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Research Article

A Prospective Pilot Study to Monitor the Impact of a High Fiber 'Enteral Formula with Food-Derived Ingredients' on Fecal Short-Chain Fatty Acid Concentrations in Children Admitted to Intensive Care with Sepsis

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Abstract

Background: Dietary fiber undergoes fermentation by the microbiota to produce intestinal short-chain fatty acids (SCFA). The synergistic relationship between the host and SCFA inhibits the colonization of pathogenic microorganisms. Sepsis is the leading cause of mortality in hospitalized children. Paradoxically, antibiotic management of sepsis can increase infections by causing dysbiosis. This study assessed the impact of an 'enteral formula with food-derived ingredients' on feed tolerance and fecal SCFA concentrations in children admitted to intensive care with sepsis.

Methods: Children were switched to Compleat®Paediatric, which contains 1g fiber/100 ml (Nestle Health Science). Stool consistency and frequency were monitored. Stool samples were collected at baseline before the formula switch and weekly thereafter to measure SCFA concentrations (acetate, butyrate, and propionate). A Wilcoxon Signed-Rank test was used to measure the change in SCFA concentrations.

Results: Twenty children switched to a high-fiber enteral formula containing food-derived ingredients. All children were prescribed at least one antibiotic, with 25% of children treated with more than two antibiotics. After the formula switch stool frequency reduced from 2.6 (± 1.08SD) at baseline to 1.2 (± 0.45SD) ($p < 0.004$). Similarly, stool consistency significantly improved from 6.6 (± 0.4SD) at baseline compared to 3.6 (± 0.4SD) ($p < 0.001$). Fecal propionate and butyrate concentrations were maintained during the children's time in intensive care.

Conclusion: Children admitted to intensive care with sepsis may benefit from a high fiber 'enteral formula with food-derived ingredients', which may mitigate the gastrointestinal symptoms associated with antibiotic dysbiosis by preserving intestinal SCFA concentrations.

Keywords: *Pediatric Intensive Care Unit; Sepsis; Enteral Formula with Food-Derived Ingredients; Enteral Feed Intolerance; Short-Chain Fatty Acids*

Highlights

- This is the first study to report on the concentrations of fecal short-chain fatty acids in critically ill patients with sepsis who are receiving Compleat®Paediatric - a high-fiber enteral formula with food-derived ingredients.
- Our study reports that the high-fiber formula was well tolerated, improving stool frequency and consistency within one week of switching formulas.
- Our pilot study found that children who had switched to the high-fiber formula maintained fecal short-chain fatty acids concentrations during their admission to PICU.
- Children may benefit from a high-fiber 'enteral formula with food-derived ingredients' to minimize symptoms associated with antibiotic-related feed intolerance.

Background

The human intestinal microbiota consists of several hundred bacterial species [1]. The microbial community of the gut conveys significant benefits to human physiology at an intestinal epithelial and systematic inflammatory level [2-4]. The diversity and relative abundance of microbial metabolites are heavily dependent on specific dietary components [5]. Non-digestible dietary fiber such as oligosaccharides and inulin demonstrate resistance to digestion in the human small intestine [6]. In the large bowel dietary fiber undergoes fermentation by colonic microbiota to produce short-chain fatty acids (SCFA); acetate, butyrate, and propionate, which act as the primary carbon energy source for colonocytes [5].

The synergistic relationship between the host and intestinal SCFA concentrations includes the concomitant reduction of the luminal pH, which by itself inhibits pathogenic microorganisms and increases the absorption of some nutrients [7]. Furthermore, intestinal SCFA controls the production of T-helper cells, antibodies, and cytokines and is also involved in maintaining homeostasis of the mucosal system [8,9]. The effects of SCFA on lymphocytes appear to work together with those on epithelial cells and myeloid cells to strengthen intestinal barrier immunity, regulate microbes, and prevent harmful inflammatory responses. A significant portion of intestinal SCFAs are transported out of the gut and affect immune cells beyond the cells in the gut [10].

