Nutrition 60 (2019) 100–105

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

Why do current strategies for optimal nutritional therapy neglect the microbiome?

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ARTICLE INFO

Article History:
Received 18 June 2018
Received in revised form 28 September 2018
Accepted 28 September 2018

Keywords:
Microbiome
Pathobiome
Gut defenses
Dysbiosis
Immune dysregulation

ABSTRACT

Strategies for providing optimal nutritional therapy have evolved over time, with the emphasis on specific directives (such as route, use of immunonutrition, high protein, organ-specific formulas, etc.), achieving variable degrees of success for improving outcomes in the intensive care unit. As the largest immune organ in the body comprising the largest interface between the host and the external environment, the gut can have an amplifying effect on a pattern of dysbiosis, immune dysregulation, and multiple organ failure seen in the critically ill patient. Conversely, maintenance of gut integrity can serve to restore a pattern of homeostasis, appropriate immune responses, symbiosis, and clinical recovery. Simply providing refined polymeric formulas as enteral nutrition may not take full advantage of the potential for optimal outcome that could be derived by giving therapy designed to directly stimulate gut defenses and support the intestinal microbiota. This article describes a series of strategies (such as use of intact whole food formulas, soluble fiber, fecal microbial transplantation, serum bovine immunoglobulin, or agents to promote commensal behavior) that should modulate the gut microbiome and shift the critically ill patient toward a pattern of health and recovery.

Introduction

The application of strategies for optimal nutritional therapy evolves over time. A variety of factors influence the decisions regarding the ideal nutritional regimen, such as patient tolerance, specific disease states, safety, altered physiology, anticipated outcomes, and preexisting malnutrition. It is not always clear which strategies are most beneficial, whether to correct deficiencies, modulate immune function, stimulate protein synthesis, promote organ function, support cellular structure, or sustain subcellular organelles like mitochondria. The current emphasis on optimal feeding does not include strategies that specifically support the gut microbiome, and as such this may represent a missed opportunity to maximize patient outcome [1–3].

Current strategies of nutritional and metabolic manipulation

In the past, different issues have been emphasized in an effort to optimize nutritional therapy [3,4]. The most simplistic issue has been the route of nutritional therapy, whether it be enteral nutrition (EN) or parenteral nutrition (PN). Although the use of EN is the most consistent strategy that would support the microbiome and maintain gut defenses, the degree to which EN does so has been questioned [5,6]. One strategy attempted to improve assimilation is the use of a formula with medium-chain triacylglyceride and small peptide formulas. Still another strategy employed immunomodulating formulas that included nutrients such as arginine to optimize T-cell function and fish oil to attenuate the stress response and enhance the resolution of the inflammatory response. An organ-focused strategy in the past led to the design of formulas directed at organ failure subsets (such as formulas designed for pulmonary, hepatic, or renal insufficiency), whereas a separate strategy led to other formulas focused on disease subsets (such as use of branched-chain amino acids for trauma, alternate glucose substitutes for diabetes, and high-protein, low-calorie formulas for obesity). Despite the volumes of literature in both animal and human models, this strategy has resulted in limited and very few consistent successes.

The current emphasis in nutritional therapy still focuses on the use of EN rather than PN; however, recently this strategy has encouraged an effort to reach protein rather than energy goals sooner and more reliably [2,3]. Refined polymeric formulas are being recommended with no supplemental immunomodulatory

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https://doi.org/10.1016/j.nut.2018.09.024
0899-9007/

nutrients, and strong emphasis is placed on maintaining muscle mass or lean body mass, and function of skeletal muscle [7]. Trophic feeding or permissive underfeeding is promoted in the early phase of critical illness, with the ultimate goal to provide high-protein hypocaloric feeding (where ~80% of goal calories are provided over the first 1 to 2 wk of hospitalization and protein goals are met in a range of 1.2–2 g/kg daily) [8]. A strategy of slow advancement of EN has been promoted in order to reduce the risk associated with EN from a number of factors. Slow advancement avoids overfeeding, as exogenous nutrients are added to the endogenous hepatic gluconeogenesis that occurs with oxidative stress [9]. For patients on vasopressor therapy, slow advancement is thought to minimize risk for enteric ischemia [10]. Evidence of hypophosphatemia with initiation of nutritional therapy indicates the potential for refeeding syndrome and slow advancement of feeding reduces mortality in that situation (compared with more rapid advancement) [11]. Slow advancement alters the timing of initiation of nutritional therapy in order to support autophagy [12]. A slow advancement over the initial phase of critical illness allows the clinician to monitor intestinal intolerance, making adjustments for abdominal distention, hypoactive bowel sounds, or prolonged failure to pass stool and gas [13].

