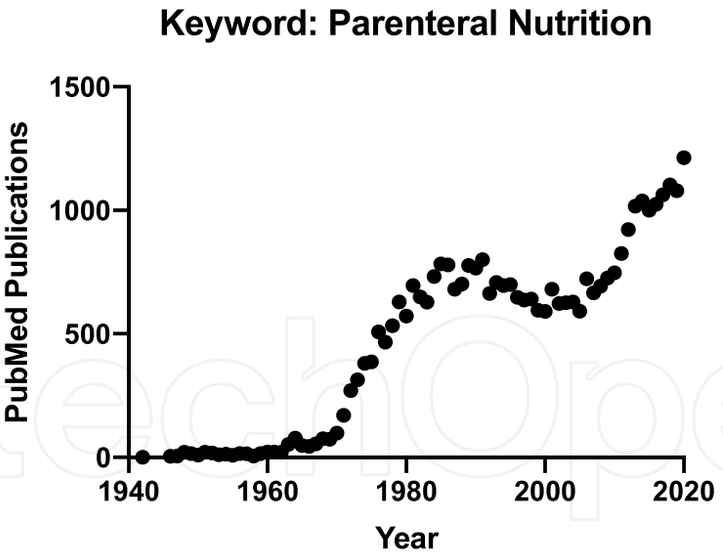

Figure 1.
The rise in parenteral nutrition biomedical research publications determined by pubmed keywords used between 1940 and 2020.

energy requirements [11]. Under acute infectious or injurious challenge, enhanced immune activation, increased oxygen consumption, and elevated muscle catabolism rapidly results in negative nitrogen balances. Even patients with no existing nutritional deficiencies may require PN when their energy needs are increased beyond their stored nutrient capacity. These settings also present challenges to the clinician, as it is established that a greater degree of injury leads to a higher risk of malnutrition [12, 13].

It is now accepted that enteral nutrition with a functional GI tract is the preferred route of nutrition in stable patients who can feed or tolerate feeding of either normal diet or standardized formula. Enteral nutrition is not without challenges, especially in patients where obtaining enteral access is difficult and the intestine requires time to adapt to calories. Specific to the latter case, enteral feeding also increases the risk of diarrhea, gut distention and upset. When tolerated, enteral nutrition leads to better clinical outcomes, including decreased risk of intra-abdominal abscess and respiratory infection, total length of stay, medical costs, and mortality [5, 9, 13–19]. PN remains essential for patients who cannot feed enterally, but these risks must always be considered. This chapter will discuss how PN impacts the gut immune system and microbiome, gut-liver axis, gut-brain axis, and future opportunities in PN research (**Figure 1**).

3. Models used to study parenteral nutrition

Animal have become a valuable preclinical model for nutritional studies. This includes mice, rats, rabbits, guinea pigs, dogs, and pigs [20–22]. As with all models, some species are considered to be more physiologically relevant to humans, and hence better models for understanding mechanistic pathways influenced by PN in pediatric and adult patients.

Rodents (mice and rats) have many similarities to humans including stages of development, anatomical features, immune responses, and associated physiology. Mice share many common genes, many of which can be knocked out or modified, as well as similar metabolic pathways compared with humans. Rodents are also cost effective and easily manipulated in a controlled environment, with a relatively short gestational period (19–22 days). These animals also offer a valuable tool for easy

genetic/transgenic manipulation. These practical considerations make rodents suitable for many studies. One important difference to note is that the poorly developed guts and brains of pups at birth mature gradually during the early lactational period before weaning, whereas human infants show mature guts at full gestational birth. This feature of mice pups offers a great model to compare rodent guts with the guts of premature human infants. This allows the modeling of PN under the premature setting following a short time protocol [23]. Neonatal dogs are also used to determine the effect of enteral and parenteral feeding on GI growth and maturation because of immature intestines at birth relative to mature newborn human intestines [24–26].

Rabbit models have been used to characterize the nutritional value of different combinations to determine the effect of different TPN components on hepatic cholestasis and bacterial translocation. This includes characterization of nutrition supplements using different solutions such as carbohydrate-based solution, lipid-based solution, enriched amino acid-based solution, and protein deficient solution on newly born rabbits. Rabbits with protein deficient calories developed cholestasis after 7 days of administration [27]. Additionally, newborn rabbits provided with protein deficient solution had increased bacterial translocation [28]. Guinea pigs have been used to study multivitamin mixed lipid emulsion vs. amino-acid and dextrose based mixed solution [29]. Additionally, guinea pigs have been used to study the effect of light exposure on multivitamin mixed lipid emulsion which generates peroxide free radicals and induces oxidative stress in the lung [30].

Extensive research has demonstrated that premature neonatal piglets are a preferred model over rodents to study long term PN related chronic and acute effects on organ size and developmental outcome. This includes effects on tissue components such as immune cells, hepatocytes, neurons, and other metabolic tissues. In particular, the neonatal pig, unlike rodents, rabbits, guinea pigs, and dogs, has been shown to be highly homologous with the human neonate regarding the function of numerous organ systems, especially the liver and the gastrointestinal tract, several aspects of metabolism, and stages of development [22, 31]. Although the piglet has a slightly immature digestive system and shorter gestational length (~115 days) compared with humans, it offers a very good animal model to study the effect of enteral/parenteral nutrition in early life on postnatal growth and development [20]. In early postnatal days, the rapid intestinal growth, adaptation to food, bacterial colonization and improved nutrient absorption provides an elegant model to study PN related issues in premature children. Newborn piglets have been used to study gut maturation and functional changes in preterm piglets (107 day of gestation) and full-term piglets (115 day of gestation) because they are physiologically similar to human preterm infants [20, 22, 31]. Further, preterm neonatal piglets are a well-established model to study PN associated PNALD including hepatic cholestasis and brain related disorders [32, 33]. In late postnatal days, the growth of the intestine is gradual, reflecting the transition from milk-feeding to solid-food feeding. This may provide a model for TPN in immature children/neonates and adults. The piglet model is also favored over other model organisms because of body size, which allows for extensive surgical manipulation.

