



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

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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 phylogenetic 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

Table 1 Impact of common critical care practices on gut microbiome and potential effect on host

Interventions	Changes to gut environment and microbiome	Potential clinical effects
Opioids	<ul style="list-style-type: none"> • Decreased IL-6 secretion by the epithelial cells (13) • Reduced phagocyte activation and migration towards mucosal surfaces (13) • Increased bacterial translocation to mesenteric lymph nodes complex (14,16) 	<ul style="list-style-type: none"> • Reduced gut propulsion (14) • Increases susceptibility to <i>Streptococcus pneumoniae</i> infection (15) • Increased risk of <i>Escherichia coli</i>, <i>Proteus mirabilis</i>, <i>Clostridium difficile</i> infection (17,18) • Increases <i>Pseudomonas aeruginosa</i> virulence expression (19)
PPIs	<ul style="list-style-type: none"> • Increase <i>Enterococcus</i>, <i>Lactobacillus</i>, <i>Streptococcus</i>, <i>Staphylococcus</i>, genus (20-22) • Decrease <i>Faecalibacterium</i> genus (21) 	<ul style="list-style-type: none"> • Increase enteric infections by <i>Clostridium difficile</i>, <i>Salmonella</i>, and <i>Campylobacter jejuni</i> (20,23)
Broad-spectrum antibiotics	<ul style="list-style-type: none"> • Reduce in gut microbiome diversity (24-26) • Increase antibiotic resistance genes-carrying plasmids (24) • Recovery of microbial composition occurs only months after cessation of antibiotics (26,28,29) 	<ul style="list-style-type: none"> • Increase in <i>Clostridium difficile</i> infection (26) • Increase susceptibility to infection by multi-drug resistant organism (27)
Fasting	<ul style="list-style-type: none"> • Dominance of pathogens such as <i>Klebsiella pneumoniae</i>, <i>Providencia alcalifaciens</i> and <i>Clostridium perfringens</i> (30,31) • Increase in <i>Firmicutes</i> • Decrease in <i>Bacteroidetes</i> genus and <i>Roseburia</i> species (32) 	<ul style="list-style-type: none"> • Not reported

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.

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

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 dysbiosis 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 an 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- α) compared to placebo group ($P \leq 0.01$) (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* stains 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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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.