Critical Care Explorations

OPEN

Impact of Fiber-Based Enteral Nutrition on the Gut Microbiome of ICU Patients Receiving Broad-Spectrum Antibiotics: A Randomized Pilot Trial

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Objectives: Dietary fiber increases the abundance of bacteria that metabolize fiber into short-chain fatty acids and confers resistance against gut colonization with multidrug-resistant bacteria. This pilot trial estimated the effect of fiber on gut short-chain fatty acid–producing bacteria in the ICU.

Design: Randomized, controlled, open label trial.

Setting: Medical ICU.

Patients: Twenty ICU adults receiving broad-spectrum IV antibiotics for sepsis.

Intervention: 1:1 randomization to enteral nutrition with mixed soy- and oat-derived fiber (14.3 g fiber/L) versus calorie- and micronutrient-identical enteral nutrition with 0 g/L fiber.

Measurements: Rectal swabs and whole stools were collected at baseline and on study Days 3, 7, 14, and 30. The primary outcome was within-individual change in the cumulative relative abundance of short-chain fatty acid–producing taxa from baseline to Day 3 based on 16S sequencing of rectal swabs. The secondary outcome was Day 3 cumulative short-chain fatty acid levels based on mass spectrometry of whole stools. Analyses were all intent to treat.

Main Results: By Day 3, the fiber group received a median of 32.1 g fiber cumulatively (interquartile range, 17.6–54.6) versus 0 g fiber (interquartile range, 0–4.0) in the no fiber group. The median within-individual change in short-chain fatty acid producer relative abundance from baseline to Day 3 was +61% (interquartile range −51 to +1,688) in the fiber group versus −46% (interquartile range, −78 to +13) in the no fiber group ($p = 0.28$). Whole stool short-chain fatty acid levels on Day 3 were a median of 707 µg short-chain fatty acids/g stool (interquartile range, 190–7,265) in the fiber group versus 118 µg short-chain fatty acids/g stool (interquartile range, 22–1,195) in the no fiber group ($p = 0.16$).

Conclusions: Enteral fiber was associated with nonsignificant trends toward increased relative abundance of short-chain fatty acid–producing bacteria and increased short-chain fatty acid levels among ICU patients receiving broad-spectrum IV antibiotics. Larger studies should be undertaken and our results can be used for effect size estimates.

Key Words: antimicrobial resistance; Clinical Trial; colonization; fiber; ICU; microbiome; nutrition; probiotics; prebiotics; sepsis; short-chain fatty acids

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Up to a third of ICU patients have gastrointestinal colonization with multidrug-resistant organisms (MDROs) such as vancomycin-resistant Enterococcus or MDR Gram-negative bacteria (1). Once colonized, ICU patients are at increased risk for subsequent infection with the same organisms (2–5). If gut colonization could be prevented, many high-mortality ICU infections would be avoided.

Loss of commensal gut bacteria facilitates colonization with MDROs. Nonpathogenic colonic anaerobes compete with

MDROs for shared resources and in some cases directly antagonize them by producing antibacterial small molecules (6). Among the commensal microbiota, the bacteria that ferment fiber into short-chain fatty acids (SCFAs) have drawn attention. In animal models, SCFA-producing bacteria confer protection against MDRO colonization (7, 8). Administration of fiber, either by increasing the abundance of SCFA producers or by raising SCFA levels themselves, confers similar protective effects (9–12). Fiber also may attenuate the damage caused by antibiotics on the commensal microbiota (13).

Fiber therefore appears to be a suitable therapy to test for the prevention of MDRO gut colonization in the ICU. Yet the effects of fiber on the gastrointestinal microbiota of ICU patients, and whether such effects can still be observed in the face of broad-spectrum antibiotics, is unknown. This pilot study was designed to test the hypothesis that fiber-based enteral nutrition increases the levels of SCFA-producing bacteria and SCFA levels in ICU patients receiving broad-spectrum IV antibiotics, with a goal of generating effect size estimates that could be used as the basis for future studies involving fiber.

