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ORIGINAL ARTICLE

Supplementation with *Lactobacillus reuteri ATCC PTA 4659* in patients affected by acute uncomplicated diverticulitis: a randomized double-blind placebo controlled trial

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Abstract

Introduction Acute uncomplicated diverticulitis (AUD) is an inflammation of the colon diverticulum. We tested the efficacy of *Lactobacillus reuteri* 4659 (*L. reuteri*) in treating AUD. Primary outcome was reduced abdominal pain and inflammatory markers (C-RP). Secondary outcome was reduced hours of hospitalization.

Patients and methods A double-blind, placebo RCT was conducted with 88 (34M/54F mean age 61.9 ± 13.9) patients with a diagnosis of AUD. Group A (44 patients, 26F): ciprofloxacin 400 mg/bid and metronidazole 500 mg/tid for 1 week, plus *L. reuteri*/bid for 10 days. Group B (44 patients, 28F): same antibiotic therapy for 1 week, plus placebo/bid for 10 days. All patients completed a daily visual analog scale (VAS) for abdominal pain.

Results Between days 1 and 3, the group A pain decreased by 4.5 points; group B decreased by 2.36 points ($p < 0.0001$). Between days 1 and 5, the group A decreased by 6.6 points; group B by 4.4 points ($p < 0.0001$). Between days 1 and 7, the group A decreased by 7.6 points; group B decreased by 5.6 points ($p < 0.0001$). Between days 1 and 10, the group A decreased by 8.1 points; group B decreased by 6.7 points ($p < 0.0001$).

For C-RP value, the mean decrease between admission and after 72 h was 45.3 mg/L for group A and 27.49 mg/L for group B ($p < 0.0001$).

Conclusions Our RCT showed that supplementation of the standard AUD therapy with *L. reuteri* strain 4659 significantly reduced abdominal pain and inflammatory markers compared with the placebo group. It also resulted in a shorter period of hospitalization, and thus has economic benefits.

Trial registration TRIALGOV: NCT03656328

Keywords Acute uncomplicated diverticulitis · *Lactobacillus reuteri* · Inflammatory markers

Introduction

Colon diverticular disease (diverticulitis) is an increasing frequent clinical condition in industrialized countries, mainly due to the greater life expectancy of the population, and is a frequent cause of hospitalization [1].

The term diverticular disease includes several pathological entities. Diverticulosis is characterized solely by the presence at colonic level of diverticula, which are generally acquired and result from herniation of the mucosa and submucosa through the bowel wall, more frequently in the left portion of the colon. Uncomplicated symptomatic diverticular disease (SUDD) is characterized by abdominal symptoms such as pain and bloating, in the absence of other pathological conditions [2].

Acute diverticulitis is an inflammation of one or more diverticulum associated with the presence of severe and prolonged abdominal pain, fever, and leukocytosis. Development of complications such as abscesses, perforations, and peritonitis defines the framework of acute complicated diverticulitis. Patients with acute diverticulitis typically have a sudden onset of abdominal pain, usually located on the lower left, that requires access to a hospital emergency department (ED) [3, 4].

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Acute uncomplicated diverticulitis (AUD) is defined as the absence of any complication, such as abscess, perforation, fistula, or bleeding (Hinchey 0) [5].

Overcrowding of EDs and hospital wards is an ongoing problem in Italy. In fact, while the government is seeking annual reductions in bed numbers in public hospitals, the number of patients attending EDs is increasing [6].

Brief observation units (BOU) have been introduced for patients needing short-term treatment (48–72 h) who attend an ED without meeting the government criteria for a full in-hospital admission (http://www.regione.lazio.it/binary/rl_sistemi_informativi_sanitari/tbl_documenti/SIS_DGR_946_23_11_2007_Allegato.pdf) [7].

In the 2015 guidelines, medical treatment of AUD is conservative, with antibiotic therapy, effective on aerobes and anaerobes, a liquid diet, and infusion therapy (level of evidence III, recommendation B) [8].