The composition and diversity of the intestinal microbiome in critical illness are impacted by poor intestinal perfusion, hypoxia, lack of enteral feeds, and antibiotic therapy. This creates opportunities for the proliferation of potentially pathogenic species associated with adverse outcomes, including secondary infection and mortality [11]. The gut microflora in critically ill patients can consist of ultra-low-diversity communities of multidrug-resistant pathogenic microbes [12].

Sepsis is the leading cause of mortality in hospitalized children. Antibiotics are one of the most prescribed drugs in children and disrupt the normal maturation of the microbiome altering basic physiological equilibria and causing dysbiosis [13]. Paradoxically, antibiotic management of sepsis can increase susceptibility to opportunistic and nosocomial infections by affecting the resistance of the intestinal microbiota to colonization [14]. An additional consequence of antibiotic-associated dysbiosis is diarrhea. Clinicians manage these symptoms by imposing gut rest and implementing a hydrolyzed protein formula to aid absorption [15]. Dietary and microbiome-based therapies are being explored for the potential to support the recovery of healthy gut commensal populations during and after critical illness. In the pediatric population, interest is growing in the use of a blended diet for the management of feed intolerances [16].

The industry has responded to this shift in feeding practices and developed a high-fiber enteral formula with food-derived ingredients, which has been shown to improve enteral feed tolerance [17]. It is unclear whether the reported improvement in feed tolerance seen in children receiving enteral formula with food-derived ingredients is associated with the rehydrated food within the formula or due to its

impact on intestinal microflora. Therefore, this prospective observational pilot study aimed to monitor the impact of a high fiber 'enteral formula with food-derived ingredients' on feed tolerance and fecal SCFA concentrations in children admitted to intensive care with sepsis.

Materials and Methods

Study population

Children were recruited from our tertiary pediatric intensive care unit (PICU), which cares for children with serious medical and surgical conditions. The inclusion criteria were critically ill children who were admitted to the PICU, aged between 1 and 16 years, required exclusive enteral nutrition, were on antibiotics for sepsis management, and had developed diarrhea (diarrhea was defined as three or more loose stools a day lasting longer than 48hrs) [18]. We excluded children if they were under the age of 1 year old, started antibiotics before admission to our PICU, were receiving total or partial parenteral nutrition, had a dairy intolerance, or were vegetarian (formula contains cow's milk protein and rehydrated chicken).

Children who met the inclusion criteria switched from their standard enteral formula to Compleat®Paediatric Nestlé Health Science, a nutritionally complete enteral tube feed 1.2 kcal/ml, containing 14% food-derived ingredients in the form of rehydrated chicken, peas, and green beans, and orange juice, providing 1g fiber/100 ml.

Fecal short-chain fatty acid concentrations

Fecal samples were collected at baseline (within 48 hours of PICU admission), then weekly thereafter up until discharge from PICU. Of note, fecal SCFA reflects both colonic SCFA production and absorption rates. Samples were collected from nappies, placed in sterile plastic containers, and stored at -80°C until aliquoted. We first calibrated our fecal SCFA quantification using a pool of five fecal samples. The frozen stool was aliquoted to an average of 100 mg and transferred into a separated plastic vial and weighed (precision scale). To reduce the degradation of the SCFA, the stool samples were kept on dry ice whilst homogenization [in 1 ml buffer (0.1M Tris, 0.15M NaCl, 1M urea, 10 mM $CaCl_2$, 0.1M citric acid monohydrate, 5 g/L bovine serum albumin and 0.25 mM thimerosal, pH 8.0) in fresh glass vial] was performed [18].

The homogenized samples were centrifuged at 15000 rpm for 5 minutes at 4°C. 20 µL of supernatant was transferred in a sterile glass vial and mixed with 15 µL internal standard (400 µM stock of labeled 13C2-acetate, d5-propionate, and 13C4-butyrate 100 µL H_2O, 500 µL of 0.1M tetrabutylammonium and 500 µL of 2% pentafluorobenzyl bromide in dichloromethane. Each sample was sonicated for 60 minutes and then extracted into 2 mL hexane and centrifuged at 1500 rpm for 5 minutes. The extract was eluted into a new glass vial and submitted to mass spectrometry. Briefly, all samples undergo vaporization in the hot inlet (280°C) before the gaseous sample is carried by helium and column separation [19].