MATERIALS AND METHODS

Population

Adults 18-years-old or more at the time of medical ICU admission were eligible for the study if they were expected to receive 3 or more days of enteral nutrition and had received a broad-spectrum IV antibiotic for sepsis within the previous 24 hours. Empiric antibiotics were accepted, and subjects were enrolled without a requirement for positive cultures. The following antibiotic classes were considered broad spectrum: β-lactam/β-lactamase inhibitor combinations, carbapenems, cephalosporins, fluoroquinolones, and clindamycin. Patients were excluded if they lacked capacity and had no health surrogate, had surgery involving the intestinal lumen within 30 days, or had limited treatment goals (i.e., do not resuscitate/do not intubate). This study was approved by the institutional review board of Columbia University Medical Center and registered on clinicaltrials.gov (NCT03509753).

Study Intervention

Patients were randomized in blocks of four with 1:1 assignment to one of two forms of complete enteral nutrition. They received either mixed soy- and oat-derived enteral nutrition with 14.3 g fiber/L (brand name: Promote 1.0 with Fiber; Abbott Nutrition, Chicago, IL) or calorie- and micronutrient-identical nutrition with 0 g/L fiber (brand name: Promote 1.0). Enteral nutrition higher in fiber is available but these formulas were selected because they are identical aside from fiber. The formula manufacturer, Abbott Nutrition, had no involvement in the study. After patients were randomized, ICU teams were instructed to continue the assigned formula as long as possible, but not to withhold ad lib nutrition once patients were ready to transition to oral diets. Enteral feeding rates were individualized based on estimated energy requirements using the Mifflin-St. Jeor equation and the Penn State University 2003b and 2010 equations, as recommended by the American Society of Parenteral and Enteral Nutrition (14).

Study Assessments and Sample Collection

Patients were assessed at baseline/Day 0 (i.e., before starting enteral nutrition) and subsequently on Days 3, 7, 14, and 30. Assessments continued until withdrawal from the study, hospital discharge, Day 30, or death (whichever came first). At each study assessment, a deep flocked rectal swab (Copan Diagnostics, Murrieta, CA) was collected with fecal soilage to verify sample adequacy. Interval spontaneous stools were also collected because rectal swabs do not provide enough material to directly test SCFA levels. Swabs and stools were flash frozen at −80°C immediately after collection.

Measurement of Fiber Received

To ascertain the amount of fiber actually received, the hourly enteral nutrition infusion rate was multiplied by the fiber content of the formula after accounting for interruptions in the feeding. For patients taking food by mouth, the type of meals, number of meals, and percentage of meal consumption was recorded by the patient's nurse. Nutritional values for each meal type were obtained from the Department of Nutrition, including fiber content, so that fiber intake could be calculated even among patients who had transitioned to an oral diet.

SCFA Producers

The primary outcome was the within-individual change from baseline (preintervention) to Day 3 in the relative abundance of SCFA-producing bacteria from rectal swabs. At the end of the study, rectal swabs were thawed and DNA was batch extracted for sequencing of the V4 region of the 16S rRNA gene (additional details in **Supplemental Methods**, Supplemental Digital Content 1, http://links.lww.com/CCX/A194) (15). Using this data, operational taxonomic units (OTUs) were classified as SCFA-producing or non-SCFA-producing based on the study by Vital et al. (16), which identified 17 taxa that account for 85% of colonic butyrate production. The relative abundance of these SCFA-producing OTUs was summed within each patient and calculated as [(Day 3 − baseline)/baseline]. Differences between study groups were assessed as an intent-to-treat Wilcoxon rank-sum test. Later study assessments were used to investigate durability of effect using similar methods. Sequencing FASTQ data files are publicly available within the Short Read Archive under BioProject PRJNA603980.

SCFA Levels

The secondary outcome was SCFA levels, measured from whole stool samples. Because baseline stools were unavailable, SCFA levels were determined from the stool sample closest to Day 3 rather than as change from baseline. At the end of the study, homogenized fecal samples were thawed and assessed using liquid chromatography–mass spectrometry (Supplemental Methods, Supplemental Digital Content 1, http://links.lww.com/CCX/A194). The concentrations of eight SCFAs including butyrate were summed within each sample to yield a single total SCFA concentration in μg/g of stool.

