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Beatriz E. Valdés-Duque[a] , Nubia A. Giraldo-Giraldo[b] , Ana M. Jaillier-Ramírez[c] , Adriana Giraldo-Villa[d] , Irene Acevedo-Castaño[e] , Mónica A. Yepes-Molina[f] , Janeth Barbosa-Barbosa[g] , Carlos J. Barrera-Causil[h] and Gloria M. Agudelo-Ochoa[b]

[a]Bioscience Research Group, Institución Universitaria Colegio Mayor de Antioquia – IUCMA, Medellín, Antioquia, Colombia; [b]Food and Human Nutrition Research Group, Universidad de Antioquia – UdeA, Medellín, Antioquia, Colombia; [c]Departamento de nutrición, Hospital Universitario San Vicente Fundación Rionegro, Rionegro, Antioquia, Colombia; [d]Departamento de nutrición clínica, Hospital Pablo Tobón Uribe, Medellín, Antioquia, Colombia; [e]Departamento de nutrición y dietética, Hospital General, Medellín, Antioquia, Colombia; [f]Departamento de nutrición y dietética, Hospital Universitario San Vicente Fundación Medellín, Medellín, Antioquia, Colombia; [g]Departamento de nutrición, área de soporte nutricional, Clínica Las Américas, Medellín, Antioquia, Colombia; [h]Research Group in Teaching and Modeling in Applied Exact Sciences, Instituto Tecnológico Metropolitano – ITM, Medellín, Antioquia, Colombia

ABSTRACT

Objective: To determine the concentration of stool short-chain fatty acids (SCFAs) in critically ill patients with sepsis and to compare the results between the critically ill patient and the control group.

Methods: This descriptive, multicenter, observational study was conducted in five health institutions. Over a 6-month study period, critically ill patients with sepsis who were admitted to the intensive care unit (ICU) and met the inclusion criteria were enrolled, and a control, paired by age and sex, was recruited for each patient. A spontaneous stool sample was collected from each participant and a gas chromatograph coupled to a mass spectrometer (Agilent 7890/MSD 5975 C) was used to measure the concentrations SCFAs.

Results: The final sample included 44 patients and 45 controls. There were no differences in the age and sex distributions between the groups ($p > 0.05$). According to body mass index (BMI), undernutrition was more prevalent among critically ill patients, and BMI in control subjects was most frequently classified as overweight ($p = 0.024$). Propionic acid, acetic acid, butyric acid, and isobutyric acid concentrations were significantly lower in the critically ill patient group than in the control group ($p = 0.000$). No association with outcome variables (complications, ICU stay, and discharge condition) was found in the patients, and patients diagnosed with infection on ICU admission showed significant decreases in butyric and isobutyric acid concentrations with respect to other diagnostic criteria ($p < 0.05$).

Conclusions: The results confirm significantly lower concentrations of stool SCFAs in critically ill patients with sepsis than in control subjects. Due to its role in intestinal integrity, barrier function, and anti-inflammatory effect, maintaining the concentration of SCFAs may be important in the ICU care protocols of the critical patient.

List of abbreviations: SCFAs: short-chain fatty acids; APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; BMI: body mass index; CRP: C-reactive protein; ICU: intensive care unit; IM: intestinal microbiota; ROS: reactive oxygen species; SOFA: Sequential Organ Failure Assessment

Introduction

Short-chain fatty acids (SCFAs) are compounds with two to six carbon atoms in their structure. SFCAs play a key role in promoting intestinal barrier integrity. The main SCFAs include acetic (C2), propionic (C3), and butyric (C4) acids. Although they are naturally produced by host metabolic pathways, they are mainly synthesized in the colon due to polysaccharide fermentation by anaerobic bacteria (1). In the intestinal lumen, SCFAs are found in different concentrations depending on the site; 13 mM SCFAs are found in the terminal ileum, 130 mM in the cecum, and 80 mM in the descending colon (2). SCFA concentration is variable, and its production is regulated by factors related to the host, environment, diet, substrate availability, and microbiological conditions such as the metabolic capacity of the gut intestinal microbiota (IM). In healthy individuals, the molar proportion of acetic, propionic, and butyric acids is 60:25:15 and remains relatively stable over time (3, 4).