Meanwhile, in a more recent published guidelines, it is shown that antimicrobial therapy can be avoided in immunocompetent patients with uncomplicated diverticulitis without systemic manifestations of infection (Recommendation 1A) [8].

A recent study analyzed the results of the two trials published comparing antibiotic therapy vs non antibiotic therapy (AVOD trial and DIABOLO trial). Out of a total of over 1000 patients, it was concluded that omitting antibiotic therapy in AUD does not imply greater risks in the patient, in particular, it does not increase the severity of diverticulitis, it does not increase recurrences and the risk of colic resection in the long-term follow-up. By the way, these studies have several limitation, including that it must me a first episode of AUD left-sited diverticulitis, no standardized antibiotic therapy, long accrual period, and patients without fever and without high level of inflammatory markers [9].

Older patients or patients with significant comorbidities should be hospitalized and receive intravenous antibiotic treatment. Even in these cases, adequate antibiotic pharmacological treatment in hospital guarantees a good prognosis in acute diverticulitis. After initiation of intravenous antibiotic therapy, an appropriate decrease in white blood cells and body temperature should occur. The vast majority of patients with AUD respond to therapy within a few days [10].

The etiopathogenetic factors of diverticular disease, particularly symptomatic and AUD, have a common denominator represented by the intestinal microbiota [11]. An altered bacterial flora can determine, through an inflammatory state, altered activation of afferent and efferent fibers with relative muscular and neuronal dysfunction, which leads to the development of abdominal symptoms [12].

The main agents that can favorably modify the balance of the intestinal microbiota are antibiotics and probiotics, which do not eliminate the intestinal bacterial flora, but modulate it in a favorable way. Antibiotics act by reducing the bacterial load and thereby the fermentation processes, the production of gas, in order to reduce the intraluminal pressure and the presence of associated symptoms [13]. Probiotics are useful in the treatment of diverticular disease because they counteract adhesion of harmful bacteria to the intestinal mucosa, modify metabolic aspects at the mucosal level, and reduce the synthesis of inflammatory cytokines. A recent review of the scientific data concluded that probiotics alone, or in combination with mesalazine, are safe and potentially useful in treating the symptoms of diverticular disease, but pointed out that the quality of existing studies is low, the number of patients is limited, and there are methodological problems [14].

One of the most studied probiotics in the literature is *Lactobacillus reuteri*, which is reported to be most effective in reducing antibiotic-associated diarrhea, traveler's diarrhea, and infantile colic [15]. There are numerous strains of *L. reuteri* on the market with specific characteristics of action. Strain 4659 has been shown to have a powerful anti-inflammatory action in inhibiting experimental colitis, by modulating toll-like receptors (TLR4) and NF-κB [16]. It also reduces the levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) [17]. This indicates therapeutic potential of *L. reuteri* strain 4659 in inflammatory diseases of the intestine.

To date, there have been no scientific studies on AUD being diagnosed and promptly treated in the ED, using antibiotics alone or an association of antibiotics and probiotics.

Study objective

The objective of the present study was to evaluate the efficacy of administration of a probiotic with anti-inflammatory action together with the normal antibiotic therapy used in clinical practice in the treatment of AUD in hospital EDs.

The primary endpoint was modification of inflammation index and a reduction in clinical symptoms in the group receiving the probiotic, compared with the group of patients treated with placebo. The secondary endpoint was a reduction in hours of hospitalization in the group receiving the probiotic, compared with the group of patients treated with placebo.

Patients and methods

A double-blind, placebo-controlled, randomized trial was conducted (October 2017–May 2018) on 88 consecutive adult patients (34M/54F; mean age 61.9.6 ± 13.9 years) with a diagnosis of acute uncomplicated diverticulitis (Hinchey = 0) admitted to the BOU at the ED of Fondazione Policlinico Gemelli hospital, Catholic University of Rome.