Clinical Effects of Fiber

The clinical effects of fiber administration were assessed focusing on caloric intake, stool frequency, and stool consistency.

Stool frequency was measured by asking ICU nurses at each study assessment to report the number of stools during the prior 24-hour period. Stool consistency was measured on a 5-point Likert scale analogous to the Bristol Stool Scale (0 = watery; 1 = loose/mucousy; 2 = loose with solid elements; 3 = formed, soft; 4 = formed, hard) (17). Nutritional intake was measured as the proportion of goal calories consumed.

Adverse Effects

Adverse effects were assessed in two ways. First, daily medical progress notes were reviewed to ascertain untoward health events, which were graded in terms of severity and relatedness to the study intervention. Second, because untoward health events are so common in the ICU and because it is challenging to determine relatedness (18), three types of adverse events were prespecified that could be ascertained objectively: death, culture-proven infection, and electrolyte abnormalities. Death was ascertained from the electronic medical record, which interfaces with the social security death index; culture-proven infection was operationalized as previously described (2); and electrolyte abnormalities were recorded as the maximum and minimum values for serum potassium, sodium, calcium, and phosphate.

Statistical Approach

All analyses were performed intent-to-treat, among the patients who provided baseline and Day 3 samples. Primary analyses were conducted using the baseline and Day 3 data, with the later study assessments used to assess for durability of effects. Categorical data were compared using Fisher exact text and continuous data were compared using rank-sum tests. A power calculation was performed before the study was begun as a two-sample test of means. It was estimated that a sample size of 10 patients per group would yield 80% power to detect a difference of 1.4 SD between groups. All testing was two-sided with alpha 0.05 considered statistically significant.

RESULTS

Population

From August 2018 to June 2019, 22 patients were enrolled all of whom had received either a third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination antibiotics within the preceding 24 hours (for antibiotics received and duration, see **Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCX/A195). One patient was randomized to fiber with surrogate consent but self-extubated the next day and declined to continue the study. Another was randomized to no fiber and died before Day 3. This left 20 patients who provided baseline and Day 3 samples and were analyzed. Clinical characteristics were similar for the fiber and no fiber groups (**Table 1**).

Intervention

Four patients crossed over, two in each group. Two patients assigned to fiber had delays initiating of enteral nutrition and did not receive any within 3 days of enrollment. Two patients assigned to no fiber transitioned to oral diets more rapidly than anticipated and received small amounts of fiber before Day 3. These four patients were analyzed based on their original study assignment (i.e., intent-to-treat). Overall, the fiber group received a median of 10.7 g/d (IQR, 5.9–18.2; maximum, 27.2) fiber by Day 3 versus 0 g/d (IQR, 0–1.3) in the no fiber group ($p < 0.01$). By the Day 7 study assessment, there was no difference in observed fiber intake between study groups (**Fig. 1**).

SCFA Producers

Within-individual change in SCFA-producing bacteria from baseline to Day 3 was compared between study groups. There was a median +61% (IQR −51 to +1,688) in the fiber group versus −46% (IQR, −78 to +13) in the no fiber group ($p = 0.28$) (**Fig. 2**). This nonsignificant trend toward increased SCFA producer relative abundance in the fiber group remained for subsequent study assessments. When SCFA-producing OTUs were considered as individual data points (i.e., with a given patient contributing a data point for each OTU), the difference in SCFA producers seen with fiber became statistically significant (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCX/A196; **legend**, Supplemental Digital Content 10, http://links.lww.com/CCX/A203). Among the SCFA producers, the greatest changes with fiber were seen within OTUs corresponding to Faecalibacterium and Odoribacter (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCX/A197; legend, Supplemental Digital Content 10, http://links.lww.com/CCX/A203; and **Supplemental Table 2**, Supplemental Digital Content 5, http://links.lww.com/CCX/A198).