Tolerability assessment

Stool consistency is a central component in the description of normal or altered bowel habits. Stool form can be considered as a proxy measure for stool consistency and refers to the shape and apparent texture of the stool, which can be assessed visually. Stool form scales are a standardized and inexpensive method of classifying stool form into a finite number of categories that can be used by healthcare professionals and researchers.

The Bristol stool form scale is an ordinal scale of stool types ranging from the hardest (Type 1) to the softest (Type 7) [20]. Types 1 and 2 are abnormally hard stools (and in conjunction with other symptoms indicative of constipation) while types 6 and 7 are considered abnormally loose/liquid stools (and in conjunction with other symptoms indicative of diarrhea). Type 3, 4, and 5 are therefore generally considered to be the most 'normal' stool forms [21,22].

Tolerance and details of stooling patterns will be recorded each day at a ward level. Descriptions of feeding intolerance included: stool consistency and frequency (number of stools in 24 hours) constipation was defined as Rome IV Criteria, less than three defecations a week, and painful and hard stools [23].

Other clinical data collection

Children's clinical information was collected from the hospital's electronic records (EPIC, Madison, WI, USA), including demographics (age and gender), anthropometric measurements, feeding information (ml/day), and admission diagnosis. Enteral feeding was delivered as a continuous infusion as per our PICU feeding protocol. The nutrition status (weight-for-age and height-for-age) was assessed using z-scores [24]. Moderate undernutrition was identified if z-scores were between -2 and -3 standard deviation (SD) and severe undernutrition was identified if the z-scores were below -3 (SD) [25]. Conversely, moderate overnutrition was defined if z-scores were between +2 and +3 SD [25].

Serial C-Reactive Protein (CRP) levels, at least two CRP levels, obtained 24 hours apart, with levels below or equal to 10 mg/L, are needed to identify infants unlikely to be infected [26]. CRP was measured daily as part of the patient's routine assessment to classify the degree of sepsis. CRP data were collected from the hospital's electronic system. The CRP reading that was recorded closest to stool sample collection was used for data analysis. Children's diagnosis that required intensive care admission was recorded and then categorized into single organ category. Days free of intensive care and days free of mechanical ventilation at 30 days were used as a measure of clinical outcome.

Statistical analysis

Normally distributed continuous variables are expressed as means ± SD, while medians and interquartile ranges (IQR) are used to describe non-normal distributions. We defined the intensive care-free days as 30 minus the number of days in the PICU (range, 0 - 30 days). For patients who survived and were in PICU for less than 30 days, the intensive care-free day's outcome measure was obtained by subtracting the length of the PICU stay from 30. Ventilation-free days are defined as 30 minus the number of days on conventional ventilation (excluding non-invasive ventilation).

Descriptive statistics of between-group differences in subject characteristics were tested for significance. Individual SCFA concentrations of acetate, propionate, and butyrate (μmol per gram dry feces), distribution violated the assumption of normality, therefore the difference between timepoints was analyzed using a Wilcoxon Signed-Rank tests, presented as Z statistics. Statistical tests were conducted in a two-sided manner and the significance level was set at 5% ($p < 0.05$). The Statistical analysis was performed using Package for the Social Sciences Version 21 (SPSS Statistics 22, IBM Corp., Armonk, NY).

Results

This study recruited 20 critically ill children, the mean age was 10.8 years (± 5.6 years SD), of which 30%, 6 of the 20 children were female. The most common organ to fail due to sepsis was the respiratory tract (50%). The mean duration of mechanical ventilation was 9 days (± 4 SD). The median 30-day free of intensive care and 30-day free from ventilation were 8 days (IQR: 1, 22) and 10 days (IQR: 10, 25), respectively (Table 1). All children recruited to the study survived PICU discharge. The general characteristics of the population and nutritional information are described in table 1. Before the formula switch, 12 of the 20 (60%) children were receiving a whole protein polymeric formula and 6 of the 20 (40%) children were either receiving a hydrolyzed or amino acid formula. The mean daily feed volume during intensive care admission was 950 ml (± 230 SD), providing a mean fiber dose of 9.5 g/day (± 3 SD).