4. Importance of enteral feeding

In the 1970s and 1980s, early researchers focused on sepsis found that enterally-fed, well-nourished animals had a 70% survival rate, whereas animals given PN had only a 10% survival rate, regardless of whether they were malnourished [34]. Initially this observation was hypothesized to occur from a lack of essential

nutrients in the PN formulation. However, further experiments showed that animal survival improved when the same volume and composition of PN components were provided orally [35, 36]. This outcome demonstrated the importance of gut stimulation and homeostasis.

5. Overview of gastrointestinal innervation and immunity

The gastrointestinal (GI) tract has several vital functions, acting as not only a digestive organ but also as an important endocrine and immune organ. The GI tract handles the breakdown and acquisition of nutrients as well as influences peripheral nutrient handling. The GI tract is home to vital neurological networks, including both the autonomic nervous system (with sympathetic and parasympathetic fibers that communicate with the spinal cord and central nervous system (CNS) through the dorsal root ganglia) and the unique enteric nervous system (ENS) [37]. The ENS, unlike the autonomic nervous system, is autonomous from the CNS and is comprised of over 10^8 sensory, motor, and interneurons that release acetylcholine and neuropeptides [38]. In response to ingested nutrients and bulk, GRP triggers enteroendocrine cell hormone release that regulate intestinal motility, digestive enzyme release from the pancreas, bile acid and bicarbonate release, stimulation of splanchnic blood flow, and electrolyte balances, each of which shape the stability and composition of the gut microbial ecology [39].

Approximately, 70 and 80% of all active immune cells in the body are innervated by ENS fibers connected to the epithelial and immune cells that make up the gut's huge surface area of over 400 m^2 [40]. This immune function is the vital barrier between the host and its environment. The gut and other mucosal surfaces are tasked with defending against dietary, microbial, and environmental products through innate barriers, adaptive immunity, and stable microbial colonizers. Barriers include ranging from simple cellular layers, complex secreted products such as antimicrobial peptides and glycoproteins, specific and non-specific immunoglobulins (IgA), and maintenance of the gut microbiome [38]. During periods of both feeding and fasting, the defenses provided by ENS-innervated immune cells facilitate digestion, maintenance of immune response, and the prevention of pathogens from entering systemic circulation.

6. Changes in gastrointestinal immunity following PN

6.1 The gut-associated lymphoid tissues (GALT) following PN

The Gut-Associated Lymphoid Tissues (GALT), a compartment which contains an astonishing 70–80% of all active immune cells, consists of both innate and adaptive cells residing beneath the epithelium and sampling the intestinal lumen [41]. The GALT facilitates release of sIgA on mucosal surfaces throughout the body. sIgA serves as an opsonin that can bind pathogens either specifically or non-specifically [42]. sIgA can mediate tolerance leading to attenuated inflammatory responses and induction of Treg lymphocytes [43]. One of the major detrimental effects of PN is GALT atrophy which occurs quickly after cessation of enteral feeding, and is driven by changes in blood flow, decreased expression of leukocyte binding, and decreased cellularity throughout the splanchnic bed. Grossly, PN-induced gut atrophy is observed with decreased organ wet and smaller bowel circumference approaching declines of 10% [44].

In rodent models of PN, Peyer's patch lymphocyte numbers begin to decline within 1–2 days of PN, where 75% of total cells are lost by 3 days compared with

controls [45]. While total cellularity decreases, the ratios of T to B-lymphocytes, CD4+ to CD8+ cells, and relative percentages of memory, activated, and naïve cells remain stable [46]. In normal Peyer's patch function, specialized microfold cells cover Peyer's patches and sample luminal antigen to present to dendritic cells and naïve αβ+ T and B-lymphocytes within underlying germinal centers [47]. The naïve cells are localized to the Peyer's patches via expression of the integrins L-selectin and to a lesser extent α4β7. The integrins interact with mucosal addressing cellular adhesion molecule-1 (MadCAM-1) [41]. Diapedesis of the naïve cells into the Peyer's patch is facilitated by the chemokines CXCL13, CCL19, and CCL21 [48].

PN alters MAdCAM-1 expression within the Peyer's patch tissues by altering two MAdCAM-1 regulatory networks, through the lymphotoxin β receptor (LTβR) and noncanonical NFkB signaling pathways [49]. In the LTβR pathway, lymphotoxin α and β on the surface of systemic lymphocytes bind LTβR within the GALT tissues, elevating MAdCAM-1 and Th2 cytokines including IL-4 [50]. Following PN, Peyer's patch and GALT expression of LTβR rapidly declines, leading to decreased MAdCAM-1 within 4 h [51]. Mechanistically, inhibition of LTβR alone with blocking antibodies significantly decreases MAdCAM-1 expression. Conversely, providing stimulation of the LTβR under PN feeding through anti-LTβR monoclonal antibodies increase Peyer's patch lymphocyte numbers and mucosal release of sIgA in the gut and respiratory tract [44].

The second MAdCAM-1 regulatory signaling pathway is noncanonical NFkB, which is regulated in-part through lymphoid receptors and LTβR signaling described above. The canonical (or classical) NFkB pathway is stimulated in infectious and injurious insults, driving inflammatory tissue responses. In contrast, noncanonical NFkB triggers nuclear P52/RelB dimer formation and subsequently elevation of MAdCAM-1. Animal studies providing PN have demonstrated that both the canonical and noncanonical NFkB pathways are reduced during PN feeding [52]. Experimental inhibition of LTβR signaling significantly decreases nuclear P52/RelB dimerization and leads to lower MAdCAM-1, CCL19, CCL20, and CCL25 expression, but blockade of LTβR does not affect canonical NFkB protein levels [51]. Experimental stimulation of LTβR with agonists during PN drives expression of MAdCAM-1, P52/RelB, and IL-10. On the other hand, blocking ligands administered to control animals result in less MadCAM-1, L-selectin, and α4β7 [51]. These studies highlight the changes that occur in gut signaling following PN with lack of enteral stimulation. Fortunately, providing enteral stimulation drives normalization of these parameters in experimental animals within 2 days [53].