SCFA Levels

The median Day 3 fecal SCFA concentration was 707 μg/g stool (IQR, 190–7,265) in the fiber group versus 118 μg/g stool (IQR, 22–1,195) in the no fiber group ($p = 0.16$) (**Fig. 3**). There were no significant differences between SCFA levels during subsequent assessments, although the trend remained higher in the fiber group (**Supplemental Fig. 3**, Supplemental Digital Content 6, http://links.lww.com/CCX/A199; legend, Supplemental Digital Content 10, http://links.lww.com/CCX/A203).

Taxonomic Differences

There were no differences in alpha diversity between study groups, with both groups declining in diversity as the study progressed (**Supplemental Fig. 4**, Supplemental Digital Content 7, http://links.lww.com/CCX/A200; legend, Supplemental Digital Content 10, http://links.lww.com/CCX/A203). When sequencing data were assessed in a hypothesis-free manner, there were Day 3 declines in the non-SCFA-producing OTUs classified as Finegoldia genus ($p = 0.01$) and Erysipelotrichaceae family ($p = 0.03$), comparing fiber versus no fiber.

Clinical Effects of Fiber

Through Day 3, a median of 58% (IQR, 24–84%) of goal calories were provided in the fiber group versus 33% (IQR, 2–52%) in the no fiber group ($p = 0.24$). There was a median of 1 stools/d (IQR, 0.33–3.33) in the fiber group versus 1.67 stools/d (IQR, 0.67–2.67) in the no fiber group ($p = 0.85$). Stool consistency was 1.7 (IQR,

TABLE 1. Characteristics of Patients, Stratified Based on Study Assignment

Characteristics	Fiber ($n = 10$)	No Fiber ($n = 10$)	p
Demographics			
Age (tertiles)			0.74
< 50 yr	4 (40%)	3 (30%)	
50–70 yr	4 (40%)	3 (30%)	
> 70 yr	2 (20%)	4 (40%)	
Gender, male	5 (50%)	7 (70%)	0.65
BMI, median (IQR)	26.5 (23.5–31.2)	24.2 (19.1–28.5)	0.41
SOFA variables			
Pao_2/Fio_2			1.0
≥ 300	4 (40%)	3 (30%)	
100–300	3 (30%)	4 (40%)	
< 100	3 (30%)	3 (30%)	
Platelets			0.20
≥ 150 × 10^3/μL	3 (30%)	7 (70%)	
100–150 × 10^3/μL	4 (40%)	1 (10%)	
< 100 × 10^3/μL	3 (30%)	2 (20%)	
Glasgow Coma Scale			0.40
15 points	3 (30%)	5 (50%)	
10–14 points	3 (30%)	4 (40%)	
< 10 points	4 (40%)	1 (10%)	
Bilirubin			0.37
< 1.2 mg/dL	6 (60%)	9 (90%)	
1.2–5.9 mg/dL	2 (20%)	1 (10%)	
≥ 6.0 mg/dL	2 (20%)	0 (0%)	
Mean arterial pressure (MAP) or vasoactive agents			0.85
No hypotension	3 (30%)	3 (30%)	
MAP < 70 mm Hg	4 (40%)	2 (20%)	
Vasoactive agents	3 (30%)	5 (50%)	
Creatinine or urine output (UOP)			0.40
< 1.2 mg/dL	3 (30%)	5 (50%)	
1.2–3.4 mg/dL	3 (30%)	4 (40%)	
≥ 3.5 mg/dL or UOP <500 mL/d	4 (40%)	1 (10%)	
Total SOFA score (tertiles)			0.52
≤ 6 points	2 (20%)	5 (50%)	
7–10 points	5 (50%)	3 (30%)	
≥ 11 points	3 (30%)	2 (20%)	
ICU interventions			
Broad-spectrum antibiotics	10 (100%)	10 (100%)	1.0
Mechanical ventilation	8 (80%)	10 (100%)	0.47
Proton pump inhibitors	2 (20%)	4 (40%)	0.63
Opioids	9 (90%)	9 (90%)	1.0

BMI = body mass index in kg/m^2; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

