Enteral feeding and the microbiome in critically ill children: a narrative review

Lijia Fan¹, Jan Hau Lee²,³

¹Division of Paediatric Critical Care, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore, Singapore; ²Children's Intensive Care Unit, KK Women's and Children's Hospital, Singapore, Singapore; ³Duke-NUS Medical School, Singapore, Singapore

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Correspondence to: Dr. Lijia Fan, MBBS, MMed (Paeds), MRCPCH (UK). Division of Paediatric Critical Care, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, NUHS Tower Block, Level 12, 1E Kent Ridge Road, Singapore 119228, Singapore. Email: li_jia_fan@nuhs.edu.sg.

Objective: This narrative review summarizes our current knowledge on the interplay between enteral nutrition (EN) and gut microbiota in critically ill children, using examples from two commonly encountered diagnoses in the pediatric intensive care unit (PICU): severe sepsis and acute respiratory distress syndrome (ARDS). This review will also highlight potential areas of therapeutic interventions that should be explored in future studies.

Background: Critically ill children display extreme dysbiosis in their gut microbiome. Factors within the PICU that are often associated with dysbiosis include the use of broad-spectrum antibiotics, proton-pump inhibitors (PPIs), intravenous morphine, and fasting. Dysbiosis can potentially lead to adverse clinical outcomes (e.g., nosocomial infection, and prolonged hospitalization). EN may modulate dysbiosis. The gut microbiota is involved in the breaking down of macronutrients, mainly carbohydrates and proteins. Fermentation of undigestible carbohydrate (e.g., inulin and oligosaccharides), and amino acids by large intestine microbiota produces short chain fatty acids (SCFAs). SCFAs serve as the main fuel source for enterocytes and help to maintain healthy gut lining. Changes to selected components of macronutrients can result in alterations in gut microbiome and have potentially beneficial effects in patients in the PICU.

Methods: A comprehensive search of the MEDLINE, Cochrane Library and Google Scholar databases was conducted using appropriate MESH terms and keywords. In this narrative review, we provide a summary of current knowledge on effect of EN on gut microbiota in pediatric studies, but also describes animal- and lab-based, as well as adult studies where relevant.

Conclusions: The gut microbiome can be altered by dietary modifications and common PICU practices and treatment. Although there are strong associations in restoring eubiosis and improvement in clinical outcomes, proving causality remains challenging. Further microbiome research is needed to provide mechanistic insights into the impact of the ever changing gut microbiome. In the future, new microbiota targeted therapies could potentially be the treatment of challenging PICU conditions and restore homeostasis in these children.

Keywords: Pediatrics; critically ill; enteral nutrition (EN); microbiome; dysbiosis

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Introduction

Since the initiation of the human microbiome project in 2008 there has been an explosion of literature on the interaction between the host and its microbiome (1). Trillions of bacteria exist in a well-balanced ecosystem in the human gut (2,3). The symbiotic relationship between bacteria and their host has been responsible for colonization resistance, immune regulation, tolerance, and gut mucosal homeostasis (4-6). Through direct competition for nutrition and space, healthy commensal microbiota protect the gut from overgrowth of pathogens. They also exhibit direct bacteriophage-like activity and produce inhibitory metabolites to maintain a healthy balanced ecosystem (4). The host, in turn, provides complex polysaccharides which are otherwise indigestible and can only be fermented by anaerobic bacteria in the large intestine. This process of fermentation produces short chain fatty acids (SCFAs), which are the main fuel source for colonocytes and are also involved in regulation of glucose and lipid metabolism of the host (7).

The gut microbiome of patients in the intensive care unit (ICU) can be vastly differently from those of healthy individuals (8,9). In critically ill patients, dysbiosis, which is a disruption in the microbiome homeostasis, is common. There is a loss of both alpha and beta diversity, as well as predominance of certain bacterial taxa, in these patients (8-10). Alpha diversity is a measurement of how rich an ecological bacterial community and beta diversity is the degree of difference of one community from another (11,12). Healthy commensal genera such as Faecalibacterium and Ruminococcus are depleted while pathogenic genus such as Enterococcus becomes predominant (8,9). Although there are many postulations on the implications of dysbiosis, there remains a paucity of studies that have demonstrated clinical importance of dysbiosis in the ICU.

In this narrative review, we first describe the impact of critical illness on the microbiome, with emphasis on how prolonged fasting, enteral feeding and various macronutrients modulates this micro-environment within the patient. We will illustrate the impact of enteral nutrition (EN) on the microbiome; and describe the changes in the microbiome in two common diagnoses in the pediatric intensive care unit (PICU): sepsis and acute respiratory distress syndrome (ARDS). We conclude by highlighting future directions for clinical research in this exciting area of pediatric critical care. The following article is presented in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tp-20-349).

Methods

A comprehensive search of the MEDLINE, Cochrane Library and Google Scholar databases was conducted for all published literature relating to EN, gut microbiome and critically ill children. Keywords were searched using thesaurus (e.g., MeSH) and adapted for each database (Table S1). Articles in the English language and published between 1990–2020 were included. Where possible, we review pediatric studies, but also describe animal- and lab-based, as well as adult studies, where relevant.

Gut microbiome alterations in PICU

Many practices in the ICU potentially affect gut microbiome homeostasis and gut mucosal integrity. The use of opioids, proton-pump inhibitors (PPIs), parenteral nutrition (PN) and broad-spectrum antibiotics are common in the PICU. Many of these practices decrease phylogenic diversity of the gut microbiota and increase the host susceptibility to infection by the predominant pathogenic organisms (Table 1). These common treatments can result in a state of extreme dysbiosis in the critically ill. This was demonstrated in an observational study involving 37 critically ill children, which showed depletion of healthy commensals such as Faecalibacterium and Ruminococcus, as well as an abundance of pathogens such as Enterococcus in the gut (8). The same study also demonstrated a loss of microbial site specificity in patients. It is well reported that different body sites contain unique microbial community signatures (33). However, in these patients, pathogenic taxa were simultaneously present at relatively high abundance across all three sampled body sites; the tongue, skin and gut. The predominant presence of pathogenic microbial community can be worrying and may predispose these vulnerable individuals to nosocomial infections (34,35).