Peyer's patches serve as important induction sites for gut immune responses, where cells subsequently enter the lymphatics and circulation before returning to mucosal effector sites throughout the body. During transit through these compartments, plasma cells are activated and return producing IgA [54]. Through the same anatomical transit, T helper lymphocytes subpopulations are stimulated, including Th1, Th2, Th17, Th22, and Treg [55]. Th2 lymphocytes generate IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and IL-25, which plasma cell IgA production by plasma cells. These cytokines also have important roles in driving epithelial machinery that is required to translocate IgA to the luminal surface, such as polymeric immunoglobulin receptor (pIgR) [56]. Enterocyte pIgR bonds with a dimeric for of IgA where endocytosis moves the complex to the luminal surface before releasing secretory IgA (sIgA). The ratios of cytokines expressed in the lamina propria balance the release of sIgA production and release. For instance, IL-10, IL-17, and TGF-β drives plasma cell IgA production and pIgR expression, while IL-2, IFN-γ, and TNFα decrease pIgR expression [57, 58]. Of these cytokines, TGF-β appears to be critical,

as mutant animals lacking TGF-β fail to present sIgA at mucosal surfaces, perhaps in part due to the need for this cytokine in plasma cell maturation [59].

By reducing the expression of α4β7, the integrin that binds MadCAM-1to help localize lymphocytes to the lamina propria, PN functionally results in reduced systemic lymphocytes dedicated for mucosal defense (CD4+CD25+) as well as resident lymphocytes in GALT tissues [46]. Furthermore, the activated lymphocyte population has a reduced capacity for tolerance or memory of self-antigens, as evidenced by reduced expression of Treg (CD4+CD25+Foxp3+) and memory (CD44+). The reduction in Treg cells also results in less TGFβ and IL-10 are produced, which usually support plasma cell function by counteracting the pro-inflammatory Th1 cytokine IFN-γ. PN decreases GALT IL-4 and IL-10 levels [45].

PN alters Th1:Th2 ratios by reducing the production of Th2 but not Th1 cytokines. Implications are increased neutrophil recruitment through ICAM-1 expression due to loss of IL-4 and IL-10 with stable IFN levels [60, 61]. Following PN, elevates neutrophils are observed in multiple organs, which may result in greater injury following hemorrhagic shock, ischemia, and sepsis. Experimental injury demonstrates that the percentage of activated neutrophils is significantly higher following PN, functionally resulting in greater mortality (50%) than enterally fed controls (5%).

Mucosal IgA responses are specific and vital, as has been shown in IgA mucosal vaccination studies for poliovirus and enterotoxigenic *Escherichia coli*, where specific sIgA appears at all body surfaces following mucosal exposure [62, 63].

Viral and bacterial challenges in rodent models have shown that functionally, PN leads to lower IgA-mediated immunity for antigen recognition and elimination of pathogens. Immunizing mice against *Pseudomonas (Ps) aeruginosa* leads to 90% survival when exposed to an intra-tracheal challenge compared with only 10% survival in control animals [64]. Given the dramatic effect of PN on adaptive immune responses, immunized animals provided PN survive intra-tracheal Ps at the rate of unimmunized animals. Similar results were obtained with influenza shedding studies, illustrating the loss of adaptive immunity to specific pathogens in the absence of gut feeding [65]. These findings draw a larger working schematic that PN feeding, without enteral intake, functionally alters the GALT compartment into a state that is far less protective. Unfortunately, these adaptive immune changes occur in parallel with increased pro-inflammatory neutrophil infiltrates that make any subsequent injury or infection more severe.

7. Changes in gut barrier defense following PN

The epithelial barrier of the intestine, which turns over rapidly due to highly proliferative pluripotent Lgr5+ stem cells in the intestinal crypts, serve as the first line of defense against the external environment of the gut. The epithelium turns over every 3–5 days [66]. One cell type that does not turn over rapidly are small intestinal Paneth cells, that turn over every 20–30 days. The selective barrier allows absorption of water, electrolytes, and some macromolecules via tight-junction proteins, including zonulins, occludins, and claudins between enterocytes. Epithelial permeability increases significantly during PN feeding [67, 68], in parallel with a loss of tight-junction proteins [69]. In addition to the physical barrier along the gut lining, subepithelial dendritic cells extend dendrites between epithelial cells, which are hypothesized to sample luminal antigens and augment barrier responses [70]. A smaller proportion (10%) of intestinal cells secretory cells, including enteroendocrine cells and mucous secreting goblet cells [47].

The epithelium's contribution to defense includes not only physical barrier formation, but release of antimicrobial molecules that influence microbial community composition and membership. Enterocytes comprise 90% of total epithelial cells in the gut and release β-defensins and RegIIIγ enzymes that limit microbial growth at the mucous barrier [71]. The far less abundant Paneth cells, found at the crypt bases, produce a large array of antimicrobial peptides and enzymes, including lysozyme, RegIIIγ, secretory PLA_2, Angiogenin4, and α-defensins (murine cryptdins) [72]. These cationic antimicrobials localize to the negatively-charged mucous surface and work by targeting conserved aspects of microbial cell walls and membranes [67]. Studies demonstrate Paneth cell antimicrobial molecules reach 15–100 mg/mL within intestinal crypts, exceeding antimicrobial concentrations [73]. The colon exhibits two layers of mucous, an inner sterile layer and an outer more loosely colonized layer.