The key issue is that clinicians choose EN over PN to maintain gut integrity, but little evidence exists to confirm that the optimal effect has been achieved by such a strategy [5,6]. Very few clinicians provide probiotics. The results of recent large, randomized controlled trials (RCTs) such as the CALORIES (Clinical and Cost-Effectiveness of Early Nutritional Support in Critically Ill Patients via the Parenteral versus the Enteral Route) trial and the NUTRIREA-2 (Impact of Early Enteral vs. Parenteral Nutrition on Mortality in Patients Requiring Mechanical Ventilation and Catecholamines) trial, reported no difference in outcomes between EN and PN in critically ill patients, which may lead to greater use of PN in the future [10,14]. All of this may represent a missed opportunity to truly alter the systemic inflammatory response syndrome (SIRS) seen in critical illness and instead restore the patient on a path to recovery. Failure to design a nutrition regimen that directly supports the microbiome would be expected to contribute to dysbiosis, immune dysregulation, breakdown of gut barrier defenses, and a clinical picture of sepsis, multiple organ failure, and heightened mortality [15].

Why are gut defenses immune responses in the microbiome important?

The gastrointestinal (GI) tract represents the greatest area of interface between the host and the external environment (estimated at 300–400 square meters or roughly the surface area of a tennis court). Although a similar interface probably exists in the lung and genitourinary tract, the total surface area is the greatest with regard to the gut. The GI tract is the largest immune organ in the body, containing >65% of all immune tissue in the body [16]. There are more lymphocytes in the gut than in the spleen. There are more genes present in the intestinal microbiome than there are in the host (estimated >3 million genes in bacterial genome versus 19 000 to 20 000 protein-coding genes in the human genome) [17].

A number of elements promote gut health, effect barrier defense, and support the growth of commensal organisms (preventing the conversion to a “pathobiome”). There is ongoing crosstalk signaling between commensal bacteria and the intestinal epithelium [18,19]. Commensal organisms do not have the mechanistic capability to adhere to the intestinal epithelium. Thus, fragments of the commensal bacteria (flagella, parts of the cell wall, or endotoxin) serve as microbial-associated molecular patterns that bind to the toll-like and nod-like receptors on the intestinal epithelium, which serve as pattern recognition receptors (PRRs) [18,19]. This crosstalk signaling maintains appropriate immune responses, promotes tolerance, and stimulates appropriate contained physiologic inflammation [18,19]. It also helps maintain the commensal lifestyle of the microbiome and its phenotypic expression [18].

This physiologic scenario shifts dramatically in critical illness. With the emergence of a virulent pathobiome, the crosstalk signaling that existed before is altered [20,21]. Now the toll-like and nod-like receptors serving as PRRs instead bind pathogen-associated molecular patterns (PAMPs; which are the actual pathogens themselves binding to the intestinal epithelium) and danger-associated molecular patterns (DAMPs; which are pieces of necrotic cells, mitochondrial DNA, or inflammatory cytokines) [18,22]. Alarmins is another name for DAMPs. Breakdown in gut barrier defense systems and the crosstalk signaling between intestinal PRRs and the PAMPs and DAMPs generate immune dysregulation and proinflammatory responses. The emergence of a virulent pathobiome through quorum sensing further contributes to a picture of gut sepsis, characterized by septic morbidity, antibiotic resistance, and multiple organ failure [20,23–25], a process now encompassed by the term *nonresolving organ dysfunction syndrome* [25].