On admission, all children have been prescribed antibiotics, of which, 5 of the 20 (25%) children were treated with more than two classes of antibiotics, aminoglycoside being the most frequently prescribed. The type of antibiotic class administered at the time of the

Gender, n, (%)	
Male	14 (70)
Female	6 (30)
Age, decimal years (SD)	10.8 (5.6)
Primary Organ Failure, n (%)	
Respiratory Tract	10 (50)
Cardiovascular	4 (20)
Neurological/Traumatic Head Injury	3 (15)
Gastrointestinal Tract	3 (15)
Pre-trial enteral formula, n (%)	
Whole protein - polymeric	12 (60)
Partially hydrolysed - peptide	7 (35)
Amino acid	1 (5)
Average time on formula before change to high fibre formula, days (± SD)	3 (1)
Mean duration on ventilation, days (± SD)	9 (4)
Mean feed volume per day, ml/day (± SD)	950 (230)
mean fiber dose, grams/day (± SD)	9.5 (3)
30 Days Free intensive care, median, (Inter Quartile Range)	8 (1, 22)
30 Days free conventional ventilation, median (Inter Quartile Range)	10 (10, 25)

Table 1: *Demographic characteristics and clinical details of study participants.*

first fecal sampling is indicated by the number of children receiving each antibiotic class (Table 2). The mean CRP on admission to PICU was 67 mg/l (± 10 SD), which remained raised after one-week 58 mg/l (± 10 SD) (Table 3).

Antibiotic Administered	n (%)
Aminoglycoside	10 (34)
Meropenem (Carbapenems)	8 (27)
Penicillin	5 (17)
Glycopeptides Fluoroquinolones	4 (13)
Clindamycin	2 (9)

Table 2: *Antibiotic class prescribed on admission to intensive care.*

Inflammatory marker	Admission	Week 1	Week
C-Reaction protein, mean (± SD)	67.17 (10)	58.75 (10)	15.00 (3)
Mean difference (± SD); p-value		13 (10); 0.246	35 (21); 0.001

Table 3: *Children's C-reactive protein concentration during stay in intensive care.*

Both stool frequency and consistency improved within one week after the formula was switched to the high-fiber enteral formula with food-derived ingredients. Stool frequency reduced from 2.6 (± 1.1 SD) to 1.2 (± 0.45 SD), p < 0.004 (95% confidence interval: 0.65; 2), and stool consistency (Bristol Stool Chart) improved from 6.6 (± 0.4 SD) to 3.6 (± 0.4 SD), p < 0.001 (95% confidence interval: 2.72, 3.72) (Table 4). At baseline the mean weight-Z-score and height-Z-score were -1.79 (± 1.7 SD); -0.9 (± 0.9 SD), respectively, suggesting children admitted to our intensive care unit were in an undernourished state. After one week in PICU, the weight-z-scores continued to decrease to -2.14 (± 1.8 SD); p-value 0.05 (95% confidence interval: -3.69, -0.59) but normalized to baseline after two weeks in PICU (Table 5).

	Baseline	One week	p-value, (95% Confidence Interval)
Stool Frequency, mean (± SD)	2.6 (1.08)	1.2 (0.45)	p < 0.004, (0.65; 2)
Stool consistency, mean (± SD)	6.6 (0.4)	3.6 (0.4)	p < 0.001, (2.72; 3.72)

Table 4: *Stool consistency and frequency of study participants after one week receiving an enteral formula with food derived ingredients.*

	Baseline	One week on high fibre formula	p-value (95% Confidence Interval	Two weeks on high fibre formula	p-value (95% Confidence Interval
Weight, kg Mean (± SD)	31.3 (9)	27.3 (6)	0.01 (13, 42)	30.1 (7)	0.4 (32, -12)
Weight-Z-score Mean (± SD)	-1.8 (1.7)	-2.1 (1.8)	0.05 (-3.7, -0.6)	-1.87 (0.9)	0.1 (-2.77, 0.96)