Paneth cell antimicrobial release is regulated by Th2 cytokines, including IL-4, IL-9, and IL-13, GLP-2, and insulin [37, 74, 75]. Stimulatory triggers include the ligands TLRs and NOD2 and parasympathetic cholinergic stimulation [76]. PN decreases antimicrobial production through lower levels of intestinal IL-4 and IL-13 [77, 78]. Enterocyte release of RegIIIγ is also lost during PN [79]. Exogenous administration of IL-25 stimulates production of IL-4 and IL-13 cytokines and levels of Lysozyme, $sPLA_2$, and RegIIIγ compared with PN feeding alone [80]. Following PN, mucosal secretions contain less Paneth cell antimicrobial products, leading to decreased killing of bacteria in vitro [76]. Tissue explants from PN fed animals have been demonstrated to be more susceptible to enteroinvasive *E. coli* compared with controls [81].

The function of goblet cells is to produce the mucous barrier, composed of glycoprotein mucins. These proteins have numerous carbohydrate residues including *O*-glycosylation, *N*-actyl-galactosamine, galactose, and *N*-actyl-glucosamines [82]. Functionally, mucins mucous serves as a selective physical barrier that allows for movement of luminal digesta, absorption of nutrients, and limiting bacterial access to the gut wall. Mucins also help concentrate Paneth cell antimicrobial molecules and sIgA through charge interactions [83]. The importance of mucins is demonstrated by in mutant animals lacking the more abundant mucin, MUC2, which leads to inflammatory enteritis and increased risk of tumor formation [45].

PN decreases the release of MUC2, RELMβ, and trefoil factor 3 (TFF3) in neonatal piglets and adult mice [75, 84]. TFF3 promotes epithelial response to injury. Animals deficient in RELMβ display increased susceptibility to *Citrobacter rodentium* challenge. The release of goblet cell products are influenced by Th2 cytokines, including IL-4 and IL-13, which are decreased under PN feeding [85]. Exogenous administration of the Th2 stimulating cytokine, IL-25, elevates luminal MUC2 levels [77].

Although only 1% of the total intestinal epithelial cells are enteroendocrine cells (EECs), they collectively make up the largest endocrine organ, expressing almost 2 dozen peptide hormones that shape metabolism, immunity, and behavior [86, 87]. EECs respond to enteral nutrients as well as microbial ligands [88]. EECs are also intricately linked to innate immunity, indirectly activating and recruiting immune cells by producing the chemokines CXCL-1, CXCL-3, and the cytokine IL-32. EEC hormones can also influence epithelial cell function in the gut, including Paneth cell release of antimicrobial molecules. GLP-2 mutant animals are at increased susceptibility to gut infection than wild-type littermates [37].

8. Changes in the gut microbiome under PN

The microbial communities within the gut contain vast numbers of microorganisms from the domains of bacteria, archeae, yeasts and fungi, protists, and

virus. The number of individual microbial cells rivals that of the human host and contains upwards of 150 fold the genetic content of the mammalian host [89]. The bacterial population, which accounts for >99% of all microbial DNA, contains trillions of organisms from numerous phyla, including *Firmicutes*, *Bacteroidetes,* and *Actinobacteria*. The basic role of the microbes in digestion is to breakdown nutrients and to synthesize novel compounds—including short chain fatty acids (SCFAs) and vitamins, including vitamin K and numerous B vitamins. Intestinal colonizers play complex roles in gut colonization and community establishment, creating barriers to intruding pathobionts and serve the host through modification of secreted molecules, including bile acids, and consumption of secreted glycoproteins. *O*-glycosylated mucin glycoproteins secreted by the host serve both as nutrients for the microorganisms and as a substrate for colonization by *Akkermansia muciniphila*, *Bacteroides thetaiotaomicron*, and *Bacteroides fragilis* [89].

PN challenges the host with a unique set of circumstances. On one hand, elemental nutrients are plentiful in the bloodstream, yet the physiology required for host adaptation are bypassed. From a gastrointestinal standpoint, lack of central intake only occurs during hibernation and prolonged fasting or starvation. These circumstances are associated with catabolism. However, the goal of PN is to prevent catabolism and drive stable metabolic homeostasis or anabolism. Given the close interdependence of the gut microbiome and diet, it is unsurprising that the primary driver of microbial community structure is host nutrition [90]. Resident got colonizers are adapted to metabolize the breakdown of indigestible fiber and play important roles in coordinating host responses to dietary intake, influencing incretins, bile acid pools, and gut enterohormones [91]. Some of these hormones have direct effects on the pancreatic islet and acinar cells (GLP-1, secretin), liver homeostasis (FGF15/19), and gall bladder (CCK).

Given that *Firmicutes* are efficient degraders of dietary carbohydrate, this phylum is decreased under PN while increased relative abundance of *Proteobacteria* are frequently observed [92]. *Proteobacteria* can digest alternate food sources, such as amino acids and various host secretions, making them more resilient in a fasted or starved state. Prior work showed that elemental nutrients from PN enter the gut lumen in low abundance through the use of tracers and that these nutrients are utilized by resident *Enterobacteriaceae* [93]. Since PN reaches the lumen, it is perhaps unsurprising that dirurnal variations in host metabolism may also influence gut community structure, even in the absence of dietary intake. Leone et al. demonstrated that the intestinal microbiome oscillates in composition over 24-h circadian rhythms, regardless of whether the host is enterally fed or PN [79]. This finding further illustrates the role of the diet, host, and combined metabolites in shaping and selecting for gut microbial community members.