When a patient is admitted to the intensive care unit (ICU), the diagnosis itself may not be the best determinant of disease severity. What better determines disease severity is the patient’s position on a pathophysiologic spectrum from health and homeostasis on one end to dysbiosis and immune dysregulation on the other [25,26]. Strategies provided through nutritional therapy have the potential to support the commensal bacteria; restore, maintain, and repair gut defense systems; and steer the patient toward a pattern of recovery. On the other hand, greater severity of critical illness combined with inability to provide optimum nutritional therapy facilitates a shift on this spectrum where the patient moves toward dysbiosis, immune dysregulation, multiple organ failure, and heightened mortality [19,27]. The key issue is whether the current focus of strategies for nutritional therapy effectively moves patients on this spectrum and promotes the pattern of recovery that is so needed.

How does the effect of EN on gut defenses and microbiome differ from that of PN?

The use of EN in critically ill patients is associated with less intestinal inflammation than use of PN [5,28]. Titlebaum et al. demonstrated that the use of EN promotes a less inflammatory response in the intestinal submucosa than PN, with EN showing an increase in the generation of T-regulatory cells and the production of interleukin (IL)-4 and IL-10. Transforming growth factor-β and IL-10 is increased, whereas the production of tumor necrosis factor (TNF)-αlpha and interferon (IFN)-γ is reduced [5,28]. In contrast, PN is associated more with inflammation, reduced production of T-regulatory cells, and an increase in nuclear factor κ-β expression in the laminar propria. This leads to a reduction in IL-4 and IL-10 and an increase in inflammatory cytokines of TNF-α and IFN-γ [5,28]. However, both commercial EN formulations and PN result in a relative nutrient deprivation at the level of greatest microbial burden, which is the cecum of the large intestine [29,30]. Refined enteral formulas tend to be absorbed very proximally in the GI tract and have limited quantity and variety of soluble fibers, which would limit or reduce their effectiveness in manipulating the microbiome and maintaining gut defenses in the distal bowel.

How do blenderized whole food formulas compare with refined polymeric formulas?

A simple but underused strategy to promote gut defenses and support commensal microbiota is to switch from refined polymeric formulas to blenderized whole food formulas. Theoretically, such blenderized whole food formulas should have a greater trophic effect on the bowel, and may be absorbed more distally in the GI tract with greater likelihood to influence the microbiota. In an animal model, mice fed a commercial whole food formula (Liquid Hope, Functional Formularies, Centerville, OH, USA) compared with similar rats fed a chemically defined formula (either Vital or Pediasure, Abbott Nutrition, Columbus, Ohio) showed reduced systemic inflammation (decreased IL-6 plasma levels), less weight loss, and greater colonic bacterial species diversity with less alteration in the composition of the microbiota [31]. The blenderized whole food formula resulted in a less abundance of *Enterobacteriaceae* (a family containing primarily gram-negative bacterial commonly associated with pathogenic states in the ICU population and associated with greater gut inflammation) and a higher abundance of clostridials (an order containing many commensal bacteria associated with immune homeostasis). The cecal contents of the mice fed the whole food formula had a significantly higher concentration of beneficial anti-inflammatory compounds metabolized by the microbiota, including lithocholic acid and hydroxycinnamic acid (a plant-derived polyphenol) [31]. This would suggest that blenderized whole food formulas, compared with refined polymeric formulas, are better at maintaining a healthy gut microbiota and stimulating anti-inflammatory metabolites in the gut, protecting against dysregulated inflammatory responses.

How well does soluble fiber enhance growth of commensals?

The recent Society for Critical Care Medicine/American Society for Parenteral and Enteral Nutrition guidelines suggest that soluble prebiotic fermentable fiber be given to all patients in the ICU [3]. The value of soluble fiber is believed to be derived from the generation of short-chain fatty acids (SCFAs), particularly butyrate, which independently has a beneficial effect on gut defenses, production of secretory immunoglobulin (Ig)A, anti-inflammatory crosstalk signaling, and support for growth of commensal organisms. Butyrate transporters in the colon have a systemic anti-inflammatory effect, influencing multiple cell lines and immune responses throughout the body. Multiple mechanisms have been described for these benefits of butyrate and other SCFAs produced by soluble fiber fermentation, including activation of G protein-coupled receptors (GPR41 and GPR43), activation of gene expression for *ICAM-1* and *e-Selectin*, function as a scavenger for reactive oxygen species, regulation of histone deacetylase, reductions in insulin resistance, and enhancement of neutrophil functions (such as chemotaxis and pathogen killing ability) [17,32–34].