SCFA production is a dynamic and complex process involving different metabolic pathways activated by bacterial

species, most frequently glycolysis, although some species can use the pentose phosphate pathway to generate the same metabolites (5). In the epithelial cells of the colon, SCFAs provide 5–10% of the basal energy requirements. Butyric acid is the most important SCFA, supplying 60–70% of the energy needed for the proliferation and differentiation of the colonic epithelial cells (6). Acetic and propionic acids reach the liver via the portal vein, where the former is metabolized and the latter is stored or released to the peripheral venous system and is the only SCFA detectable in the peripheral blood (7). In addition to provide energy, SCFAs contribute to maintain homeostasis of the intestinal mucosa by regulating colonic motility, blood flow, and intestinal pH (8). Finally, SCFAs play a role in systemic and local intestinal immunity by controlling the production of helper T cells, antibodies, and cytokine (9). Through their anti-inflammatory effect, SCFAs modulate immune cell chemotaxis and release reactive oxygen species (ROS) and cytokines. SCFAs may have a key regulatory effect on inflammatory diseases by controlling immune cell migration to sites of inflammation modulating immune cell activity, and enabling a rapid decrease in the number of pathogens present by ROS activation, thereby helping to reduce host damage and improve host survival (7).

Intestinal integrity is an essential factor in maintaining mucosal homeostasis via efficient separation of the intestinal luminal content from the host through an epithelial barrier. This separation is critical for health maintenance, and disruption in its integrity has been associated with various conditions, particularly inflammatory diseases (10).

SCFAs promote a symbiotic relationship between intestinal bacteria, and a host in critical condition. This relationship has been associated with the clinical evolution of patients (11). Among critically ill patients with sepsis, the concentration of SCFAs is significantly altered and intestinal dysfunction is a determinant of disease progression (12). Compared to control subjects, these patients have decreased concentrations of the main SCFAs (3, 11), suggesting that changes in the IM of critically ill patients (13) could decrease SCFAs concentrations (14, 15). Even though there are studies regarding the changes in SCFAs in critically ill patients, they remain few; in particular, in our population there is no data available. It is of interest to the medical community to confirm whether these substances, products of the fermentation of IM on nondigestible carbohydrates, are also altered in our critically ill patients. The benefits of such research are two-fold: on the one hand, it will provide data that consolidate the evidence, and on the other hand, it will aid in designing future clinical trials that allow SCFA modulation to improve the prognosis for patients in the ICU. The latter might be accomplished with prebiotics, probiotics, or symbiotics provided in enteral nutrition, which is the main type of nutritional support these patients receive. Therefore, the objective of this study was to compare the concentrations of SCFAs in critically ill patients diagnosed with sepsis to those found in a control group, and to explore their relationship with outcome variables and other variables of interest.

Materials and methods

This descriptive, multicenter observational study was conducted in the ICUs of five high-complexity health institutions in the city of Medellín (Hospital Pablo Tobón Uribe, Hospital San Vicente Fundación, Hospital General de Medellín and Clínica Las Américas) and Rionegro (Hospital San Vicente Fundación).

Subjects

The subjects included critically ill patients diagnosed with sepsis who were admitted to the ICU. The sample size was calculated according to the difference in butyric acid concentrations between critically ill patients with systemic inflammatory response syndrome (SIRS) and control subjects (16.85 ± 6.94 μmol/g stool) (13). With a 95% confidence level and a 2 μmol/g sampling error, 40 individuals were required per group; with 10% oversampling, 44 patients were enrolled per group, totaling 88 subjects.