Inclusion criteria were:

- Age > 18 years
- Fever > 38°
- No reported allergies to contrast agents or antibiotics
- Informed consent
- Diagnosis of AUD confirmed by abdomen CT scan

Exclusion criteria:

- < 18 years
- Prior colonic surgery
- Pregnancy or breastfeeding
- Concomitant or recent (7–10 days) participation in another clinical trial
- Concomitant or recent (7–15 days) intake of probiotics or antibiotics
- Major concurrent diseases (hepatological, renal, tumor)
- Inflammatory bowel disease (Crohn's disease, ulcerative colitis) or other organic gastrointestinal disease
- Allergies to contrast agents or antibiotics
- Mental illness or inability to adhere to protocols

Withdrawal criteria from the study:

- At the request of the patient
- Evidence of side-effects related to the drugs administered

Patients were evaluated in a clinical setting by a physician at enrollment in the study, every day during hospitalization in the BOU, and at the end of therapy. At enrollment, a medical history review (including drugs taken), physical examination, laboratory tests (blood cell count, hepatic and renal function, electrolytes, C-RP) and abdominal CT scan were performed.

All patients presented with AUD (Hinchey classification grade 0) [5]. All patients were given a visual analog scale (VAS) ranging from 0 to 10, where 0 is asymptomatic and 10 is the worst pain they could have, to complete during the 10 days of the study.

Patients were also asked to complete a diary, in order to record any "adverse experience" (causing discomfort and/or interrupting the subject's usual activity) during the treatment periods, and to record every time they did not consume the prescribed doses. The diary was analyzed by physicians.

During the enrollment period, 103 patients obtained a confirmed diagnosis of acute diverticulitis in ED; 15 do not met the inclusion criteria, in particular: 2 patients had an history of IBD, 2 patients with an history of prior colonic surgery, and 11 patients had an acute complicated diverticulitis (Hinchey > 0) [5] (Fig. 1)

The 88 patients who met the inclusion criteria were randomly assigned into two groups, according to an automatically generated randomization list in a 1:1 ratio, using statistical software:

Group A ($n = 44$, 26F) received standard antibiotic therapy, consisting of ciprofloxacin 400 mg twice a day and metronidazole 500 mg three times a day for 7 days, with supplementation of the probiotic *L. reuteri* 4659 twice a day for 10 days.

Group B ($n = 44$, 28F) received the same standard antibiotic therapy as group A and a matching placebo for the same periods.

Patients were informed by an investigator (blind) that such a supplement could help in improving the inflammation associated with diverticulitis. Boxes containing placebo had the same shape dimensions, and trade mark indication and contained the same amount of capsules as *L. reuteri* boxes, and they were provided by the same probiotic producer.

The supplement of *L. reuteri* 4659 was administered in a dose of 5×10^8 colony-forming units (CFU), in capsules 30 min after food. During the study period, patients were instructed to store the product according to the recommended temperature. In particular, the capsules could be stored at room temperature (25 °C). Because *L. reuteri* is a living organism, over long storage periods, it is preferable not to freeze the capsules, but to refrigerate them at 2–8 °C.

Finally, protocol adherence was verified through a capsule count of the boxes returned by subjects on the day after finishing the therapy, and by directly asking the subjects about completion of the therapy.

All patients gave written informed consent. The study was approved by the independent Ethics Committee of the Catholic University of Rome (ID 1398) and conducted in accordance with the Declaration of Helsinki. Subjects did not receive any payment for their participation in the study. Intention to treat and per protocol analysis was performed.

The study was registered on TRIALGOV: NCT03656328.

Statistical analysis

Data were collected in a database and statistically analyzed with STATA 14 software for MAC; results are expressed as mean ± standard deviation (SD), with 95% confidence intervals. Parametric and non-parametric statistical tests were used, depending on the type of variable under examination. Values of $p < 0.05$ were considered significant.