In the absence of enteral feeding, pathogens may proliferate in the setting of PN due to decreased commensal nutrition that would usually lead to an ecology capable of outcompeting with them. Under PN feeding *Proteobacteria* blooms include many pathogens such as *E. coli, Salmonella, Yersinia, Helicobacter,* and *Vibrio* [92, 94]. In addition to providing competitive exclusion, other beneficial bacteria, including *Bacteroides fragilis*, are decreased. The presence of *B. fragilis* can support sIgA release [95]. The problematic changes in gut microbiome communities occur in concert with a loss of gut barrier, innate, and adaptive immune responses which can render the gut susceptible to a source of infection. Fecal microbiome transplantation (FMT) have demonstrated PN microbiome communities alone can decrease gut inflammation and decrease tight junction protein expression when placed into enterally fed previously germ-free animals [93].

In addition to bacteria, PN also reduces resistance to fungal pathogens, such as *Candida albicans* [96]. While *C. albicans* is found in healthy humans, it can become

virulent in the gut and oral cavity, eventually entering systemic circulation, and causing disease. Experimental inoculation of *C. albicans* during PN results in increased gut translocation systemic infection of *C. albicans* compared with control animals [97]. As with bacteria, it is likely that changes in innate and adaptive immune arms underscore the increased susceptibility to otherwise harmless gut microbes [40, 98].

9. Changes in liver function during PN

PN is a valuable clinical method supporting complete nutrition in the case of intestinal failure. However, PN can lead to serious metabolic complications including gut atrophy and dysfunction and hepatic abnormalities. Liver dysfunction is common in infant and adult patients receiving PN for both short- and long-term. Prolonged PN feeding can lead to PN associated liver disease (PNALD), fibrosis, steatosis, and eventually liver failure [99, 100].

Depending on the patient's age and duration of the PN administration, PNALD can be classified into three types: hepatic steatosis, cholestasis and gallbladder sludge [101, 102]. PN associated steatosis is mostly seen in adult patients with higher caloric intake from carbohydrates such as dextrose or carbohydrate-nitrogen imbalance with elevated triglyceride synthesis in the liver. PN associated cholestasis is more common among premature newborns (40–60%) and infants receiving short-term and long-term PN than adults. PN associated cholestasis was first reported in premature infants receiving TPN. Cholestasis occurs when bile flow is impaired with an elevation in bilirubin level > 2 mg/dL. Other hepatic enzymes including alkaline phosphatase (ALP) and gamma glutamyl amino-transferase (GGT) involved in the synthesis and secretion of bile are also impaired. This occurs within 1–5 weeks of PN administration [103]. Gallbladder sludge is seen in both adults and children and develops due to bile storage in the bladder for an extended period. Biliary sludge develops in patients having PN between 3 and 6 weeks [104].

Several risk factors have been shown to contribute to the development of PNALD including poor nutrition with inappropriate ratio of dextrose, lipid, and amino acid, premature birth, duration of PN, bacterial/fungal infection and short bowel syndrome. Evidence from the literature suggests that PN associated liver dysfunction can be improved by avoiding excess calories and maintaining dextrose/lipid/amino acid balance. This will promote fatty acid oxidation, avoiding hyperinsulinemia in the liver and reducing the risk for the development of PN associated fatty liver disease [105].

Another key factor for the prevention or reversal of PNALD includes either fish oil-based lipid emulsion or lipid emulsion infusion of fish oil, soybean oil and olive oil mixture rather than a soybean oil-based formulation. Pro-inflammatory ω-6 fatty acids having a high amount of phytosterols in soybean oil promotes the proliferation of Kupffer cells and development of PNALD by impairing bile secretion and activating excessive secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IFN-γ, and reactive oxygen species (ROS) [106]. Soybean oil derived lipid component phytosterols alter the intestinal microbial composition including the overgrowth of specific bacterial components associated with PNALD [7]. Farnesoid X receptor (FXR) is known to inhibit bacterial overgrowth and induce the expression of genes involved in the protection of gut [107]. Soybean-derived phytosterols are FXR agonists. TPN studies in piglet and mouse models have suggested that alteration in the bile acid mediated FXR-FGF19 axis may lead to the pathophysiology of PNALD [108, 109].

Alternatively, fish oil-based lipid emulsion or lipid emulsion of fish oil, olive oil and soybean oil mixture can reverse the development of PNALD. Anti-inflammatory ω-3 polyunsaturated fatty acids (PUFA) in fish oil, which have a high amount of omegaven and a low amount of phytosterols, can reduce the development of PNALD by suppressing the cytokine TNF-α [103, 110–114]. Additionally, a study from Harris, JK et al., shows that parenteral nutrition associated liver injury (PNALI) mice receiving fish oil derived lipid emulsion with a high amount of Omegaven harbor a specific composition of fecal microbiota. Specifically, there is a reduction in *Erysipelotrichaceae,* which appears to prevent the activation of Kupffer cells and subsequent PNALD as compared to soybean oil based lipid emulsions [32, 106]. Further, piglet studies have shown that replacing soybean oil based PN with fish oil based PN in neonatal piglets results in lower bilirubin, alanine transferase (ALT), aspartate transferase (AST) and improved PNALD [115, 116].

As mentioned, bacterial overgrowth and bacterial translocation is another potential cause of PNALD, which can be augmented with antibiotics such as metronidazole. Metronidazole administration in a rat model showed reduced fat accumulation with lower alkaline phosphatase (ALP), aspartate aminotransferase (AAT), and gamma glutamyl transpeptidase in the metronidazole treated group relative to the control group receiving PN [117, 118]. Further glutamine supplementation, an essential energy source for the gut, prevented liver steatosis in a PN rat model [119]. Considering the importance of a healthy gut microbiome in early life on immune development and metabolic growth, it remains unclear what the implications of antibiotic administration in neonates have on long-term growth and development.