Inclusion and exclusion criteria

This study included patients older than 18 years of age, diagnosed with sepsis according to the criteria defined by the third consensus definition of sepsis (suspected or documented infection and Sequential Organ Failure Assessment [SOFA] score ≥2 points) as a result of infection (16). Patients with a terminal status, patients with colostomy or ileostomy, pregnant or breastfeeding women, and homeless patients were excluded. The control subjects selected were adults over 18 years of age who were nonsmokers and nonvegetarians; who had not taken antibiotics or antiparasitic drugs in the last 4 months, laxatives in the last 2 months, or fiber supplements; who were not undergoing weight loss treatment; and who were not high-performance athletes, pregnant, or breastfeeding.

Each patient who met the inclusion criteria and signed the informed consent form provided a stool sample of approximately 3 g, which was collected by spontaneous bowel evacuation. This stool sample was deposited in an amber glass vial with a polypropylene screw cap with PTFE/silicone septa. All samples were placed at −20 °C within 15 minutes from the time of collection and stored at that temperature until analysis. Upon admission, demographic (age and sex), clinical (clinical diagnosis on admission at the ICU, Acute Physiology and Chronic Health Evaluation [APACHE]-II score, SOFA score, and antibiotic use), anthropometric (body mass index [BMI]) (17, 18), and biochemical (C-reactive protein [CRP] level and serum glucose) information was collected; data on outcome variables (hospital stay, complications, and discharge status) were collected from the clinical history of each patient. The patients were followed until their discharge from the ICU. The controls, who met the inclusion criteria and signed the informed consent form, were instructed on how to collect stool samples by spontaneous bowel evacuation, which, as in patients, were deposited in an amber glass vial with a polypropylene screw cap with

Table 1. General characteristics of the study population.

	Patients with sepsis n = 44		Control subjects n = 45			
	n	%	n	%	Total	p^b
Sex						
Men	24	54.5	22	48.9	46	0.593
Women	20	45.5	23	51.1	43	
Age (years)	65 (54.3; 75.8)[a]		53 (41.5; 64.0)[a]			
18 − 40	5	11.4	11	24.4	16	0.179
41 − 59	12	27.3	14	31.1	26	
≥60	27	61.4	20	44.4	47	
BMI (kg/m²)	24.1 (22.9; 27.0)[a]		24.9 (22.3; 27.7)[a]			
Undernutrition	9	20.5	4	8.9	13	0.024
Adequate	24	54.5	25	55.6	49	
Overweight	7	15.9	16	35.6	23	
Obese	4	9.1	0	0.0	4	

[a]Numbers are medians and interquartile ranges.
[b]Chi-square test.
BMI: Body Mass Index.

polytetrafluoroethylene [PTFE]/silicone septa, placed at −20 °C within 15 minutes the time of collection, transported in a refrigerator, keeping the specimen cold (−20 °C), and stored at that temperature until analysis.

SCFAs concentration determination

The quantification of the SCFAs was carried out following the same protocol described by de la Cuesta et al 2018 (19). In brief, 1 g of each stool sample was weighed in a 20-ml vial with a magnetic screw cap and PTFE/silicone septa, and SCFAs were sampled using a CTC Combipal 3 autosampler in headspace solid-phase microextraction (HS/SPME) mode equipped with a gray fiber (Carboxen/DVB/PDMS; Supelco Part. No. SU57329U). A gas chromatograph coupled to a mass spectrometer (Agilent 7890/MSD 5975 C) equipped with a polar stationary phase capillary column (DBWAX Agilent Part. No. 122-7032) was used to separate the four SCFAs (acetic, propionic, butyric, and isobutyric acids); analyte signals were acquired in single-ion monitoring (SIM) mode and the results were expressed in micromolar units (μmol/g of sample). To calibrate the method of quantification of the SCFAs, a group of five samples was used. Fecal samples were homogenized and diluted with distilled-deionized water in a ratio 1:1. An aliquot of 1 g was spiked with a combined standard solution of SCFAs diluted in water (organic acid kit ref. 47264, Supelco (Bellefonte, PA): Acetic acid—ref. R475165; propionic acid—ref. R412368; butyric acid—ref. R420040; isobutyric acid—ref. R412415) to obtain curves in the range 25–750 ng/mL (6 concentrations; 9 replicates). The standard solution was prepared on the day of analysis. Linearity (homoscedasticity test, analysis of residuals), precision (RSD 3.0 for the detection of each analyte), and accuracy (3-way test of concentration for each analyte and 3 replicates; value = Gtable (a = 0.05; k = 3; n = 3) = 0.871 (Gexp < Gtable acceptance)) were considered in the evaluation of the analytic method. According to the method used, the LOD (limit of detection) was not calculated, the minimum calibration value (25 ng/mL) is reported, therefore, 0.00 values are below 25 ng and were not acceptably integrated by the software. For the purposes of statistical analyses, the undetected values were assumed as 0.0000.