Providing soluble fermentable fiber from higher-quality whole grains or bran can lead to increases in butyrate production and greater biodiversity of the microbiome [19,35,36]. Prebiotic therapy can act through endocannabinoid receptors in the colon and adipose tissue to alter the microbiome in a manner that improves intestinal barrier function, decreases systemic endotoxemia, and reduces inflammation [19].

The safety profile of soluble fiber in critically patients is good. Although theoretically, in patients with reduced contractility and intestinal stasis, fermentation of soluble fiber could lower the pH below 7.2. This pH change can promote excessive fermentation, bowel distention, and reduced bicarbonate backflow, which could lead to decreased mucosal perfusion and ischemia.

How well does probiotic therapy affect gut defenses?

Probiotic therapy is probably an underused strategy in the ICU. Clinicians may be reluctant to use probiotics in the ICU because societal recommendations for which probiotic, what dose, and how long to treat are not well delineated in the literature. The optimal timing for initiation of probiotics was supported recently by a report that showed that starting a probiotic at the time that antibiotics are initiated resulted in prevention of *Clostridium difficile* in 100% of patients, compared with starting the probiotics at a later time [37]. Guidelines for nutrition therapy in the adult critically ill patient recommend that probiotics be used in disease processes where they have been shown to have benefit in RCTs [3]. Those organisms with a significant quantity of literature to support a beneficial effect on brush-border defenses include *Lactobacillus salivarius*, *L. rhamnosus*, and *L. plantarum*. It may be naive, however, to think that a single organism or a blend of a few organisms would actually replenish the garden of the microbiome and redirect the patient's clinical course toward a pattern of immune homeostasis and recovery.

Probiotic therapy, through increased production of SCFAs, may increase glucagon-like polypeptides (GLP)-1 and GLP-2, which exert a trophic effect on the gut epithelium. *L. salivarius* has a direct effect on gut defenses, preventing disruption of epithelial cell tight junctions, and appearing to enhance tight junction protein localization through activation of intracellular signaling pathways. Probiotic therapy favorably alters gut–brain axis via a variety of mechanisms, including epigenetic influences and gene expression profiles [38,39]. In addition to the cellular mechanisms already discussed, probiotics exert their beneficial effect in critical illness by enhancing barrier function, competitive exclusion of pathogens, production of antimicrobial substances (bacteriocins), and modulation of immune and inflammatory responses. Other mechanisms include modulating signaling pathways, activating MAP kinase, and inducing cytoprotective heat shock proteins in the intestinal mucosa.

From a safety standpoint, PROPATRIA (Probiotics in Pancreatitis Trial) is the lone example of a study where use of probiotics in critical illness had a deleterious effect on outcome [40]. In that study, use of six probiotic organisms at full dose ($>10^6$ organisms) given twice a day for 4 wk directly into the small bowel, in combination with a mixed fiber (both soluble and insoluble) formula to patients (many of whom were on multiple pressor agents to maintain blood pressure) resulted in a greater incidence of ischemic bowel and mortality than controls who did not receive probiotic organisms [40]. This strategy was overly aggressive in patients who may not have been appropriately stable for such a regimen. Multiple other RCTs have been performed with probiotic therapy in a variety of populations in critical illness without a single case of bacteremia [41,42]. Specifically, in the patient population of severe pancreatitis, five other trials have shown a benefit of probiotic therapy compared with controls who do not receive probiotics.

Should fecal microbial transplantation be used in critical illness as the ultimate super probiotic?