10. Challenges in supporting healthy neonatal growth during PN

The ultimate goal of NICU physicians is to support optimal infant growth and maturation until the child is stable for discharge. This goal is complicated by increased metabolic needs in infants who commonly have infectious stresses and underdeveloped GI and immune organs function. Preterm infants do not require the same nutrition intake as weight-matched term infants; they often require greater caloric intake due to weight loss after birth and high metabolic rates [120]. Despite the years of research and clinical trial and error that have gone into creating the PN formulas used in NICUs today, several developmental delays are still noted in neonates during PN. Among these are neurodevelopmental delays, which have been widely observed, but the underlying mechanisms remain poorly characterized [121]. There are also delays in development of the immune system and the closely related enteric nervous system in the intestine. PN infants also show slowing of intestinal and hepatic development.

Developmental outcomes for preterm infants have mostly only been studied during the NICU stay. What is less clear is the longer-term effects of neonatal growth delay. Several studies have examined the effects of too little growth and/or the deficiency of certain nutrients during infancy on height, BMI z-scores, and other developmental factors measured later in life. In a cohort study of preterm infants receiving either standard or energy-enhanced PN (meaning an increased calorie:protein ratio), no significant difference in growth was found at 24 months of life. Both types of PN did, however, cause PN-related complications in 98% of patients [122]. Other studies have shown little or no significant difference in the effects of different protein or fat compositions of neonatal formula on height or BMI after 1 year of age [123]. It has, however, been found that breast feeding reproducibly leads to a higher IQ in childhood compared to formula feeding, and by

extension PN. As discussed in Section 12, supplementation of PN with DHA may help alleviate some detriments of neurological development [123].

Though most of the focus is on supporting adequate growth in the neonate, some researchers have questioned the effect of overcompensation and accelerated growth on later life. It has been observed that overly accelerated growth in infants may lead to increased incidence of obesity and other related diseases later in life. This appears to be true whether the infants are term or premature [124]. These long-term effects are thought to occur through "nutritional programming"; that is, the nutrients received in certain key developmental periods can lastingly alter endocrine function, immune function, and other health indices via epigenetic responses to early life nutrients [123]. A cohort study in the UK identified several risk factors in children who were obese at 7 years of age. In that study, neonatal "catch up" growth was identified as an independent risk factor for obesity. However, large birth weight was also an independent risk factor, suggesting a trade-off between these two variables [125]. The clinical goal is to strike a balance between providing enough nutrition to prevent neurodevelopmental delays and prevent hyperalimentation associated with long term obesity risk. It is also important to note that most of these studies have focused on accelerated growth with enteral feeding (either breast milk or formula), so little is known about the compound effects of over-accelerated growth on PN.

11. Changes in brain development during PN

Preterm infants on PN long-term are at high risk of having compromised brain development and delayed cognitive skills. Neurodevelopmental delays and defects are commonly seen among 40–50% of preterm infants [121]. Preterm babies born during late second and third trimesters (30 weeks) with extremely low body weight < 1 kg with poorly developed GI tracts show delayed brain development and maturation. These preterm babies rely on PN for proper growth and development. Magnetic resonance imaging (MRI) technology has shown that the total brain development including white and gray matter happens around 25–37 weeks of gestation with cerebellum enlargement [126–129]. PMID: 17151398 showed that using a preterm pig model with EN vs. PN, preterm pigs on PN for 10 days had neurodevelopment delays, smaller brains, immature myelination patterns and compromised motor skills compared to those on EN [8]. In addition, PN pigs had smaller cerebellums with slower locomotion than EN pigs regardless of similar body weight. These results suggest that maintaining preterm infants on PN long-term may be detrimental for optimal brain development [8].

The effect of soybean derived fat components of PN and their association with fatty liver disease was discussed in an earlier section. Here, we discuss the effect of soybean derived oil on the brain in PN patients. Neurodevelopmental disorders among PN infants occurs due to the effects of soybean oil derived PN and its association with the gut microbiome, and the development of gut microbiome-brain axis [130].

This raises the prudence of replacing soybean oil derived lipid emulsions with fish oil derived lipid emulsions for protection against PNALD and to ensure support of optimal brain growth and development. It has also been shown that dietary ω-3 fatty acid docosahexaenoic acid (DHA) and arachidonic acid in fish oil modulate brain development in piglets [131–133]. To date, there are no specific clinical models established to study PN associated neurodevelopmental disorders in preterm infants and children. Therefore, further studies are needed to identify the cause of PN associated neurodevelopmental disorders.

12. Metabolite supplements for restoring homeostasis during PN

PN is required in patients with progressive malnutrition, which is exacerbated by infectious and injurious challenge, leading to hypermetabolism. A major goal of recent research has been to find combinations of PN additives that will reduce the detrimental impact on the gut's immune and metabolic functions, as well as on the mucous composition in the intestinal and respiratory tract. Immune enhancing nutrition formulations include the addition of glutamine, arginine, cysteine, tyrosine, leucine, choline, ω-3 fatty acids, nucleotides, and micronutrients (vitamin C, selenium, and tracer elements including iron and zinc). Glutamine has been studied most extensively as the most prominent free amino acid that supports normal metabolism but becomes limited during gut atrophy and critical illness [134]. Recent reviews have concentrated on the effects of these additives in basic and clinical work [135]. Outside of macronutrients classes, targets that stimulate aspects of immune and neuronal signaling have promise in mediating elevated immune and barrier response when PN is necessary.

12.1 Enteric nervous system molecules

Outside of the central nervous system, the enteric nervous system contains an enormous number of autonomous neurons and glial cells that coordinate the physiological functions of digestion, gut immune homeostasis, and diverse numbers of epithelial functions. Among the targets of ENS neuropeptides, including gastrin-releasing peptide (GRP), substance P, and VIP, are GALT immune cells. During normal feeding, ENS fibers release GRP, stimulating a cascade of digestion and immune cell responses [136]. Analogues for GRP, including bombesin (BBS), have been used to efficiently stimulate the GRP receptor and mimic gut feeding responses. Administration of BBS to mice on PN significantly elevates intestinal blood flow, Peyer's patch lymphocytes [46], activated and memory lymphocytes in the lamina propria, and elevated pIgR and luminal IgA [137–139]. BBS also drives increased expression of Paneth cell antimicrobial enzymes. Functionally these changes following BBS results in increased resistance to infectious organisms, including respiratory H1N1 and *Pseudomonas* [140], and intestinal enteroinvasive *E. coli* [141], compared with PN alone. Outside of the immune compartment, BBS stimulates GI motility and pancreatic secretions during PN that are otherwise attenuated [142].