According to a pilot study performed by our group [18], which highlighted an average reduction of VAS in the control group of 7.5 (SD, 1.1), and in the treatises of 4.1 (SD, 0.8) and setting as alpha error 0.05 and beta error 0.80, it will be necessary to enroll 43 patients for arm, for a total of 86 patients. Considering a dropout rate it was decided to sample 88 subjects (with a treated ratio 1:1 controls).

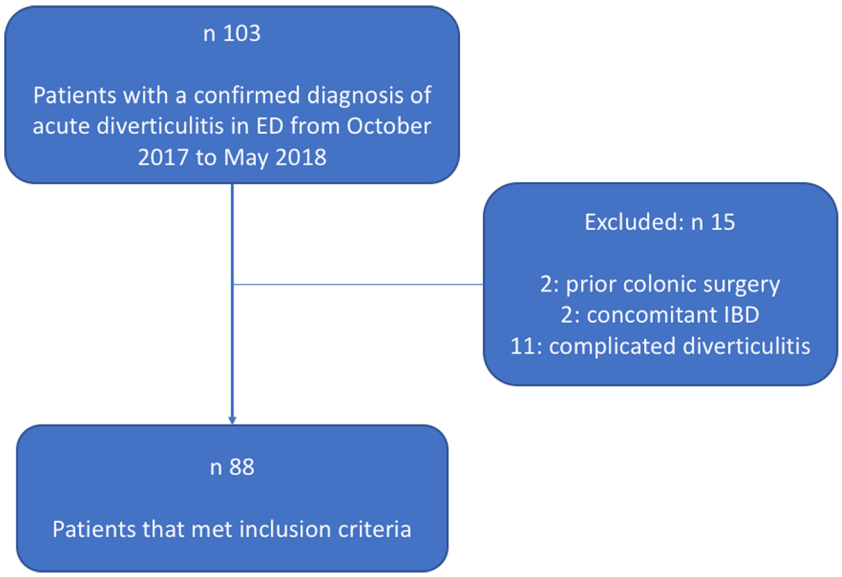

Fig. 1 Flow chart of the enrollment of the patients

Author contribution

All authors approved the final version of the manuscript.

Results

The two study groups were randomly well matched for age, gender, and grade of initial inflammation (mean C-RP value and mean VAS at enrollment), with no statistically significant difference (Table 1). All patients were well informed and took more than 95% of the prescribed doses for the 10 days of treatment. No dropouts were observed (0/88 patients). None of the patients recorded an "adverse experience" that forced them to interrupt their usual activity during the treatment periods.

All of the patients showed an AUD interesting the left colon, with only 3 patients presenting an extension of the diverticula also in the right colon, but with no sign of acute inflammation (assessed by CT scan).

Abdominal pain VAS evaluation

Mean reduction in grade of abdominal pain, based on the VAS scale completed by the patients, in the two groups in the period between days 1 and 3, days 1 and 5, days 1 and 7, and days 1 and 10 was compared.

Table 1 Characteristics of the two groups of subjects

	Group A no. 44	Group B no. 44	*p* value
Female/male	26/18	28/16	ns
Age (years)	62.2 ± 12.8	60.5 ± 14.5	ns
C-RP at enrollment (mg/L)	68.0 ± 8.8	71.3 ± 8.9	ns
VAS at enrollment	8.2 ± 0.2	7.9 ± 0.3	ns