A good argument for use of fecal microbial transplantation (FMT) in critical illness can be made, as >90% of commensal organisms are lost in the first 6 h of critical illness [26]. With the bloom of pathobiont organisms, there is loss of biodiversity [26]. Virulence expression of the pathogens results in antibiotic-resistant organisms, septic morbidity, anastomotic dehiscence, toxic lymph, and multiple organ failure [26]. Commensal organisms can be sequestered in specific niches, such as crypts of the colonic epithelium. Such sequestration

serves as a reservoir by which to repopulate the commensal organisms after antibiotic therapy [25,43]. Close proximity of these organisms with intestinal stem cells helps stabilize their function, support epithelial repair, and reestablish crosstalk signaling between the commensals and the epithelial cells [43]. However, with the combination of starvation and antibiotic use with surgical or medical oxidative stress, these niches become evacuated of any commensal microbiota [25]. Instead, the niches become replaced by pathogens, which worsen disruption of the crypt homeostasis and lead to severe inflammation of the intestinal mucosa [43]. In animal models, FMT has been shown to activate immune clearance of the pathogens from these crypts, restore crypt commensal microbiota, reestablish stem cell regenerative capacity, and suppress inflammation [43].

To date, five critically ill patients (without *C. difficile* infection) have been treated with FMT in the ICU setting [44–47]. The five patients ranged in age from the very young (16 y) to the very old (84 y), with clinical presentations ranging from trauma and traumatic brain injury to sepsis and neurologic disease, of whom all received antibiotics. The donor feces was obtained from healthy family members or graduate students and was given either very early (day 7) or late (day 72) in the ICU stay. The most uniform response to FMT that was seen was a rapid resolution of fever and the SIRs response within 1 to 2 d in all five patients [44–47]. Diarrhea decreased a little more slowly over the next 3 to 5 d. Such findings would suggest that the use of FMT shifted the patient's position on the spectrum from dysbiosis and immune dysregulation to a pattern of recovery, appropriate immune responses, eubiosis, and homeostasis.

Previous experience with use of FMT in patients with *C. difficile* has shown that variations in the method of delivery might facilitate use of this strategy in critically ill ICU patients. Delivering FMT by the "northern route" through a nasoenteric tube placed in the proximal jejunum is associated with reduced clearance of *C. difficile* compared with the "southern route" where the transplant is delivered directly to the cecum (74% versus 86%) [48,49]. However, adding a second FMT to the first increased the success rate from 62% to 83% [48,49]. Even more provocative is the fact that a lyophilized powder preparation of the FMT or a sterile fecal filtrate transfer where no live bacteria are transmitted decreased the clearance rate to only 73% to 78% compared with the delivery of fresh or frozen feces at 83% to 100% [49–52]. Thus, in a critically ill patient, a product comprised of the lyophilized powder or the sterile fecal filtrate could be delivered by the northern route through a nasojejunal feeding tube, and by repeating the procedure at least once could result in a success rate conceivably in the range of 80% to 90% [48–52]. This therapy in critically ill patients (with no history of *C. difficile*) might have the greatest likelihood of causing a shift in the spectrum from dysbiosis to eubiosis, altering outcome more than any other strategy involved within nutritional therapy.

The safety profile is what concerns most clinicians when considering use of FMT in the ICU. A recent systematic review of 50 reports involving close to 1100 patients showed that some adverse event occurred in almost half of the patients, but most of those events were related to transient GI complaints such as bloating, cramping, or constipation [53]. Such symptoms were more common by the northern route than the lower route. However, serious adverse events, such as pneumonia or perforation, were more common when FMT was given by the southern route and involved an endoscopic procedure. The mortality related to FMT was shown to be extremely low in this review (just three deaths in 1089 patients) [53]. Although severe infection was described in 2.5% of patients, the chances of it being directly related to the FMT was very low, at <1% (8 of 1089 patients). A flair of inflammatory bowel disease in response to FMT also was very low, seen in <1% (7 of 1089 patients) [53]. Of greatest concern, however, was the possibility of transmitting an autoimmune disorder. In 1 of the 50 reports, one each of four patients developed Sjogren syndrome, rheumatoid arthritis, idiopathic thrombocytopenic purpura, and a peripheral neuropathy over the 5 y after FMT [54]. Two patients in that report actually saw improvement in Combs-positive hemolytic anemia and peripheral arthritis over the same time course. It is unclear whether the autoimmune disorders in these four patients could be linked to the FMT, but no other reports have listed this complication [54].