The nursing and clinical pathology laboratory staff of the participating institutions were provided with standardized training for sample collection and storage. In each institution, a pilot test was conducted, and logistic aspects were adjusted for data collection. Patient selection, signed informed consent form collection, information registration, and follow-up until discharge were performed by the ICU nutritionist at each institution involved in this study.

According to the Colombian Ministry of Health (*Ministerio de Salud de Colombia*), pursuant to Resolution Number 8430 of October of 1993, Article 11, this research was classified as minimum risk because the selected subjects underwent standard or routine clinical procedures such as physical examination and biochemical and diagnostic tests, posing no risk to their physical or mental integrity, as part of the care they received in the ICU according to their clinical status. The study was conducted in accordance with the principles of the Declaration of Helsinki. Moreover, the rights, safety, and wellbeing of the participants (patients and controls), as well as the basic principles of respect for people, beneficence, and justice, were protected and respected in accordance with the Belmont Report. Before starting the study, all participants signed the informed consent form. Each control subject voluntarily signed the informed consent form, with no pressure whatsoever and received the corresponding copy. Additionally, a relative of each patient signed the informed consent form, given the clinical status of the patients. The study was approved by the Ethics Committees of the Odontology Faculty of the Universidad de Antioquia; Act 03 of 2015) of Hospital Pablo Tobón Uribe, Hospital San Vicente Fundación, and Clínica Las Américas.

Statistical analysis

The study population was described using central tendency and dispersion measures (mean, median, standard deviation, and interquartile ranges) using frequencies and percentages for quantitative and qualitative variables, respectively. Statistical analysis began with normality assessment of continuous variables using Shapiro–Wilk tests; if normality was not met, non-parametric statistics were used. Chi-square tests of independence and Spearman's rank correlation coefficient were used to explore the associations between categorical and quantitative variables, respectively, and Mann–Whitney U tests were used for comparative analysis of SCFAs concentrations between critically ill patients and control subjects. The relationship between SCFAs concentrations in critically ill patients with sepsis and the qualitative variables of interest was explored using Kruskal–Wallis and Mann–Whitney U tests. In all cases, $p < 0.05$ was considered significant. The statistical tests were performed using the R programing language in a free software environment.

Results

The sample consisted of 89 subjects, including 44 critically ill patients with sepsis and 45 control subjects. Among the critically ill patients, 61.4% were older than 60 years of age,

Table 2. Clinical characteristics of critically ill patients with sepsis.

	Patients with sepsis
Serum glucose (mg/dL)[a]	163 (136; 192)
CRP (mg/dL)[a]	9.5 (5.9; 22.6)
APACHE II score[a]	22 (15; 22)
SOFA score[a]	7 (4; 8)
Antibiotics[b]	42 (95.5)
Penicillin	31 (74)
Cephalosporin	4 (9)
Macrolides	3 (7)
Carbapenems	2 (5)
Glycopeptides	2 (5)
Admission diagnosis[b]	
Infectious disease	25 (56.8)
Pulmonary	12 (27.3)
Abdominal	4 (9.1)
Unknown origin	3 (6.8)
Systemic	2 (4.5)
Other infections[d]	4 (9.1)
Pulmonary disease	11 (25)
Other diagnoses[c]	8 (18.2)
Complications	
Yes	40 (90.9)
Infectious	17 (42.5)
Noninfectious	23 (57.5)
No	4 (9.1)
ICU stay (days)[a]	13 (8; 20)
Discharge condition[b]	
Alive	32 (72.7)
Dead	12 (27.3)

[a]Median and interquartile range.
[b]Number and %.
[c]Cardiovascular, gastrointestinal, hepatic, pancreatic, or biliary disease or trauma.
[d]Soft tissues, urinary tract, airways, and cardiac.
CRP: C-reactive protein.
APACHE II: Acute Physiology and Chronic Health Evaluation.
SOFA: Sequential Organ Failure Assessment.
ICU: Intensive care unit.