Fasting, enteral feeding and gut microbiome

Fasting is pervasive in the PICU. Critically ill children are fasted for various reasons (e.g., procedures, feed intolerance, and significant hemodynamic instability). Potential changes in the gut microbiome can occur with prolonged fasting (Table 1). Establishing EN can be challenging but crucial. In a survey involving PICUs in 57 countries, fasting for procedures or surgeries, lack of dietician support and
prioritizing other aspects of care over nutrition were amongst the top perceived barriers to enteral feeding (36). Given the challenges of initiating feeds in the critically ill, the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) recommended that EN be initiated within 24 hours of admission to the PICU (37). Children who are hemodynamically stable on extra-corporal life support or vasoactive medications should be also initiated on early EN. When EN cannot be established, PN would often be initiated to ensure adequate delivery of calories. However, there are growing concerns in regards to early PN use. In a multi-center randomized control trial (RCT) involving 1,440 critically ill children, delaying PN for 1 week was shown to have a more superior outcome than early PN (38). This was specific for rate of acquisition of new infections (adjusted odds ratio 0.48; [95% confidence interval (CI): 0.35–0.66]) and shorter mean duration of ICU stay (6.5±1.4 days in late PN group vs. 9.2±0.8 days in early PN group).

Enteral feeding is important to prevent gut mucosal atrophy and to maintain the gut barrier. In animal studies, villus height and crypt depths were significantly higher in mice who were enterally fed than those on exclusive PN, even when caloric intake was the same (39). The apoptotic index was two times higher in the mice who were on total PN. Through in-vitro as well as mouse model studies, it has been shown that brush border enzyme intestinal alkaline phosphatase (IAP) expression and function was lost during starvation and could be reversed by enteral feeding (40). IAP is involved in prevention of bacterial translocation and detoxifying lipopolysaccharide. These findings from bench studies potentially explain the protective effect of feeding on the gut mucosal barrier against luminal pathogens.

The effect of dietary changes on the gut microbiome has also been demonstrated in several human studies. The influence of diet on beta-diversity can occur just 1 day after alterations to diet. Such changes in microbiome diversity can also revert to its original state in 2 days (41,42). In the

| Interventions | Changes to gut environment and microbiome | Potential clinical effects |
|---------------|------------------------------------------|---------------------------|
| Opioids       | • Decreased IL-6 secretion by the epithelial cells (13) | • Reduced gut propulsion (14) |
|               | • Reduced phagocyte activation and migration towards mucosal surfaces (13) | • Increases susceptibility to Streptococcus pneumoniae infection (15) |
|               | • Increased bacterial translocation to mesenteric lymph nodes complex (14,16) | • Increased risk of Escherichia coli, Proteus mirabilis, Clostridium difficile infection (17,18) |
|               | • Increase Enterococcus, Lactobacillus, Streptococcus, Staphylococcus, genus (20-22) | • Increases Pseudomonas aeruginosa virulence expression (19) |
|               | • Decrease Faecalibacterium genus (21) | |
| PPIs          | • Increase Enterococcus, Lactobacillus, Streptococcus, Staphylococcus, genus (20-22) | • Increase enteric infections by Clostridium difficile, Salmonella, and Campylobacter jejuni (20,23) |
|               | • Decrease Faecalibacterium genus (21) | |
| Broad-spectrum antibiotics | • Reduce in gut microbiome diversity (24-26) | • Increase in Clostridium difficile infection (26) |
|               | • Increase antibiotic resistance genes-carrying plasmids (24) | • Increase susceptibility to infection by multi-drug resistant organism (27) |
|               | • Recovery of microbial composition occurs only months after cessation of antibiotics (26,28,29) | |
| Fasting       | • Dominance of pathogens such as Klebsiella pneumoniae, Providencia alcalifaciens and Clostridium perfringens (30,31) | • Not reported |
|               | • Increase in Firmicutes | |
|               | • Decrease in Bacteroidetes genus and Roseburia species (32) | |

Table 1 summarizes the changes in gut microbiome caused by some common practices. It is non-exhaustive as the focus of the review is on the influence of EN on gut microbiome. Other practices in PICU such as endotracheal tube placement, central line placement, use of steroids and immunosuppressants can lead to changes in skin or lung microbiome and will not be discussed here. PPIs, proton-pump inhibitors; EN, enteral nutrition; PICU, pediatric intensive care unit.
following sections, we will describe the effect of different dietary macronutrients on the gut microbiome.

**Effect of carbohydrates**

There are differential effects of digestible and non-digestible carbohydrates on the microbiome. This difference is also observed among various digestible carbohydrates (i.e., glucose, fructose and lactose). Diet that contains high fructose and glucose has been shown to lower proportion of *Bacteroidetes* and increase proportion of *Proteobacteria* (43,44). This observation is similar to the changes in extreme dysbiosis seen in patients in the ICU, where there is an increased relative abundance of *Proteobacteria*, with lower relative abundance of *Firmicutes* and *Bacteroidetes* (10). The result of dysbiosis was shown in an experiment involving four groups of mice fed with a fructose, glucose, fat or normal diet (43). In addition to developing gut dysbiosis, mice fed with fructose and glucose had less expression of the tight junction proteins such as Zonula occludens-1 (ZO-1) and occludin, and increased gut permeability. This corresponded to higher expression of inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL) 1b in the colon, suggestive of increased gut translocation. Fructose-induced dysbiotic has also been implicated in other various metabolic conditions such as obesity and non-alcoholic fatty liver disease (45,46). Lactose, on the other hand, has been shown to be beneficial. In a matched case-control study, lactose-free extensively-hydrolyzed formula was given for 2 months to a cohort of infants with cow’s milk protein allergy, followed by reintroduction of lactose again (47). The population of *Bifidobacterium* significantly increased with lactose-containing milk feeds, and that of *Bacteroides* decreased. This also corresponded to an increase in the median concentration of SCFAs which were important sources of fuel energy for the enterocytes (7,48,49).

Non-digestible fermentable carbohydrates (e.g., oligosaccharides and fibers such as inulin, pectin, β-glucan, β-fructan) play an important role in maintaining gut health. A diet high in fiber has been shown to be beneficial in inflammatory bowel disease (IBD), gastric cancer and colorectal cancer via a postulated mechanism of modifications to the gut microbiota (50-53). These fibers and undigestible oligosaccharides are fermented by bacteria to SCFAs (e.g., butyrate, acetate, and propionate) and make up the majority of fermented metabolites that are utilized as major energy sources by gut epithelial cells (48,49,54,55).

Butyrate, in particular, has demonstrated additional roles in enterocytes and colonocytes proliferation, cell differentiation, as well as apoptosis (56,57), leading to maintenance of healthy gut lining and prevention of mucosal atrophy. This effect of butyrate has been seen even when delivered as PN and has a dose-response relationship (58).