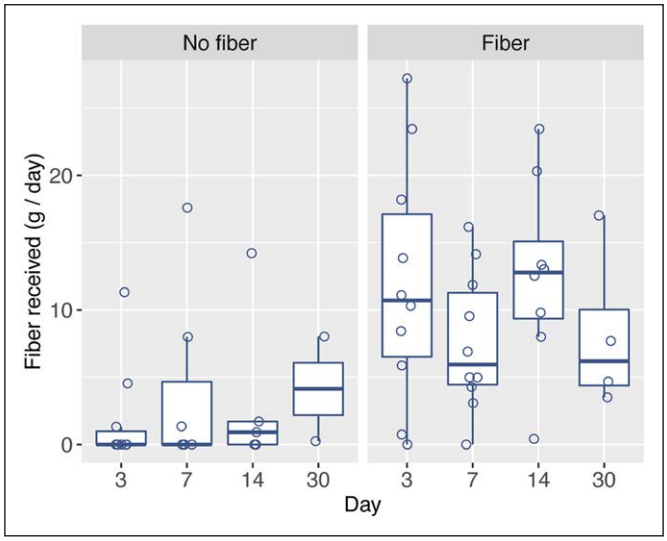

Figure 1. Actual amount of fiber received during the trial, stratified by study group. Box-and-whisker plots depict the mean amount of fiber received for each study period (between baseline and Day 3, between Day 3 and Day 7, etc.), stratified by study group. Patients were enrolled in the study if they were expected to receive enteral nutrition for a minimum of 3 days. After 3 days, as patients transitioned off enteral nutrition and onto oral diets, there was substantial crossover between study groups. Based on original study assignment, there was a statistically significant difference in the actual amount of fiber received between enrollment and Day 3 (p <0.01), but not at later study timepoints.

1.1–2.9) and 0.8 (IQR, 0.43–1.2) respectively for fiber versus no fiber (p = 0.03).

Adverse Effects

Adverse effects were monitored through study Day 30. There were no differences in the number or severity of untoward health events based on study group (**Supplemental Table 3**, Supplemental Digital Content 8, http://links.lww.com/CCX/A201). There were also no differences in deaths (two fiber vs. four no fiber, p = 0.63), culture-proven infections (three fiber vs. three no fiber, p = 1.0), or electrolyte abnormalities (**Supplemental Table 4**, Supplemental Digital Content 9, http://links.lww.com/CCX/A202).

Power

Power calculations were performed to guide sample size calculations for future studies. The observed mean change between baseline and Day 3 in SCFA producers was +26% (SD = 58%) for fiber and −0.33% (SD = 48%) for no fiber. The fiber group had +0.44 SD increase in SCFA producers, whereas the study was powered to detect a 1.4 SD or greater change. Assuming similar effect size and variance, future studies would require 132 patients (66 per group) to achieve 80% power.

DISCUSSION

This pilot study of 20 ICU patients receiving antibiotics found that a median dose of 11 g/d of mixed fiber given as enteral nutrition was associated with a 61% gain in putatively beneficial SCFA-producing bacteria over a 3 day time span, whereas patients who were not randomized to fiber had a 46% decline in the same bacteria. Actual SCFA levels paralleled the changes in SCFA producers and were six-fold higher in the fiber group. Despite these large differences, neither the SCFA producer result nor the SCFA level result was statistically significant. All observations were intent-to-treat and there was a 20% rate of crossover, a common challenge for ICU nutrition studies (19). This result provides a valuable effect size estimate for future studies. Such studies will require 100–150 patients to be adequately powered to assess effects of fiber on SCFA producers, although this will presumably depend on fiber amount and type.