Table 3. Short-chain fatty acid concentrations in patients with sepsis and in control subjects.

Short-chain fatty acid[a,b,c]	Patients with sepsis	Control subjects	p-value[d]
Acetic acid	0.880 (0.188; 2.900)	3.760 (2.315; 6.395)	0.000
Propionic acid	0.055 (0.000; 0.235)	0.440 (0.260; 0.715)	0.000
Isobutyric acid	0.010 (0.000; 0.020)	0.040 (0.020; 0.090)	0.000
Butyric acid	0.010 (0.000; 0.125)	0.240 (0.095; 0.420)	0.000
Total fatty acids	0.990 (0.188; 3.458)	5.090 (2.880; 7.790)	0.000

[a]μmol/g stool sample.
[b]Numbers are medians and interquartile ranges.
[c]Values of 0.0000 correspond to undetected (NQ) according to the method of quantification of SCFAs.
[d]Mann–Whitney U test.

occurring complications were pneumonia and bacteremia with 7.5% each. In addition, 57.5% of the complications were noninfectious. Among the noninfectious complications, the most frequently occurring complications were acute kidney injury (12.5%), bronchoaspiration (5%), and vomiting (5%). The mean ICU stay was 15.9 ± 12.2 days, and 27.3% of the critically ill patients died. Table 2 outlines the clinical characteristics of the critically ill patients with sepsis.

The total and individual concentrations of SCFAs (acetic, propionic, butyric, and isobutyric) were significantly lower in the critically ill patients with sepsis than those in the control subjects ($p = 0.000$) (Table 3). Concentrations of SCFA in critically ill patients with sepsis showed no association with outcome variables (hospital stay duration, complications, mortality) or with other clinical variables on ICU admission (BMI, SOFA score, APACHE II score, antibiotics, serum glucose, and CRP). Analysis of SCFA concentrations by sex and age showed no significant differences, although there was a trend toward higher SCFAs concentrations in men than in women and lower values of propionic, butyric, and isobutyric acids in subjects older than 60 years of age than in those aged 18–40 years. A significant difference in the concentrations of butyric and isobutyric acids was found in patients diagnosed with infection upon ICU admission with respect to other diagnostic ($p < 0.05$) (Table 4).

Discussion

SCFAs have been identified as key compounds in promoting intestinal integrity due to their protective effect on barrier function and anti-inflammatory actions. Several studies have reported decreased SCFAs concentrations in critically ill patients (3, 11, 13, 20). These results were confirmed by our study in which, compared to the control group, patients showed a significant decrease in the concentrations of acetic, propionic, isobutyric, and butyric acids, ($p < 0.05$), which account for 95% of the total SCFAs. These findings are consistent with those reported by Yamada et al. in 140 patients diagnosed with severe SIRS; the authors reported a significant decrease in the concentrations of butyric, propionic, and acetic acids (3). Shimizu et al. also reported significant decreases in the concentrations of these compounds in 25 patients with SIRS compared to those in healthy controls, suggesting that this decrease may affect the systemic inflammatory response of critically ill patients after severe damage (13). Among 15 critically ill patients admitted to an ICU for

54.5% were men, and 20.5% presented with undernutrition on ICU admission. Among the control subjects, 44.4% were older than 60 years, 48.9% were men, and 35.6% overweight. The distributions of age and sex did not differ significantly between the groups ($p > 0.05$); according to BMI, undernutrition was more prevalent among critically ill patients, and BMI in control subjects was most frequently classified as overweight ($p = 0.024$). Table 1 outlines the general characteristics of the study population.