In summary, providing rodents with exogenous neuropeptides, for example BBS, can compensate for the loss of normal enteral nutrient stimulation that drives gut physiological and immunological responses. Artificial stimulation of these gut functions may hold promise in patients where prolonged periods of PN are needed and patients may otherwise be at increased risk of mucosal immune atrophy and infectious microorganisms.

12.2 AHR molecules

Given the loss of microbial community structure and function in the absence of enteral feeding, disturbances in the gut microbiota occur rapidly following PN. One such change is the loss of microbial Aryl hydrocarbon receptor (Ahr) ligands production that normally stimulate IL-22 production. IL-22 generates epithelail barrier responses, including antimicrobial molecule production [143]. Ahr deficient animals are at increased susceptibility to infectious challenge, including *Citrobacter rodentium*. Prior work demonstrates that microbial Ahr production elevates bone marrow B cell maturation [144, 145].

12.3 SCFAs

Short chain fatty acids (SCFAs) Are generated by microbial fermentation of dietary carbohydrates. SCFAs phase can reach 130 mmol/kg in the distal gut where they stimulate the receptors, GRP41, GPR42, and GPR109a, shaping immune responses and modifying the release of enteroendocrine hormones. Exogenous administration of SCFAs stimulates the number of IgA+ producing plasma cells in the gut and elevates circulating immunoglobulins [146]. Functionally, the importance of these metabolites in immune stimulation have been demonstrated through experimental studies administering SCFA to mice during infection with *Citrobacter rodentium*, and enhanced IgA levels and pathogen clearance was observed. In addition to driving antibodies at mucosal surfaces, SCFAs mitigate pro-inflammatory responses and stimulate tolerance by inducing Treg cells [147]. Isolated plasma cells enhance production of IgG and IgA when exposed to SCFAs, demonstrating the direct effect of these metabolites on immune function [146]. At the mucosal barrier, through GRP receptors, SCFAs stimulate goblet cell mucin gene expression and improve tight junction protein expression [148, 149]. Dietary SCFAs administration improves diet induced metabolic complications including liver dysfunction via the G-protein coupled receptor FFAR3 and prevents *de-novo* lipogenesis in mice [150, 151]. SCFAs modulate gut microbiome-brain communication by crossing the blood-brain barrier and regulating signaling pathways involved in central nervous system (CNS) production of neurotransmitters such as dopamine and serotonin [152]. SCFAs alleviate blood-brain barrier permeability and microglia maturation and function [153]. Also, dietary administration of SCFAs increases serum plasma of GLP-1 and protects mice from diet-induced obesity [154].

12.4 Polyamines

Polyamines are a unique class of polycationic metabolites produced by many lifeforms. Diets lacking polyamines lead to slowing of intestinal development and atrophy of the mucosa [155]. By enhancing expression of occludin and E-cadherin, polyamines improve epithelial tight-junction function in addition to improving mucous glycoprotein release [156, 157]. Polyamines are also demonstrated to drive IgA levels and increase lamina propria CD4+ T cells [158, 159]. Considering the importance of these molecules in normal gut homeostasis, this class of molecules represents one area of innovation for researchers investigating PN additives for improved outcomes.

12.5 Bile acid agonists (INT-777, INT-747): supporting liver function and gut epithelial signaling

Bile acids play a crucial role in maintaining lipid and glucose metabolism via G-protein coupled receptor (TGR5) and farnesoid X receptor (FXR) signaling. FXR regulates key pathways involved in metabolism in the liver. Alteration in bile acid signaling reduces bile acid synthesis in the liver and leads to hepatic cholestasis and inflammation [160, 161]. Recent literature suggests that altered bile acid signaling increases insulin resistance and promotes hepatic gluconeogenesis [162, 163]. TGR5 activates the cAMP/PKA pathway to regulate lipid metabolism. INT-777 and INT-747, novel and selective agonists of TGR5 and FXR respectively, stimulate bile flow. INT-777/TGR5 activation inhibits nuclear translocation of NFkB and displays an anti-inflammatory effect by reducing the secretion of TNF-α, IL-6, IL-1β and IFN-γ. Bile acids activate FXR, which regulates the transcription of FGF19 and binds to FGFR4. FGFR4 blocks CYP7A1 and represses bile acid synthesis [164, 165].

Treatment using bile acid receptor agonists INT-777 (TGR5) and obeticholic acid/ INT-747 (FXR) can attenuate hepatic steatosis and improve the overall metabolic profile induced by high fat diet (HFD). Animal models show that INT-747 and INT-777 supplementation promote fatty acid oxidation in the liver by regulating the expression of key genes (*acyl-CoA oxidase* and *carnitine palmitoyltransferase*) involved in fatty acid metabolism [166, 167].

12.6 Lipid formulations (soy vs fish oil lipid emulsions); enhancing brain growth, normalizing PNALD

For decades, intravenous soybean oil-based lipid formulations have been used extensively in PN patients in the United States. However, the use of soybean oil-based lipid emulsion may not be optimal for the safety and benefit of PN patients. While this is a great source of essential fatty acids, soybean oil based lipid contains a higher amount of proinflammatory ω-6 PUFA including oleic acid, linoleic acid (18:2), and phytosterols [168]. A high amount of linoleic acid in ω-6 fatty acid has inflammatory properties [169]. Plant based phytosterols inhibit bile flow, increase triglyceride storage, increase hepatic cholestasis, and increase neurological disorders [170, 171]. Phytosterols are thought to be toxic to hepatocytes, but if they are taken enterally, they are absorbed by GI tract.