Prior studies have tested prebiotic interventions in the ICU. Results of these studies are mixed and, because the interventions tested have been heterogenous, hard to interpret. O'Keefe et al (20) looked at SCFA producer relative abundance and fecal SCFA levels in response to supplementation with 18–36 g wheat dextrin/d in 13 ICU patients (20). With fiber, there was a dramatic increase in Firmicutes and other SCFA producers and substantial increases in SCFA levels including a doubling of fecal butyrate concentrations. This result contrasts sharply with the decline in SCFA producers and SCFA levels usually observed in ICU patients (21, 22). It also accords well with our own retrospective study of 129 ICU patients, which found that observed mixed fiber intake correlated well with SCFA producer relative abundance during the 72 hours after ICU admission (23). In that study, patients in the highest tertile of fiber received had a two- to

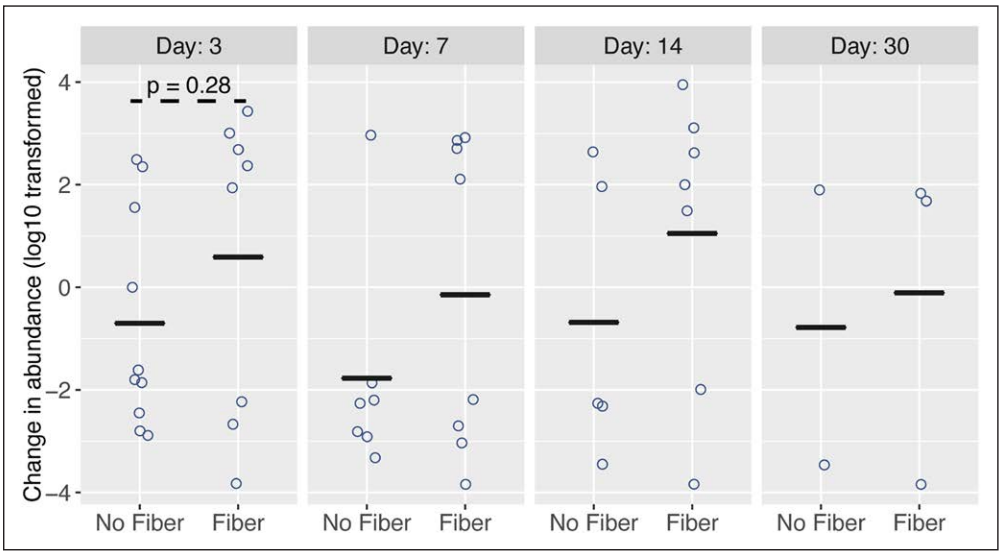

Figure 2. Within-individual change from baseline in the relative abundance of short-chain fatty acid (SCFA)-producing bacterial taxa, stratified by study group. For each patient, the within-individual change in the relative abundance of SCFA-producing operational taxonomic units (OTUs) compared with the baseline sample was calculated at each study timepoint: that is, ([Day 3 — baseline]/baseline), ([Day 7 — baseline]/baseline]), etc. These values were then compared between the two study groups as a Wilcoxon rank-sum test. None of the differences between groups were statistically significant.

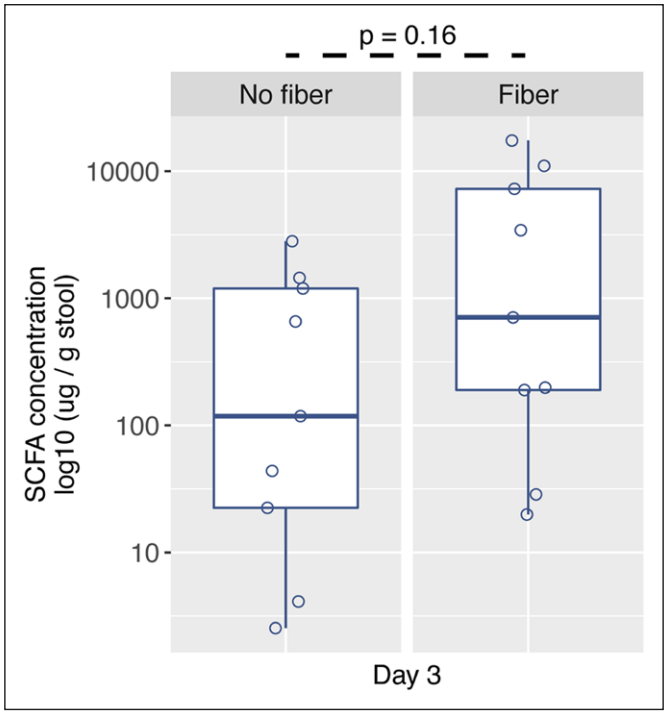

Figure 3. Short-chain fatty acid (SCFA) levels measured from whole stools on Day 3, stratified by study group. Baseline preintervention whole stools were not available so SCFA levels were compared between study groups at Day 3. The sum total of eight SCFAs was measured using an aliquot of homogenized stool: 2-methylbutyrate, acetate, butyrate, hexanoate, isobutyrate, isovalerate, propionate, and valerate.