Table 5: *Anthropometric measurements of study participants who commenced high fibre enteral formula with food derived ingredients whilst in intensive care.*

The SCFA concentrations of propionate and butyrate levels were maintained during the two weeks the children were in intensive care. However, due to a reduction in acetate concentration, the total SCFA concentrations lowered although this was not clinically significant. The total fecal SCFA concentration reduced from 2.9 µmol/g (± 2.0 SD) at baseline to 1.3 µmol/g (± 0.8SD) (Z-value-1.3018, p-value = 0.09) after two weeks in PICU (Table 6). In this small sample size, we were unable to find an association between SCFA concentration with 30 days free from intensive care or 30 days free from ventilation.

Short chain fatty acid	Baseline N = 20	Week 1 N = 20	Baseline and week 1 Z Value (p-value)	Week 2 N = 12	Baseline and week 2 Z Value (p-value)
Acetate, mean (± SD)	2.1 (2.0)	0.9 (0.7)	-1.0142 (0.3)	0.7 (0.5)	-1.7529 (0.2)
Propionate, mean (± SD)	0.5 (0.4)	0.8 (0.4)	-1.9548 (0.2)	0.5 (0.3)	-0.2962 (0.4)
Butyrate, mean (± SD)	0.3 (0.2)	0.3 (0.2)	-0.3381 (0.8)	0.2 (0.1)	-0.2011 (0.2)
Total	2.9 (2.0)	2.0 (1.0)	-0.4258 (0.7)	1.3 (0.8)	-1.3018 (0.09)

Table 6: *Comparative analysis of longitudinal faecal short chain fatty acids concentrations (µmol/ g) in study participants.a*

Discussion

Short-chain fatty acids are the end products of the fermentation of dietary fibers by the anaerobic intestinal microbiota, which have been shown to exert multiple beneficial effects on mammalian energy metabolism and immune function [27]. This is the first study to report on the concentrations of SCFA in critically ill patients with sepsis who are receiving Compleat®Paediatric - a high-fiber enteral formula with food-derived ingredients. Our study reports that the high-fiber formula was well tolerated, improving stool frequency and consistency within one week of switching formulas. Additionally, our pilot study found that children who had switched to the high-fiber formula maintained fecal butyrate and propionate concentrations during their admission to PICU.

The mechanisms as to why blended diets and enteral formulas with 'real food' are better tolerated than a standard enteral formula is unclear [28]. However, it stands to reason that 'food-derived ingredients' within the enteral formula aid normal gut functioning providing superior clinical performance to standard commercial availability enteral formula [29,30]. Similar improvements in enteral feed tolerance have been described by Samela., *et al*. (2017), who reported children with intestinal failure who were experiencing diarrhea and inconsistent stooling improved in 90% of the children who transitioned to a high-fiber enteral formula with food-derived ingredients [31].

Of note, the degree of sepsis as measured by the CRP concentration in children remained raised after one week, which has clinical relevance to the statistically significant improvements reported in stool frequency and consistency when compared during the same time, suggesting that feed tolerance may be related to formula change as opposed to an improvement in sepsis. Our findings support those of Kamerun., *et al*. (2015), who performed a meta-analysis to investigate the impact of added fiber on enteral nutrition on the incidence of diarrhea. The team reported, that overall, fiber reduces diarrhea in patients receiving enteral nutrition (OR = 0.47; 95%CI: 0.29 - 0.77; P = 0.02). However, unlike our study, subgroup analysis could not attribute the beneficial impact of fiber in critically ill patients (OR = 0.89; 95%CI: 0.41-1.92; P = 0.77). Conclusion fiber helps minimize diarrhea in patients receiving enteral nutrition, particularly in non-critically ill patients [32].