Over the years, PN with a fish oil-based lipid emulsion or a mixture of fish, soybean, and olive oil derived lipid emulsions have been preferred. Recent literature supports the idea of considering the use of fish oil based lipids solely, or a mixture of fish, olive and soybean oil based lipid emulsions as an alternative as significant improvements have been observed using fish oil based composition. This especially applies to preterm babies with immature brains and pediatric patients with PNALD. Fish oil or mixed oil lipid emulsions have increased antioxidant properties because the triglycerides formed from each lipid emulsion differ based on the fatty acid content, such as long vs. short chain fatty acid chains (LCFAs vs. SCFAs) and unsaturated vs. saturated. Different length FAs have different biological properties and clinical outcomes. Fish oil based lipid emulsions contain a high concentration of anti-inflammatory ω-3 unsaturated fatty acids with small amounts of linoleic acid and higher amounts of Omegaven, docosahexaenoic acid (DHA) and eicosapentaenoic (EPA). These have been shown reduce oxidative stress and inflammation by blocking proinflammatory cytokines to prevent or reverse PNALD with cholestasis in neonates as well as in the setting of intestinal failure [172–174]. DHA and EPA are the major metabolites of ω-3 fatty acids highly enriched in fish oil. DHA plays an important role in reducing inflammation by suppressing inflammatory markers [110]. Additionally, DHA present in Omegaven modulates the liver X-receptor involved in bile regulation [175, 176]. Further, DHA and arachidonic acid present in fish-oil or mixed lipid modulate neuronal development and brain maturation in piglets and preterm infants [132, 133, 177]. Alternatively, olive oil-based lipid emulsions have been proven as another alternative because they have a low amount of ω-6 fatty acid which reduces oxidative stress with no major changes in liver enzymes [178].

13. Future directions in PN research

Although PN is highly effective in pediatric and adult patients, the pathophysiology of its association with PNALD and neurological disorders and the underlying mechanisms are not well understood and are of high priority in the clinical setting. Over the years, most of the research has emphasized understanding the maturation

of the GI tract in PN patients. There are no specific safer therapies yet established for the prevention or treatment of multifactorial PNALD or brain abnormalities in PN patients. There are challenges to overcome in terms of the characterization and standardization of PN supplements for optimal nutrition to promote normal brain development trajectories and normal liver function. PN is essential but detrimental in preterm babies and infant patients on long term feeding, and they are at high risk for liver and brain abnormalities. Optimal nutrition with minimal side effects is highly important in early neonates for their developing brain and normal liver function. Several key questions need to be addressed including (1) the revision of PN components, (2) the characterization of current PN components, (3) the use of ω-3 fatty acid enriched fish-oil based lipid or mixed oil based lipid rather than soyabean oil based lipid, 4) the inclusion of essential short chain FA (SCFAs) and essential amino acids, and 5) the effects of specific dietary solutions in the rapidly developing brain in early life.

There is a need to consider cyclic PN (cPN) rather than continuous PN for long term in infants. Studies in neonates suggest that patients on cyclic (cPN) have delayed liver dysfunction compared to continuous PN [179]. Another study from Costadel Sol Hospital in Spain shows that patients ≥18 years had delayed hepatic abnormalities on cPN for 12–15 days compared to patients on continuous PN. The cPN patients showed significant reduction in hepatic enzymes such as Bilirubin, AST, ALT and GGT with no change in ALP [180]. However, the limitations of this study were the exclusion of patients having early liver abnormalities and sample size [180]. Future studies involving cPN instead of continuous PN administration will help in addressing early hepatic and brain related issues.

There is also the possibility for improvement of the route of PN, including partial enteral nutrition (EN) that may reduce the risk of developing PNALD. Given the limitations of current therapies, more research is needed for the optimization of current nutritional components and advancement in PN associated with neurological disorders and PNALD. The next key question in the field is to identify the driving factors and associated cellular and molecular mechanisms that modulate neurodevelopmental outcomes in the rapidly developing brain of preterm neonates and infants.

Another key factor to consider is how to maintain bacterial diversity (*Bacteriodities* vs. *Firmicuties*) and prevent unwanted bacterial overgrowth. Additionally, we need to focus on understanding the molecular mechanisms driving gut-brain maturation in pediatric patients on PN. In summary, there are several challenges remaining in clinical trials to optimize efficacy and safety of PN for patients.

14. Conclusions

The work that has been done in animal models to both characterize the molecular effects of PN on the body and to optimize PN additives has influenced the development of safer PN for patients. PN is essential and life-saving, so it is important that GI, immune, hepatic, and nervous system complications be minimized. Researchers have described the changes in intestinal cellularity, mucous composition, microbial population, innate immune function, enterohepatic circulation, and brain development induced by PN. Even though many patients requiring PN are critically ill and often malnourished making them predisposed to infection and underlying metabolic complications, a vast body of work demonstrates that route of feeding can dramatically alter the gut immune system, gut microbiome, metabolic handling, and organ function, which may contribute to

the pathophysiology observed in PN settings. The elegant work demonstrating the mechanisms by through mucosal immune cell signaling is altered under PN show that these alterations are targetable. Several additives have been explored that show promise in restoring normal function in the absence of enteric stimulation. For example, immune-enhancing metabolites like glutamine are helpful in patients with hypermetabolism. A major area of investigation has been using exogenous ENS neuropeptides to stimulate normal GALT function. Elsewhere, bile acid agonists and the use of fish oil lipid emulsions have been shown to support normal gut-liver feedback and reduce the incidence of PNALD in PN patients. Explorations of administering microbial metabolites, such as bile acid analogues, SCFAs, and polyamines are promising areas of research that can be further deliniated using translational models of PN feeding in the laboratory setting.

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