Given the beneficial effects of SCFAs, it is important to understand the production of these metabolites by microbiota in the large intestine, as they are currently being explored as possible therapeutic options for diseases such as IBD (59,60). Bacteria like *Faecalibacterium prausnitzii* (F. prausnitzii), from the *Firmicute* phylum are the major producers of butyrate (61,62). Low proportions of *F. prausnitzii* has been found in patients with Crohn’s recurrence and increasing its proportion has been shown to increase butyrate levels and correspondingly anti-inflammatory cytokines such as IL-10 (60,63,64). Other SCFAs such as acetate and propionate are produced by *Bifidobacterium* and *Prevotella* genus of bacteria, respectively (61,65-67). They are involved in other important metabolic pathways such as glucose and lipid metabolism (68).

In order to maintain a healthy gut microbiome, studies have looked at supplementation of enteral feeding with dietary fiber or oligosaccharides. The two most commonly studied oligosaccharides are fructo-oligosaccharides (FOS), and galacto-oligosaccharide (GOS). In two RCTs involving healthy infants, those who were fed with formula milk supplemented with GOS had a significantly increased abundance of *Bifidobacterium* and *Lactobacillus* than those who were on regular formula milk feeding. The counts of *Clostridium* species were also lower in those were supplemented with GOS (69,70). This change in gut microbiota was also associated with changes in SCFA level in these infants and improvement in symptoms of colic.

In the context of neonatal critical care, a RCT involving 75 premature infants demonstrated that those who had breast milk supplemented with oligosaccharides (mixture of FOS and GOS) had a significantly lower incidence of necrotizing enterocolitis compared to those on exclusive breast milk feeding alone [4.0% vs. 22.0% respectively; hazard ratio 0.49 (95% CI: 0.29–0.84); P=0.002] (27). To the best of our knowledge, there are no studies of such supplementation involving PICU patients.

**Effects of protein**

In the stomach and duodenum, protein is broken down
into amino acids via the action of digestive enzymes pepsin, trypsin and chymotrypsin. In the small and large intestine, several gut bacterial are involved in further catabolism, assimilation and utilization of amino acids.

Bacteria of the *Clostridium* genus are noted to be the key drivers of amino acid fermentation, and to a lesser extent *Bacteroides*, *Fusobacterium*, and *Veillonella* genera (71). The most abundant end products from the fermentation process are SCFAs (72,73). Some by-products such as amines, phenols and hydrogen sulfide have been implicated in disease development such as colorectal cancer (72,74-76). Others, such as polyamines, can play an important role in maintaining the health of small intestinal mucosa and immune development (77-79). To our knowledge, there are no large scale RCTs looking at the impact of protein rich diet on microbiome and its impact on clinical outcome.

**Effects of lipids**

Critically ill children often receive enteral lipid supplementation, such as medium chain triglyceride oil, in addition to their standard milk feeds. This is because the volume of fluid they can receive in a day is often restricted, which could limit the amount of calories received. Supplementation with enteral lipids allows the optimisation of calories without proportionate increment in the milk feed volume. Hence it is important to review the effects of lipid on microbiome and clinical outcomes.

Most of dietary fat does not reach the large intestine. It is digested by lipase produced by pancreas into fatty acids and glycerol. Most fatty acids are absorbed in the small intestine, while the remaining that pass through the large intestine will modulate its microbiota.

The influence of dietary fat on the gut was demonstrated in an animal study where mice were fed with diet high in saturated fat and omega-6 polyunsaturated fatty acid (PUFA), or omega-3 PUFA (80). Their gut microbiota profiles were examined during a 13-week study period. *Bilophila* species, of the *Proteobacteria* phylum, was significantly higher in the group that was fed with saturated fats and omega-6 PUFA compared to those fed with omega-3 PUFA and control. *Bilophila* is known to produce hydrogen sulfide, which is believed to be associated with gut inflammation and increase in gut permeability (81). Furthermore, in this same study, mice fed with saturated fats had reduced transepithelial resistance, suggestive of increased permeability; whilst those fed with omega-3 PUFA had higher transepithelial resistance. Bacteria DNA content in mesenteric fat, which was used as a surrogate marker for bacterial translocation, was also higher in mice fed with high dietary saturated fats. This may indicate that various forms, and sources of dietary fat impacts the gut microbiome and epithelial integrity differently.

In humans, omega-3 PUFA supplementation has been shown to increase *Lachnospiraceae* family of bacteria which were butyrate producing, which in turn increases SCFA levels in the gut (82-84). The use of omega-3 PUFA supplement has been shown to reduce overall mortality in critically ill adult with sepsis and sepsis induced ARDS (85). In critically ill children, literature is limited. In a RCT involving 120 children with mild to moderate sepsis, the use of omega-3 PUFA has been shown to significantly improved inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and IL-6, as well as PICU length of stay (5±2.5 days in the omega-3 PUFA group vs. 6.5±3 days in the control group, P<0.01) (86). Unfortunately, the effect on the gut microbiome was not reported in this study. Due to lack of large scale, good quality evidence, routine supplementation of omega-3 is still not recommended (37,87-89).

**Sepsis, enteral feeding and gut microbiome**

**Changes in microbiome in sepsis**

Sepsis is one of the leading causes of mortality in children (90,91). The onset of sepsis can cause a significant disturbance to the gut commensal microbiota community. In a pilot study using 16S rRNA technology, investigators identified marked inter-individual variation in the stool microbiota compared to healthy controls, and reduced intra-individual bacterial diversity (92). There was a significantly higher proportion of *Proteobacteria*, although the *Bacteroidetes* and *Firmicutes* were still the predominant phyla.

Intestinal barrier permeability is increased during sepsis. This has been shown in various animal models with changes not limited to the tight junction proteins such as occludin, claudin and zonulin, between intestinal epithelial cells, but also in gross morphological appearances (93-96). Some of these changes were also directly related to microvascular blood flow alterations during sepsis, affecting the protective mucin layer over the epithelial cells, resulting in more contact with gut bacteria and followed by further pro-inflammatory response (97,98).

The impact of extreme dysbiosis and impaired gut
epithelial lining is demonstrated in patients with severe systemic inflammatory response syndrome (SIRS) (99). In this adult ICU study, lower counts of Bacteroidaceae and Bifidobacterium were observed in patients with feed intolerance, and this was associated with lower SCFA level, higher incidence of bacteremia (86% vs. 18%) and mortality (64% vs. 20%, P<0.05). One possible explanation for this is the concept of gut-driven sepsis (100-104). This concept proposes that critically ill patients have their gut epithelial lining integrity challenged by microcirculatory alterations, leading to increased risk of bacterial translocation to regional mesenteric lymph nodes and portal vein system (100,105,106). If the liver is not able to clear the portal vein circulation of enteric bacteria and their products, a systemic inflammatory response could occur. Several distant end organs can be affected, leading to development of multi-organ dysfunction syndrome (MODS), which is often experienced by patients with severe sepsis.