Among the critically ill patients with sepsis, 97.7% had high CRP levels, whereas 44.2% had altered serum glucose levels (high and low values). The mean SOFA and APACHE II scores were 7 ± 3 and 21 ± 8, respectively. Additionally, 95.5% of the critically ill patients were prescribed antibiotics, among which 38.6% were treated with more than three classes of antibiotics, of which penicillin was the most frequent (74%). The main diagnoses upon admission were infectious (56.8%) and pulmonary diseases (25%). According to the admission diagnosis, 25 patients presented with infections of different origins. The most frequently diagnosed infections were pulmonary (27.3%). The most frequent comorbidities, listed in descending order of frequency, were obstructive pulmonary disease, arterial hypertension, pneumonia, respiratory failure, acute renal injury, and diabetes mellitus. Overall, 90.9% of patients experienced complications, and 42.5% of these complications were infectious. Among these infectious complications, the most frequently

Table 4. Short-chain fatty acid concentrations in patients with sepsis by sex, age, and admission diagnosis.

	Acetic acid[a,b]	Propionic acid[a,b]	Butyric acid[a,b,c]	Isobutyric acid[a,b,c]	Total fatty acids[a,b]
Sex					
Female	0.35 (0.17)	0.04 (0.15)	0.01 (0.04)	0.01 (0.02)	0.40 (1.70)
Male	1.94 (3.21)	0.13 (0.31)	0.06 (0.14)	0.01 (0.04)	2.36 (3.36)
p[d]	0.056	0.186	0.407	0.116	0.063
Age (years)					
18 − 40	2.17 (2.80)	0.31 (0.38)	0.14 (0.13)	0.04 (0.08)	2.80 (3.25)
41–59	0.66 (1.51)	0.04 (0.17)	0.01 (0.06)	0.01 (0.04)	0.77 (1.70)
≥60	0.79 (2.84)	0.05 (0.22)	0.01 (0.11)	0.00 (0.01)	0.83 (3.40)
p[e]	0.576	0.365	0.06	0.287	0.564
Admission diagnosis[e]					
Infection	0.38 (1.74)	0.04 (0.12)	0.00 (0.03)‡	0.00 (0.01)‡	0.39 (2.22)
Pulmonary	1.67 (3.97)	0.07 (0.37)	0.08 (0.14)†	0.01 (0.04)†	1.95 (4.92)
Others	1.63 (11.21)	0.21 (1.24)	0.09 (0.65)†	0.04 (0.25)†	1.93 (13.3)
p[e]	0.087	0.109	0.048	0.031	0.084

[a]μmol/g stool sample.
[b]Numbers are medians and interquartile ranges.
[c]Values of 0.0000 correspond to undetected (NQ) according to the method of quantification of SCFAs.
[d]Mann–Whitney U test.
[e]Kruskal–Wallis test.
Different symbols in the same column indicate significant differences (Mann–Whitney U test; $p < 0.05$).

trauma, outpatient cardiac arrest, and cardiovascular accident who were healthy prior to admission, Hayakawa et al. reported a significant decrease in SCFAs within 6 hours from the time of admission, highlighting that patients quickly develop changes in the concentration of these compounds after severe damage (21).

Though the mechanisms by which SCFAs decrease in critically ill patients remain unclear, the results in our study could be explained, among others factors, a reduction in obligate anaerobic bacteria, which may affect their long-term concentrations (14) due to significant decreases in fermentation substrates necessary for SCFAs production, such as dietary fiber (15). It has been reported that a decrease in butyric acid-producing species compromises the long-term production of SCFAs in critically ill patients (3). Specifically, *Faecalibacterium prausnitzii* was identified as the main commensal anti-inflammatory bacteria and one of the key butyrate producers in the human IM (22). Our patients received most enteral nutritional support with standard formulas without fiber (89%); which suggests the decrease in the availability of substrates to produce SCFAs. When the availability of the fermentable dietary fibers starts to decrease in the most distal part of the colon, the luminal pH increases to 6.5. Consequently, butyrate-producing bacteria almost completely disappear (23).