Our study found that children on a high-fiber enteral formula with food-derived ingredients maintained fecal butyrate and propionate concentrations during their time in intensive care. Our findings support Majid HA., *et al*. (2014), who delivered a randomized controlled trial and found that when fiber was added to enteral formulas and administered to critically ill patients SCFA levels were maintained [33]. Conversely, Hayakawa., *et al*. (2011) reported that critically ill patients who had all been in good health just before their admission demonstrated a significant decrease in SCFA concentration even 6 hours after admission, indicating that fecal SCFA concentrations change immediately after severe insults [34]. The dramatic decline in the concentrations of SCFA, especially butyrate, apparently resulted from the reduction of obligate anaerobes and *Lactobacillus* in critically ill patients just after the insults. Concluding, that such an effect may further impair the recovery of these patients [34].

The complications associated with a rapid deterioration in intestinal SCFA concentration are outlined in a prospective multicentre cohort study by Wijeyesekera., *et al*. (2019), who states that, the disruption to the functional activity of the intestinal microbiome may results in worsening organ failure in the critically ill child. The team identified reduced faecal excretion of SCFA (including butyrate, propionate, and acetate), demonstrating that these metabolites also distinguished between critical illness and health. Concluding, profiling of bacterial metabolites in faecal samples may support identification and treatment of intestinal dysbiosis in critical illness [35]. Furthermore, a study by Valdes-Duque., *et al*. (2020), performed a descriptive, multicentre, observational study to determine the concentration of faecal SCFA in critically ill patients with sepsis when compared with the control group (healthy non hospitalised adults). The results reported significantly lower concentrations of faecal SCFA in critically ill patients with sepsis than in control subjects. Concluding that due to SCFA's role in intestinal integrity, barrier function, and anti-inflammatory effect, maintaining the concentration of SCFAs may be important in the intensive care patient [36].

Our study found that a quarter of children were on at least two types of antibiotics within the first week of admission to the PICU. A prospective point prevalence study involving over a thousand intensive care units across the world found that on any given day 75% of patients admitted to PICU received antibiotics [37]. A study by Rooney., *et al*. (2020), reported that antibiotic exposure was associated with reduced microbiome diversity and richness, and with changes in bacterial abundance. Each additional day of antibiotics was associated with a lower richness of anaerobes and butyrate producers within one week after therapy [38].

Numerous questions remain to be answered, including to what extent microbial disturbance influence dietary needs, metabolic status, intestinal permeability, and immunity in critically ill patients. More detailed knowledge of the short- and long-term health consequences of these major shifts in intestinal bacterial communities is needed [39]. The discontinuation of inappropriate antibiotic therapy is an important target for stewardship intervention [38].

The main strength of this study is its ability to compare and combine comprehensive clinical characterization of feed tolerance with fecal SCFA in critically ill children. As a pilot investigation, this study has limitations, the most crucial being its small sample size with no comparative group. Additionally, stool collection was difficult to obtain when diarrhea was severe, which is a barrier associated with the clinical and pathological condition of these critically ill patients. However, a consideration for our future comparative study is the ability to assess the intestinal microbiome using urine metabolic profiling [35].

Conclusion

Children admitted to PICU may benefit from a high-fibre 'enteral formula with food-derived ingredients' to minimize symptoms associated with antibiotic related feed intolerance by improving stool frequency and consistency. Furthermore, the high fibre formula may protect and preserve the production of SCFA, thereby optimising enterocyte function maximising nutrient absorption minimising weight loss. A comparative validation study is required to substantiate our preliminary findings and confirm the potential impact of dietary fiber to support the recovery of a healthy gut commensal populations during and after critical illness.

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Nestle Health Science covered the costs for the mass spectrometry analysis of faecal short chain fatty acids, which were performed independently at the Institute of Child Health. This was a clinician led study where all results are owned by Great Ormond Street Hospital, University College London. The authors have no other conflicts of interest.

Declarations

Ethics approval and consent to participate: Ethical approval was sought through the Health Research Authority and Health and Care Research Wales: 279901-21/PR/0809 on the 1st of July 2021 and was conducted in accordance with the Declaration of Helsinki and STROBE statement.

Author Contributions

GOC conceived and designed the study. BG and GA collected clinical data at a ward level. YS, SE and MBE analyzed faecal samples and short chain fatty acids. GOC and SE performed the statistical analyses. GOC wrote the manuscript. All the authors have read and approved the final version of the manuscript.

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Volume 18 Issue 4 April 2023