**Effect of enteral feeding on microbiome in sepsis**

Enteral feeding has been shown to have a beneficial effect on the gut mucosal barrier during sepsis. In a murine endotoxin-induced sepsis model, enteral feeding was shown to significantly reduce mucosal epithelial cell apoptosis, whereas fasting for 16 hours increased gut mucosal permeability significantly (107). Though limited data is available looking at impact of enteral feeding on gut microbiome of septic children, specific dietary modification (e.g., omega-3 PUFA) and use of probiotics have been studied (86). In a RCT involving 100 critically ill children with severe sepsis, 50 were randomized to receive multi-strain probiotics consisting of Lactobacillus, Bifidobacterium, and Streptococcus. At the end of 7 days, those who received probiotics had lower proinflammatory cytokine (IL-6, IL-12p70, IL-17 and TNF-a) compared to placebo group (P<0.01) (108). The use of the same probiotics strains have also been reported by Banupriya et al. in an open label RCT involving 150 critically ill children who were expected to be mechanically ventilated for more than 48 hours. Children who received probiotic containing Lactobacillus, Bifidobacterium, and Streptococcus strains had lower incidence of ventilator associated pneumonia than those in the control group (adjusted relative risk of 0.227; P=0.016) (109).

The mechanism through which probiotics helps to maintain a healthy gut ecosystem and prevent colonization of pathogens include competitive exclusion and production of bioactive compounds, such as bacteriocins and hydrogen peroxide that have antipathogenic properties (110,111). In various animal- and lab-based experiments, its use has also been shown to tighten intestinal barrier, increase cell proliferation and re-epithelialization (112-114).

Despite these benefits, routine use of probiotics in PICU is not recommended and should be used with caution (115). This is because its use has been associated with development of Lactobacillus bacteremia in the critically ill population (116,117). Large scale pediatric RCTs are still lacking to determine the true efficacy and safety profile of the use of probiotics in this special group of patients.

**Pediatric acute respiratory distress syndrome (PARDS), enteral feeding and gut microbiota**

PARDS is a significant cause of mortality and morbidity for children admitted to the ICU (118,119). In recent years, there has been an emerging interest in intestinal crosstalk and gut-lymph theory that proposes that the gut could be the driving motor for the pathogenesis of ARDS.

**Intestinal crosstalk and gut-lymph theory**

In 2007, Clark et al. proposed that the gut epithelium, mucosal immune system and the commensal bacteria communicate with each other, as well as with extra-intestinal tissues (120). Commensal bacteria interact with the intestinal epithelial cells by regulating mucin production by the goblet cells, which prevents adherence of pathogens onto the epithelium, initiating process of mucosal repair. Through the presence of local dendritic cells, and mesenteric lymph nodes, commensal bacteria are also able to build immune tolerance towards themselves and control host inflammation. Epithelial cells serve as immune-effector cells for the mucosal immune system within the gut-associated lymphoid tissue (GALT) (120,121). GALT comprises of the Peyer’s patches, mesenteric lymph nodes, lamina propria and intraepithelial lymphocytes. The intestinal epithelial cells serve as antigen presenting cells, and produce cytokines and chemokines that regulate immune response in the gut (120,122). In the presence of a pathogen, inflammatory cytokines, such as TNF-α, interferon gamma (IFN-γ), IL-4 and IL-13, would be produced from the intestinal mucosal immune system (121). They increase tight junction permeability as well as apoptosis of the intestinal epithelial cells (120). With this increased intestinal leakiness, gut derived toxic factors can be easily carried via the mesenteric lymph node.
to distant organ sites such as the lung or kidney to cause secondary injury, as a prelude to the onset of MODS.

This gut-lymph theory was demonstrated in a series of mice experiments by Senthil et al. in 2006 and Deitch et al. in 2010. Both groups showed that the mesenteric lymph node carries various factors such as protein components of dead bacteria, cell wall fragments, cytokines and chemokines to the systemic circulation via the thoracic duct through the left subclavian vein (123,124). Upon reaching the lungs, these factors were responsible for activation of macrophages in alveoli leading to ARDS. This explains why the lungs are generally the first organ to fail following severe critical illness. Further evidence emerged in 2016, when Dickson et al. showed that the lung microbial community changed significantly after induced sepsis in a murine model (125). In this study, after mice had sepsis induced by caecal ligation, gut microbiome bacteria from the Bacteroides order, Enterococcus and Lachnospiraceae species became the predominant lung communities. This was then repeated in adult ARDS patients’ and healthy volunteers’ bronchoalveolar lavage samples. There was an abundance of gut associated Bacteroides species which was not found in healthy individuals. There was also relative enrichment of Proteobacteria phylum, which positively correlated with alveolar TNF-α level, which reflects degree of alveolar inflammation (125). The gut-lymph theory offers further insight to the pathophysiology of ARDS, and this provides an avenue for exploration of therapeutic options that involved modulation of the gut microbiome.

Effect of enteral feeding on PARDS

Nutrition is an important component of daily management of patients with PARDS. In a prospective cohort study involving 385 critically ill children, malnutrition was found to be an independent predictor of clinical outcome (126). More specific to PARDS, malnourished children have been observed to have a high mortality (127). In a retrospective study involving 107 children with PARDS, patients who received adequate calories (defined by achieving 80% of resting energy expenditure), and adequate protein (defined as receiving 1.5 g/kg/day), were found to have significant reductions in ICU mortality (34.6% vs. 68.5%, P=0.025) (128). This suggests that aside from advances in lung protective ventilation strategies, optimizing nutrition in these critically ill children could potentially impact on their clinical outcomes.

The use of immuno-nutrition in ARDS (e.g., omega-3 PUFA, glutamine, and arginine) has been studied. Most of these studies have been conducted in adults. Arginine and glutamine have shown some immunomodulatory effects in animal studies; however, no evidence of significant clinical improvement in humans has been demonstrated (129-132). The use of omega-3 PUFA, on the other hand, has been associated with clinical benefit with reduction in mortality, risk of developing new organ failure, and duration of mechanical ventilation and ICU stay (133). However, this effect is not consistent. In an adult RCT of patients with acute lung injury, the use of omega-3 PUFA and other antioxidants have been evaluated for the main outcome of reducing ventilator free days (134). Twice daily enteral omega-3 PUFA, γ-linolenic acid and antioxidants were given to the intervention group and the control group received isocaloric nutrition via a feeding protocol. Despite the increment in plasma eicosapentaenoic acid (EPA) levels, the intervention group had fewer ventilator-free days (14.0 vs. 17.2 days, P=0.02). The study was also stopped early for futility.