Another aspect that could explain the reduction of SCFA in our study was the regimen of antibiotics received by 95.5% of patients. These medications alter IM composition, generating changes in the levels of IM-derived metabolites, especially SCFAs whose changes have been associated with the growth of enteric pathogens (24); the risk increases among immunocompromised individuals such as critically ill patients (25).

We found no significant association between SCFAs concentrations and outcome variables such as complications, ICU stay, and mortality. We also observed that there were no significant differences by sex, although there was a trend toward higher concentrations in men than in women and a trend toward decreased SCFAs concentrations in older subjects, which could result from age-related gastrointestinal alterations causing changes in intestinal physiology such as gastric hypochlorhydria and motility disorders (26, 27).

The anti-inflammatory effect of butyric acid is associated with decreased concentrations of pro-inflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor-α (TNF-α), presumably based on the topical inhibition of inflammatory mediators in the epithelium (28). In our study, the significant decrease in butyric acid concentration in critically ill patients with infection (pneumonia, abdominal sepsis, septic shock) suggests compromised availability of these two SCFAs possibly due to dysbiosis, intestinal epithelium deterioration, or both.

The results of other studies have also shown how IM and SCFAs modulation with prebiotics, probiotics, and symbiotics administered with nutritional support increase intestinal SCFAs production and may help IM maintenance (11, 12, 15, 29) thereby decreasing complications, mortality, and ICU stay (30, 31). In this regard, O'Keefe et al. reported a significant increase in SCFAs concentration in 13 ICU patients diagnosed with necrotizing pancreatitis, administered a jejunal feeding with a semi-elemental formula (with a progressive increase in fiber) (15).

This study is the first to report the concentrations of SCFAs in critically ill patients with sepsis in Colombia, using the most recent criteria to define sepsis. Since SCFAs are products of fermentation of non-digestible fiber by the IM, one of the limitations of the study was that the IM in patients and control subjects were not comparatively evaluated to identify the richness and abundance of the bacteria associated with the production of the SCFAs. Although the required sample size to determine differences in SCFAs concentration between critically ill patients and control subjects was met, it was insufficient to show differences between the outcomes and other variables of interest. It is generally difficult to obtain non-diarrheal spontaneous stool samples from critically ill patients due to the clinical and pathological conditions of these patients. This made it difficult to measure SCFA concentrations in these patients.

Conclusions

The results of this study confirmed decreased concentrations of SCFAs in critically ill patients with sepsis. Additional studies are necessary to simultaneously evaluate the IM and SCFAs, as well as their short- and long-term changes. Due to its role in intestinal integrity, barrier function and anti-inflammatory effect, maintaining the concentration of SCFAs may be important in the ICU care protocols for treating the critically ill patient.

Author contributions

GMAO, BEVD, and NAGG conducted research; performed data analysis; and raised, managed, and administered research funds. CJBC performed statistical analysis. AMJR, AGV, IAC, MYM, and JBB participated in the study design; selected patients; and coordinated the collection, storage, and transport of biological samples. BEVD, GMAO, and NAGG wrote the manuscript. BEVD is responsible for the final content of the manuscript. All authors contributed to manuscript preparation and writing and read and discussed the results and conclusions. All authors read and approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Beatriz E. Valdés-Duque http://orcid.org/0000-0002-4446-9797
Nubia A. Giraldo-Giraldo http://orcid.org/0000-0001-7795-9947
Ana M. Jaillier-Ramírez http://orcid.org/0000-0002-7034-834X
Adriana Giraldo-Villa http://orcid.org/0000-0001-6204-6897
Irene Acevedo-Castaño http://orcid.org/0000-0002-2423-0914
Mónica A. Yepes-Molina http://orcid.org/0000-0002-2728-8580
Janeth Barbosa-Barbosa http://orcid.org/0000-0001-9714-6150
Carlos J. Barrera-Causil http://orcid.org/0000-0001-7288-7710
Gloria M. Agudelo-Ochoa http://orcid.org/0000-0002-4692-7632

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