three-fold increase in the relative abundance of SCFA producers compared with patients in the lowest tertile of fiber received. Other trials have had contradictory results. A study testing 7 days of 7 g/d inulin versus maltodextrin supplementation in 22 ICU adults initiating enteral nutrition found no difference in fecal abundance of *Faecalibacterium prausnitzii* or Bifidobacteria, or in fecal SCFA levels (24). Across these studies, differences in the type and amount of fiber, mode of delivery (supplementation vs. fiber-containing enteral nutrition), and outcome ascertainment could account for the differences in findings (25).

In this study, there were trends toward clinical benefits associated with fiber, some of which reached statistical significance. With fiber, there was a 25% absolute increase in goal calories consumed through Day 3 (equivalent to an additional 400 kcal/patient/d), which was not statistically significant. Also, with fiber there was firmer stool consistency and a decrease in stool frequency by about 1 stool/patient-day. This last finding was significant despite the small study size and some crossover. Improved stool consistency is not likely to impact survival in the ICU but probably does impact patient comfort, hygiene, and nursing care. Importantly, fiber did not cause diarrhea, bezoars/intestinal obstruction, or other adverse effects in the ICU as has been suggested in the past (26).

This study has strengths but also limitations. By randomizing patients to one of two forms of complete enteral nutrition that were calorie and micronutrient identical other than fiber, it allowed us to reasonably attribute any observed differences to fiber itself. On the other hand, the difference in actual fiber intake between study groups—11 g/d for 3 days—was neither as high in dose nor as long in duration as we would have wished. Indirect calorimetry was not performed to measure energy consumption, and we instead relied upon estimating equations (27). The fiber was integrated within enteral nutrition rather than supplementation with a specific fiber type (e.g., inulin, psyllium, wheat dextrin). This improves generalizability but might obscure biological effects that would only be seen with monosupplementation using a specific fiber type. We have initiated a follow-up trial testing up to 32 g/d of inulin for 7 days in the ICU in part to address these limitations (NCT03865706). Last, the trial was small but rigorously prespecified the primary outcome and a supporting secondary outcome, and carefully assessed relevant clinical and adverse effects.

CONCLUSIONS

In summary, this randomized ICU pilot trial found that mixed fiber, given as part of enteral nutrition, was associated with nonsignificant increases in fecal SCFA-producing bacteria and in fecal SCFA levels. The study did not seek to investigate the clinical consequences of these microbiome changes. Fiber improved stool consistency and was apparently safe up to a maximum of 27 g/d. The results of this trial provide effect size estimates that can be the basis for future trials testing whether fiber, by increasing SCFA producers and/or SCFA levels, might confer benefit in the ICU.

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REFERENCES

1. World Health Organization: Antimicrobial Resistance: Global Report on Surveillance. WHO Library Cataloguing-in-Publication Data. 2014. Available at: http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1. Accessed December 20, 2019
2. Freedberg DE, Zhou MJ, Cohen ME, et al: Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. *Intensive Care Med* 2018; 44:1203–1211
3. Frencken JF, Wittekamp BHJ, Plantinga NL, et al: Associations between enteral colonization with Gram-negative bacteria and intensive care unit-acquired infections and colonization of the respiratory tract. *Clin Infect Dis* 2018; 66:497–503
4. Kass EH, Schneiderman LJ: Entry of bacteria into the urinary tracts of patients with inlying catheters. *N Engl J Med* 1957; 256:556–557
5. Safdar N, Maki DG: The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. *Intensive Care Med* 2004; 30:62–67
6. Jacobson A, Lam L, Rajendram M, et al: A gut commensal-produced metabolite mediates colonization resistance to salmonella infection. *Cell Host Microbe* 2018; 24:296–307