For children with PARDS, feasibility of administering EPA and γ-linolenic acid were evaluated in a small study of 26 patients (135). In this study, the use of EPA and γ-linolenic acid was associated with a significant increase in anti-inflammatory circulating markers, though other clinical outcomes such as change in oxygenation index, ventilator-free days, PICU length of stay and mortality were not reported. Further studies are needed to conclusively determine if immuno-nutrition is beneficial for children with ARDS.

Future directions and avenues for research

Literature on gut microbiota in the critically ill child are limited. Most studies remain observational in nature, describing the degree of dysbiosis during the patients’ stay and its association with severity of diseases. These studies form the basis for future research for various therapeutic options to restore eubiosis and the clinical implications that are associated with it. Recent studies have shown that probiotics could reduce the incidence of antibiotic associated diarrhea, ventilator associated pneumonia, and nosocomial infections in critically ill children, possibly by lowering the colonization of pathogenic organisms (109,136-139). Synbiotics, which are mixture of prebiotics and probiotics, have also been studied recently in other pediatric conditions such as childhood infections and atopic dermatitis (140,141). In a RCT involving 100 infants with
cyanotic congenital heart disease, those supplemented with synbiotics (inulin and *Bifidobacterium lactis*) have been shown to have lower incidence of culture-proven sepsis than those on placebo (18% vs. 4%, *P*=0.03) (142). There are no further large scale RCTs about the use of synbiotics in preventing nosocomial infections and improving outcomes such as length of stay or mortality in critically ill children. The optimal choice and dose of microbes remains to be determined.

Another area which should be explored would be manipulation of certain microbiota using targeted EN changes or prebiotics such as human milk oligosaccharides or other indigestible carbohydrate. Large scale clinical trial would be needed to translate the successful manipulation of microbiome with these interventions to clinically relevant outcomes, such as ventilator-free days, length of stay or mortality.

Other microbiome directed interventions such as fecal microbiota transplant, which have already shown positive results in pediatrics IBD and refractory *Clostridium difficile* infection, could also be explored in the future (29,143-145).

**Conclusions**

The gut microbiome can easily be altered by dietary modifications and common PICU practices and treatment. There is increasing evidence to show benefits of EN in critically ill children. However, although there are strong associations in the change of gut microbiome and improvement in clinical outcomes, proving causality remains challenging. As advancements in microbiota detection technology and mechanistic research offer insights into the unanswered questions about the impact of the ever changing gut microbiome, more therapeutic options are surfacing for children in the ICU. In the future, new microbiota targeted therapies could potentially treat challenging PICU conditions and restore homeostasis in these children.