What other strategies might be combined or included with nutritional therapy to alter the spectrum?

A bovine serum–derived immunoglobulin of the IgG type has been used in humans with diarrheal disease [55]. Compared with secretory IgA produced by humans, the IgG immunoglobulin produced by cows is a more mature immunoglobulin with greater ability to bind potential pathogens. The IgG immunoglobulin preparation is directed against common pathogens also seen in humans, such as *Staphylococcus, Streptococcus*, *C. difficile*, and *Enterobacteriaceae* [55]. Although this product has not been studied in critically ill patients, its ability to bind potential pathogens would suggest a possible role for use in altering the intestinal dysbiosis.

Avoiding foods, formulas, or medications combined with dietary emulsifiers can improve gut mucosal defenses [56,57]. Low-dose ingestion of emulsifiers such as carboxymethylcellulose or polysorbate-80 can cause gut mucosal damage, thinning of the mucus layer, alterations in the luminal microbiota, reduced butyrate production, and intestinal inflammation. The presence of these emulsifiers may interfere with the normal crosstalk signaling between commensal organisms and the intestinal epithelium, while inducing a low-grade virulence expression in potential pathogens [56,57].

A number of therapeutic strategies have the potential to promote commensalism. Phosphate given to a patient orally or via nasoenteric feeding tube into the stomach would be absorbed proximally [26,58]. However, phosphate can be bound to a carrier such as polyethylene glycol, enabling it to be carried down to the distal colon where bacteria cleave the bond making the phosphate available to the microbiota. The presence of phosphate in the colon promotes a commensal phenotype and will actually cause pathogens to come out of their virulence phenotype [26,58]. Another strategy includes limiting opioid narcotics to promote better motility and to reduce the effect of opioids on expression of virulence by potential pathogens. Using multimodal strategies such as sedatives, hypnotics, or propofol helps prevent the need for higher doses of opioid narcotics. Judicious use of antibiotics, where clinicians shorten the duration of the

Table 1
Strategies to support the intestinal microbiome in critical illness

Current strategies:
Enteral feeding
Avoidance of dietary emulsifiers
Limited use of narcotics (with alternative use of sedatives, hypnotics, propofol)
Judicious use of antibiotics (shortened duration, de-escalation therapy)
Blenderized whole food formulas
Provision of soluble fermentable fiber
Use of probiotics
Investigational strategies:
Specialized proresolving molecules (SPMs)
Bovine serum-derived immunoglobulin
Provision of a Farnesoid X receptor (FXR) antagonist
Polyethyline glycol-bound phosphate
Fecal microbial transplantation

antibiotic regimen or employ de-escalation therapy based on close follow-up of culture results, helps to minimize their effect on reducing biodiversity and promoting growth of potential pathogens.

The Farnesoid X receptor (FXR) plays an important role in mediating the crosstalk signaling between the host epithelium and the intestinal microbiome, through a process that involves modulation of the enterohepatic circulation of bile acids [59]. In an animal model, provision of an FXR antagonist, glycine-β-muricholic acid (Gly-MCA) altered gut microbiota (reducing the ratio of *Firmicutes* to *Bacteroidetes*) in a manner that improved lipid metabolism and insulin sensitivity, thereby reducing risk from diet-induced obesity and fatty liver disease [59].

Conclusion

Strategies for nutritional therapy need to focus on promoting a healthy gut microbiome. Early EN combined with soluble fiber and probiotic therapy helps sustain growth of commensal organisms and maintain gut barrier defenses. Minimizing use of enteral medications and formulas mixed with emulsifiers helps prevent the accumulation of chemicals within the gut that can alter the microbiome. Consideration should be given to use of an entirely new line of enteral products that can cause specific microbiome changes, such as those that increase butyrate, those that alter microbiome through the FXR, or those that enhance growth of specific organisms known to be beneficial. Switching from refined polymeric formulas to blenderized whole food formulas and even use of FMT in the future may increase the degree to which nutritional therapy promotes appropriate immune responses, maintenance of an intact barrier function, eubiosis, and a pattern of recovery and homeostasis.

Table 1.

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