7. Fukuda S, Toh H, Hase K, et al: Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* 2011; 469:543–547
8. Rivera-Chávez F, Zhang LF, Faber F, et al: Depletion of butyrate-producing clostridia from the gut microbiota drives an aerobic luminal expansion of salmonella. *Cell Host Microbe* 2016; 19:443–454
9. Desai MS, Seekatz AM, Koropatkin NM, et al: A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell* 2016; 167:1339–1353.e21
10. Morowitz MJ, Di Caro V, Pang D, et al: Dietary supplementation with nonfermentable fiber alters the gut microbiota and confers protection in murine models of sepsis. *Crit Care Med* 2017; 45:e516–e523
11. Di Caro V, Cummings JL, Alcamo AM, et al: Dietary cellulose supplementation modulates the immune response in a murine endotoxemia model. *Shock* 2019; 51:526–534
12. Schnizlein MK, Vendrov KC, Edwards SJ, et al: Dietary Xanthan gum alters antibiotic efficacy against the murine gut microbiota and attenuates *Clostridioides difficile* colonization. *mSphere* 2020; 5:e00708-19
13. Ng KM, Aranda-Diaz A, Tropini C, et al: Recovery of the gut microbiota after antibiotics depends on host diet, community context, and environmental reservoirs. *Cell Host Microbe* 2019; 26:650–665.e4
14. Gottschlich MM, DeLegge MH, Guenter P, et al: *The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach: The Adult Patient*. Silver Spring, MD, American Society for Parenteral and Enteral Nutrition, 2007
15. Turnbaugh PJ, Ley RE, Hamady M, et al: The human microbiome project. *Nature* 2007; 449:804–810
16. Vital M, Karch A, Pieper DH: Colonic butyrate-producing communities in humans: an overview using omics data. *mSystems* 2017; 2:e00130–17
17. Lewis SJ, Heaton KW: Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997; 32:920–924
18. Cook D, Lauzier F, Rocha MG, et al: Serious adverse events in academic critical care research. *CMAJ* 2008; 178:1181–1184
19. Arabi YM, Casaer MP, Chapman M, et al: The intensive care medicine research agenda in nutrition and metabolism. *Intensive Care Med* 2017; 43:1239–1256
20. O'Keefe SJ, Ou J, Delany JP, et al: Effect of fiber supplementation on the microbiota in critically ill patients. *World J Gastrointest Pathophysiol* 2011; 2:138–145
21. Yamada T, Shimizu K, Ogura H, et al: Rapid and sustained long-term decrease of fecal short-chain fatty acids in critically ill patients with systemic inflammatory response syndrome. *JPEN J Parenter Enteral Nutr* 2015; 39:569–577
22. Livanos AE, Snider EJ, Whittier S, et al: Rapid gastrointestinal loss of Clostridial Clusters IV and XIVa in the ICU associates with an expansion of gut pathogens. *PLoS One* 2018; 13:e0200322
23. Fu Y, Moscoso DI, Porter J, et al: Relationship between dietary fiber intake and short-chain fatty acid-producing bacteria during critical illness: a prospective cohort study. *JPEN J Parenter Enteral Nutr* 2020; 44:463–471
24. Majid HA, Cole J, Emery PW, et al: Additional oligofructose/inulin does not increase faecal bifidobacteria in critically ill patients receiving enteral nutrition: a randomised controlled trial. *Clin Nutr* 2014; 33:966–972
25. Shane AL, Cabana MD, Vidry S, et al: Guide to designing, conducting, publishing and communicating results of clinical studies involving probiotic applications in human participants. *Gut Microbes* 2010; 1:243–253
26. McIvor AC, Meguid MM, Curtas S, et al: Intestinal obstruction from cecal bezoar; A complication of fiber-containing tube feedings. *Nutrition* 1990; 6:115–117
27. McClave SA, Taylor BE, Martindale RG, et al; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition: Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; 40:159–211