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**References**

1. Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. Nature 2007;449:804-10.
2. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59-65.
3. Bull MJ, Plummer NT. Part 1: The human gut microbiome in health and disease. Integr Med (Encinitas) 2014;13:17-22.
4. Pickard JM, Zeng MY, Caruso R, et al. Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev 2017;279:70-89.
5. Neish AS. Mucosal immunity and the microbiome. Ann Am Thorac Soc 2014;11 Suppl 1:S28-32.
6. Lazar V, Ditu LM, Pircalabioru GG, et al. Aspects of gut microbiota and immune system interactions in infectious diseases, immunopathology, and cancer. Front Immunol 2018;9:1830.
7. Roediger WEW. Utilization of nutrients by isolated epithelial cells of the rat colon. Gastroenterology 1982;83:424-9.
8. Rogers MB, Firek B, Shi M, et al. Disruption of the microbiota across multiple body sites in critically ill children. Microbiome 2016;4:66.
9. Wijeyesekera A, Wagner J, De Goffau M, et al. Multi-compartment profiling of bacterial and host metabolites identifies intestinal dysbiosis and its functional consequences in the critically ill child. Crit Care Med 2019;47:e727-34.
10. McDonald D, Ackermann G, Khailova L, et al. Extreme dysbiosis of the microbiome in critical illness. mSphere 2016;1:e00199-16.
11. Willis AD. Rarefaction, alpha diversity, and statistics. Front Microbiol 2019;10:2407.
12. Goodrich JK, Di Rienzi SC, Poole AC, et al. Conducting a microbiome study. Cell 2014;158:250-62.
13. Brosnahan AJ, Jones BJ, Dvorak CM, et al. Morphine attenuates apically-directed cytokine secretion from intestinal epithelial cells in response to enteric pathogens. Pathogens 2014;3:249-57.
14. Runkel NS, Moody FG, Smith GS, et al. Alterations in rat intestinal transit by morphine promote bacterial translocation. Dig Dis Sci 1993;38:1530-6.
15. Wang J, Barke RA, Charboneau R, et al. Morphine impairs host innate immune response and increases susceptibility to Streptococcus pneumoniae lung infection. J Immunol 2005;174:426-34.
16. Meng J, Yu H, Ma J, et al. Morphine induces bacterial translocation in mice by compromising intestinal barrier function in a TLR-dependent manner. PLoS One 2013;8:e54040.
17. Hilburger ME, Adler MW, Trauant AL, et al. Morphine induces sepsis in mice. J Infect Dis 1997;176:183-8.
18. Wang F, Roy S. Gut homeostasis, microbial dysbiosis, and opioids. Toxicol Pathol 2017;45:150-6.
19. Babrowski T, Holbrook C, Moss J, et al. Pseudomonas aeruginosa virulence expression is directly activated by morphine and is capable of causing lethal gut-derived sepsis in mice during chronic morphine administration. Ann Surg 2012;255:386-93.
20. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut 2016;65:740-8.
21. Takagi T, Naito Y, Inoue R, et al. The influence of long-term use of proton pump inhibitors on the gut microbiota: an age-sex-matched case-control study. J Clin Biochem Nutr 2018;62:100-5.
22. Hojo M, Asahara T, Nagahara A, et al. Gut microbiota composition before and after use of proton pump inhibitors. Dig Dis Sci 2018;63:2940-9.
23. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011;34:1269-81.
24. Willmann M, Vehreschild M, Biehl LM, et al. Distinct impact of antibiotics on the gut microbiome and resistome: a longitudinal multicenter cohort study. BMC Biol 2019;17:76.
25. Jernberg C, Lofmark S, Edlund C, et al. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. ISME J 2007;1:56-66.
26. Bhalodi AA, van Engelen TSR, Virk HS, et al. Impact of antimicrobial therapy on the gut microbiome. J Antimicrob Chemother 2019;74:i6-15.
27. Armanian AM, Sadeghnia A, Hoseinzadeh M, et al. The effect of neutral oligosaccharides on reducing the incidence of necrotizing enterocolitis in preterm infants: a randomized clinical trial. Int J Prev Med 2014;5:1387-95.
28. Rashid MU, Zaura E, Buiks MJ, et al. Determining the long-term effect of antibiotic administration on the human normal intestinal microbiota using culture and pyrosequencing methods. Clin Infect Dis 2015;60 Suppl 2:S77-84.
29. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4554-61.
30. Baker JL, Hendrickson EL, Tang X, et al. Klebsiella and Providencia emerge as lone survivors following long-term starvation of oral microbiota. Proc Natl Acad Sci U S A 2019;116:8499-504.
31. Deplancke B, Vidal O, Ganessunker D, et al. Selective growth of mucolytic bacteria including Clostridium perfringens in a neonatal piglet model of total parenteral nutrition. Am J Clin Nutr 2002;76:1176-83.
32. Seitz J, Belheouane M, Schulz N, et al. The impact of starvation on the microbiome and gut-brain interaction in anorexia nervosa. Front Endocrinol (Lausanne) 2019;10:41.
33. Lozupone CA, Stombaugh J, Gonzalez A, et al. Meta-analyses of studies of the human microbiota. Genome Res
34. Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. Lancet Gastroenterol Hepatol 2017;2:135-43.
35. Adelman MW, Woodworth MH, Langelier C, et al. The gut microbiome’s role in the development, maintenance, and outcomes of sepsis. Crit Care 2020;24:278.
36. Tume LN, Eveleens RD, Verbruggen S, et al. Barriers to delivery of enteral nutrition in pediatric intensive care: a world survey. Pediatr Crit Care Med 2020;21:e661-71.
37. Tume LN, Valla FV, Joosten K, et al. Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. Intensive Care Med 2020;46:411-25.
38. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111-22.
39. Sun X, Spencer AU, Yang H, et al. Impact of caloric intake on parenteral nutrition-associated intestinal morphology and mucosal barrier function. JPEN J Parenter Enteral Nutr 2006;30:474-9.
40. Goldberg RF, Austen WG Jr, Zhang X, et al. Intestinal alkaline phosphatase is a gut mucosal defense factor maintained by enteral nutrition. Proc Natl Acad Sci U S A 2008;105:3551-6.
41. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559-63.
42. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011;334:105-8.
43. Do MH, Lee E, Oh MJ, et al. High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change. Nutrients 2018;10:761.
44. Eid N, Enani S, Walton G, et al. The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. J Nutr Sci 2014;3:e46.
45. Campo L, Eiseler S, Apfel T, et al. Fatty liver disease and gut microbiota: a comprehensive update. J Clin Transl Hepatol 2019;7:56-60.
46. Jegatheesan P, De Bandt JP. Fructose and NAFLD: the multifaceted aspects of fructose metabolism. Nutrients 2017;9:230.
47. Francavilla R, Calasso M, Calace L, et al. Effect of lactose on gut microbiota and metabolome of infants with cow’s milk allergy. Pediatr Allergy Immunol 2012;23:420-7.
48. Meier RF. Basics in clinical nutrition: fibre and short chain fatty acids. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 2009;4:e69-71.
49. Roy CC, Kien CL, Bouthillier L, et al. Short-chain fatty acids: ready for prime time? Nutr Clin Pract 2006;21:351-66.
50. Liu X, Wu Y, Li F, et al. Dietary fiber intake reduces risk of inflammatory bowel disease: result from a meta-analysis. Nutr Res 2015;35:753-8.
51. Pituch-Zdanowska A, Banaszkiewicz A, Albrecht P. The role of dietary fibre in inflammatory bowel disease. Prz Gastroenterol 2015;10:135-41.
52. Zhang Z, Xu G, Ma M, et al. Dietary fiber intake reduces risk for gastric cancer: a meta-analysis. Gastroenterology 2013;145:113-20.e3.
53. Alhinai EA, Walton GE, Commane DM. The role of the gut microbiota in colorectal cancer causation. Int J Mol Sci 2019;20:5295.
54. Fu X, Liu Z, Zhu C, et al. Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria. Crit Rev Food Sci Nutr 2019;59:S130-52.
55. den Besten G, van Eunen K, Groen AK, et al. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013;54:2325-40.
56. Sanderson IR. Short chain fatty acid regulation of signaling genes expressed by the intestinal epithelium. J Nutr 2004;134:2450S-4S.
57. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 2001;81:1031-64.
58. Bartholome AL, Albin DM, Baker DH, et al. Supplementation of total parenteral nutrition with butyrate acutely increases structural aspects of intestinal adaptation after an 80% jejunooileal resection in neonatal piglets. JPEN J Parenter Enteral Nutr 2004;28:210-22; discussion 222-3.
59. Russo E, Giudici F, Fiorindi C, et al. Immunomodulating activity and therapeutic effects of short chain fatty acids and tryptophan post-biotics in inflammatory bowel disease. Front Immunol 2019;10:2754.
60. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol 2019;10:277.
61. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol
2788

Fan and Lee. Enteral feeding and the microbiome in critically ill children

2017;19:29-41.

62. Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiol Lett 2009;294:1-8.

63. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 2008;105:16731-6.

64. Lopez-Siles M, Khan TM, Duncan SH, et al. Cultured representatives of two major phylogroups of human colonic Faecalibacterium prausnitzii can utilize pectin, uronic acids, and host-derived substrates for growth. Appl Environ Microbiol 2012;78:420-8.

65. Rivière A, Selak M, Lantin D, et al. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. Front Microbiol 2016;7:979.

66. Derrien M, Vaughan EE, Plugge CM, et al. Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. Int J Syst Evol Microbiol 2004;54:1469-76.

67. Reichardt N, Duncan SH, Young P, et al. Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. ISME J 2014;8:1323-35.

68. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human health. Nutr Cancer 2016;68:189-200.

69. Giovannini M, Verduci E, Gregori D, et al. Prebiotic effect of an infant formula supplemented with galacto-oligosaccharides: randomized multicenter trial. J Am Coll Nutr 2014;33:85-93.

70. Sierra C, Bernal MJ, Blasco J, et al. Prebiotic effect during the first year of life in healthy infants fed formula containing GOS as the only prebiotic: a multicentre, randomised, double-blind and placebo-controlled trial. Eur J Nutr 2015;54:89-99.

71. Dai ZL, Wu G, Zhu WY. Amino acid metabolism in intestinal bacteria: links between gut ecology and host health. Front Biosci (Landmark Ed) 2011;16:1768-86.

72. Yao CK, Muir JG, Gibson PR. Review article: insights into colonic protein fermentation, its modulation and potential health implications. Aliment Pharmacol Ther 2016;43:181-96.

73. Wong JM, de Souza R, Kendall CW, et al. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 2006;40:235-43.

74. Bingham SA, Pignatelli B, Pollock JR, et al. Does increased endogenous formation of N-nitroso compounds in the human colon explain the association between red meat and colon cancer? Carcinogenesis 1996;17:515-23.

75. Christl SU, Eisner HD, Dusel G, et al. Antagonistic effects of sulfide and butyrate on proliferation of colonic mucosa: a potential role for these agents in the pathogenesis of ulcerative colitis. Dig Dis Sci 1996;41:2477-81.

76. Attene-Ramos MS, Nava GM, MueLLer MG, et al. DNA damage and toxicogenic analyses of hydrogen sulfide in human intestinal epithelial Fh3 74 Int cells. Environ Mol Mutagen 2010;51:304-14.

77. Hughes R, Kurth MJ, McGilligan V, et al. Effect of colonic bacterial metabolites on Caco-2 cell paracellular permeability in vitro. Nutr Cancer 2008;60:259-66.

78. Rao JN, Xiao L, Wang JY. Polymamines in gut epithelial renewal and barrier function. Physiology (Bethesda) 2020;35:328-37.

79. Timmons J, Chang ET, Wang JY, et al. Polymamines and Gut Mucosal Homeostasis. J Gastrointest Dig Syst 2012;2:001.

80. Lam YY, Ha CW, Hoffmann JM, et al. Effects of dietary fat profile on gut permeability and microbiota and their relationships with metabolic changes in mice. Obesity (Silver Spring) 2015;23:1429-39.

81. Devkota S, Wang Y, Musch MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Ili0-/- mice. Nature 2012;487:104-8.

82. Watson H, Mitra S, Croden FC, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. Gut 2018;67:1974-83.

83. Pu S, Khazanehei H, Jones PJ, et al. Interactions between obesity status and dietary intake of monounsaturated and polyunsaturated oils on human gut microbiome profiles in the Canola Oil Multicenter Intervention Trial (COMIT). Front Microbiol 2016;7:1612.

84. Noriega BS, Sanchez-Gonzalez MA, Salyakina D, et al. Understanding the impact of omega-3 rich diet on the gut microbiota. Case Rep Med 2016:3089303.

85. Chen H, Wang S, Zhao Y, et al. Correlation analysis of omega-3 fatty acids and mortality of sepsis and sepsis-induced ARDS in adults: data from previous randomized controlled trials. Nutr J 2018;17:57.

86. Al-Biltagi MA, Abo-Elezz AA, Abd-Elhafez MA, et al. Beneficial effects of omega-3 supplement to the enteral feeding in children with mild to moderate sepsis. J Intensive Care Med 2017;32:212-7.

87. Elke G, Hartl WH, Kreymann KG, et al. Clinical nutrition in critical care medicine - guideline of the German Society
for Nutritional Medicine (DGEM). Clin Nutr ESPEN 2019;33:220-75.

88. Kristine Koekkoek W, Panteleon V, van Zanten AR. Current evidence on omega-3 fatty acids in enteral nutrition in the critically ill: a systematic review and meta-analysis. Nutrition 2019;59:56-68.

89. Lu C, Sharma S, McIntyre L, et al. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. Ann Intensive Care 2017;7:58.

90. Kissoon N, Reinhart K, Daniels R, et al. Sepsis in children: global implications of the world health assembly resolution on sepsis. Pediatr Crit Care Med 2017;18:e625-7.

91. Tan B, Wong JJ, Sultana R, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. JAMA Pediatr 2019;173:352-62.

92. Wan YD, Zhu RX, Wu ZQ, et al. Gut microbiota disruption in septic shock patients: a pilot study. Med Sci Monit 2018;24:8639-46.

93. Yu P, Martin CM. Increased gut permeability and bacterial translocation in Pseudomonas pneumonia-induced sepsis. Crit Care Med 2000;28:2573-7.

94. Jiang LY, Zhang M, Zhou TE, et al. Changes of the immunological barrier of intestinal mucosa in rats with sepsis. World J Emerg Med 2010;1:138-43.

95. Li Q, Zhang Q, Wang C, et al. Disruption of tight junctions during polymicrobial sepsis in vivo. J Pathol 2009;218:210-21.

96. Zhou H, Liang H, Li ZF, et al. Vagus nerve stimulation attenuates intestinal epithelial tight junctions disruption in endotoxemic mice through alpha7 nicotinic acetylcholine receptors. Shock 2013;40:144-51.

97. Haussner F, Chakraborty S, Halbgebauer R, et al. Challenge to the intestinal mucosa during sepsis. Front Immunol 2019;10:891.

98. Schroeder BO. Fight them or feed them: how the intestinal mucus layer manages the gut microbiota. Gastroenterol Rep (Oxf) 2019;7:3-12.

99. Shimizu K, Ogura H, Asahara T, et al. Gastrointestinal dysmotility is associated with altered gut flora and septic mortality in patients with severe systemic inflammatory response syndrome: a preliminary study. Neurogastroenterol Motil 2011;23:330-5, e157.

100. MacFie J, O’Boyle C, Mitchell CJ, et al. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut 1999;45:223-8.

101. Yu LC, Shih YA, Wu LL, et al. Enteric dysbiosis promotes antibiotic-resistant bacterial infection: systemic dissemination of resistant and commensal bacteria through epithelial transcytosis. Am J Physiol Gastrointest Liver Physiol 2014;307:G824-35.

102. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. Infect Immun 1979;23:403-11.

103. O’Boyle CJ, MacFie J, Mitchell CJ, et al. Microbiology of bacterial translocation in humans. Gut 1998;42:29-35.

104. Woodcock NP, Sudheer V, El-Barghouti N, et al. Bacterial translocation in patients undergoing abdominal aortic aneurysm repair. Br J Surg 2000;87:439-42.

105. Deitch EA. Bacterial translocation of the gut flora. J Trauma 1990;30:S184-9.

106. Deitch EA. Gut-origin sepsis: evolution of a concept. Surgeon 2012;10:350-6.

107. Alscher KT, Phang PT, McDonald TE, et al. Enteral feeding decreases gut apoptosis, permeability, and lung inflammation during murine endotoxemia. Am J Physiol Gastrointest Liver Physiol 2001;281:G569-76.

108. Angurana SK, Bansal A, Singh S, et al. Evaluation of effect of probiotics on cytokine levels in critically ill children with severe sepsis: a double-blind, placebo-controlled trial. Crit Care Med 2018;46:1656-64.

109. Banupriya B, Biswal N, Srinivasaraghavan R, et al. Probiotic prophylaxis to prevent ventilator associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial. Intensive Care Med 2015;41:677-85.

110. Domeneghini C, Di Giancamillo A, Arrighi S, et al. Gut-trophic feed additives and their effects upon the gut structure and intestinal metabolism. State of the art in the pig, and perspectives towards humans. Histol Histopathol 2006;21:273-83.

111. George Kerry R, Patra JK, Gouda S, et al. Benefaction of probiotics for human health: a review. J Food Drug Anal 2018;26:927-39.

112. Petit V, Greco V, Laterza L, et al. Impact of the trophic effects of the secretome from a multistrain probiotic preparation on the intestinal epithelia. Inflamm Bowel Dis 2021;27:902-913.

113. Mangell P, Nejdfors P, Wang M, et al. Lactobacillus plantarum 299v inhibits Escherichia coli-induced intestinal permeability. Dig Dis Sci 2002;47:511-6.

114. Baum B, Liebler-Tenorio EM, Ems ML, et al. Saccharomyces boulardii and bacillus cereus var. Toyoi influence the morphology and the mucins of the intestine.
115. Hojsak I, Fabiano V, Pop TL, et al. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. Acta Paediatr 2018;107:927-37.

116. Yelin I, Flett KB, Merakou C, et al. Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. Nat Med 2019;25:1728-32.

117. Vahabnezhad E, Mochon AB, Wozniak LJ, et al. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. J Clin Gastroenterol 2013;47:437-9.

118. Schouten LR, Veltkamp F, Bos AP, et al. Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis. Crit Care Med 2016;44:819-29.

119. Wong JJ, Jit M, Sultana R, et al. Mortality in pediatric acute respiratory distress syndrome: a systematic review and meta-analysis. J Intensive Care Med 2019;34:563-71.

120. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the “motor” of critical illness. Shock 2007;28:384-93.

121. Acheson DW, Luccioli S. Microbial-gut interactions in health and disease. Mucosal immune responses. Best Pract Res Clin Gastroenterol 2004;18:387-404.

122. Hershberg RM, Mayer LF. Antigen processing and presentation by intestinal epithelial cells - polarity and complexity. Immunol Today 2000;21:123-8.

123. Deitch EA. Gut lymph and lymphatics: a source of factors leading to organ injury and dysfunction. Ann N Y Acad Sci 2010;1207 Suppl 1:E103-11.

124. Senthil M, Brown M, Xu DZ, et al. Gut-lymph hypothesis of systemic inflammatory response syndrome/multiple-organ dysfunction syndrome: validating studies in a porcine model. J Trauma 2006;60:958-65; discussion 965-7.

125. Dickson RP, Singer BH, Newstead MW, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol 2016;1:16113.

126. de Souza Menezes F, Leite HP, Koch Nogueira PC. Malnutrition as an independent predictor of clinical outcome in critically ill children. Nutrition 2012;28:267-70.

127. Yadav B, Bansal A, Jayashree M. Clinical profile and predictors of outcome of pediatric acute respiratory distress syndrome in a PICU: a prospective observational study. Pediatr Crit Care Med 2019;20:e263-73.

128. Wong JJ, Han WM, Sultana R, et al. Nutrition delivery affects outcomes in pediatric acute respiratory distress syndrome. JPEN J Parenter Enteral Nutr 2017;41:1007-13.

129. Ewaschuk JB, Murdoch GK, Johnson IR, et al. Glutamine supplementation improves intestinal barrier function in a weaned piglet model of Escherichia coli infection. Br J Nutr 2011;106:870-7.

130. Ruth MR, Field CJ. The immune modifying effects of amino acids on gut-associated lymphoid tissue. J Anim Sci Biotechnol 2013;4:27.

131. Yeh DD, Heyland D. Immune-enhancing diets: what is the final answer? Current Trauma Reports 2016;2:79-87.

132. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med 2013;368:1489-97. Erratum in: N Engl J Med 2013;368:1853.

133. Pontes-Arruda A, Demichele S, Seth A, et al. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. JPEN J Parenter Enteral Nutr 2008;32:596-605.

134. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA 2011;306:1574-81.

135. Jakobs BR, Nadkarni V, Goldstein B, et al. Nutritional immunomodulation in critically ill children with acute lung injury: feasibility and impact on circulating biomarkers. Pediatr Crit Care Med 2013;14:e45-56.

136. Weng H, Li JG, Mao Z, et al. Probiotics for preventing ventilator-associated pneumonia in mechanically ventilated patients: a meta-analysis with trial sequential analysis. Front Pharmacol 2017;8:717.

137. Yang Y, Gao L, Zhang YH, et al. Efficacy of probiotic therapy in full-term infants with critical illness. Asia Pac J Clin Nutr 2014;23:575-80.

138. Johnston BC, Supina AL, Vohra S. Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials. CMAJ 2006;175:377-83.

139. Szajewska H, Kolodziej M. Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. Aliment Pharmacol Ther 2015;42:1149-57.

140. Chang YS, Trivedi MK, Jha A, et al. Synbiotics for prevention and treatment of atopic dermatitis: a meta-analysis of randomized clinical trials. JAMA Pediatr

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### Table S1: Specific key words used for collecting research articles

| Section                                               | Keywords                                                                                                                                 |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Introduction                                          | Dybiosis, alpha diversity, beta diversity                                                                                               |
| Gut microbiome alterations in PICU                    | Dybiosis, starvation, opioids, proton-pump inhibitors, antibiotics, pediatrics                                                           |
| Fasting, enteral feeding and gut microbiome           | Feeding, nutrition, starvation, parenteral nutrition, pediatrics                                                                         |
| Effect of carbohydrates                               | Carbohydrates, fructose, lactose, fructo-oligosaccharides, galacto-oligosaccharide, short chain fatty acids, butyrate, inflammatory bowel disease, pediatrics |
| Effects of protein                                   | Protein, amino acid, digestion                                                                                                           |
| Effects of lipids                                     | Lipid, digestion, pediatrics, omega-3                                                                                                |
| Changes in microbiome in sepsis                       | Sepsis, septic shock, intestinal mucosa, tight protein junction, mucosa barrier, gut-driven sepsis                                         |
| Effect of enteral feeding on microbiome in sepsis     | Feeding, enteral nutrition, sepsis, probiotics, trophic, intestinal mucosa, pediatrics                                                     |
| Pediatric acute respiratory distress syndrome (PARDS), enteral feeding and gut microbiome | Acute respiratory distress syndrome, pediatric acute respiratory distress syndrome, enteral nutrition                                       |
| Intestinal crosstalk and gut-lymph theory            | Acute respiratory distress syndrome, pediatric acute respiratory distress syndrome, gut-lymph theory                                        |
| Effect of enteral feeding on PARDS                    | Acute respiratory distress syndrome, pediatric acute respiratory distress syndrome, enteral nutrition, immune, inflammation, omega-3 PUFA, glutamine, and arginine |
| Future directions and avenues for research            | Synbiotic, fecal microbiota transplant, eubiosis, pediatrics                                                                         |

The above key words were searched as MeSH terms in combination with AND Gut microbiome AND/OR critical care.