On day 1, the mean abdominal pain value was 8.2 ± 0.19 for the *L. reuteri* group (group A), and 7.9 ± 0.27 for the placebo group (group B) (p = ns). On day 3, the *L. reuteri* group reported abdominal pain of 3.7 ± 0.22, with a reduction of 4.5 points on the VAS scale, while the value for the placebo group decreased to 5.6 ± 0.2, a reduction of 2.3 points ($p < 0.0001$). On day 5, the *L. reuteri* group reported abdominal pain of 1.5 ± 0.23, with a reduction of 6.6 points on the VAS scale from day 1, while the placebo group value decreased to 3.5–0.3, a reduction of 4.4 points from day 1 ($p < 0.0001$). On day 7, the *L. reuteri* group rated their abdominal pain at 0.6 ± 0.14, a reduction of 7.6 points on the VAS scale from day 1, while the placebo group value decreased to 2.2 ± 0.23, a reduction of 5.6 points from day 1 ($p < 0.0001$). Finally, on day 10, the *L. reuteri* group reported abdominal pain of 0.13 ± 0.06, a reduction of 8.1 points on the VAS scale from day 1, while the value for the placebo group decreased to 1.1 ± 0.25, a reduction of 6.7 points from day 1 ($p < 0.0001$; Fig. 2).

The mean delta reduction in abdominal pain from day 1 to day 3 was 4.5 VAS points in the *L. reuteri* group, compared with 2.3 in the placebo group ($p < 0.0001$; Fig. 3).

Grade of inflammation, C-RP evaluation

The mean change in C-RP, determined at enrollment and at 72 h from hospital admission, was compared. At enrollment, the *L. reuteri* group had C-RP of 68 ± 8.8 mg/L and the placebo group had C-RP of 71.3 ± 8.9 mg/L (p = ns). At 72 h from enrollment, the C-RP value was 22.6 ± 4 mg/L for the *L. reuteri* group, a significant reduction of 45.4 ± 5.3 mg/L from day 1 ($p < 0.0001$), while the C-RP mean value for the placebo group was 43.8 ± 5.2 mg/L, a

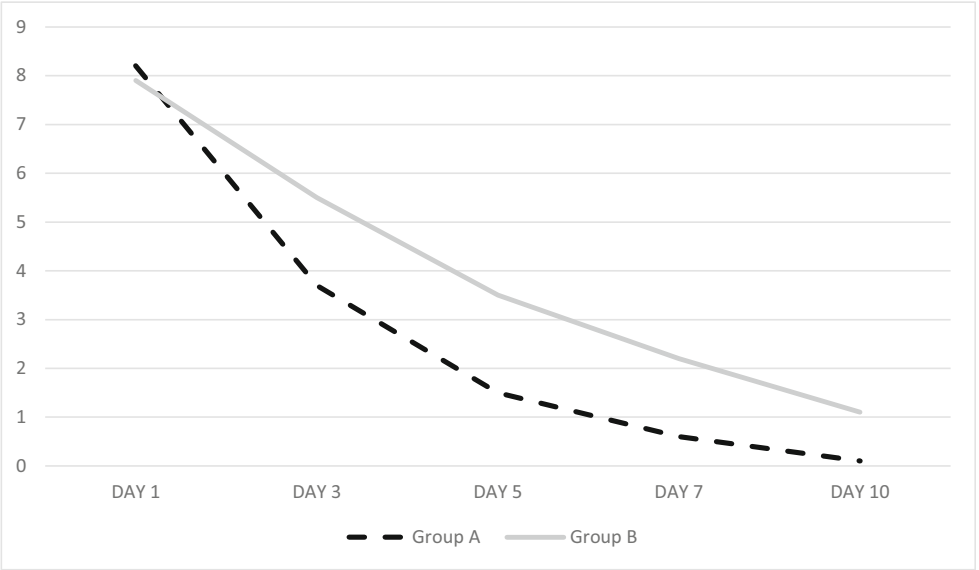

Fig. 2 Mean rating of abdominal pain, as assessed by the visual analog scale (VAS) completed by subjects in groups A (*L. reuteri*) and B (placebo) on days 1, 3, 5, 7, and 10

significant reduction of 27.5 ± 10.3 mg/L ($p < 0.004$). The mean reduction in C-RP after 72 h was significantly higher in the *L. reuteri* group than in the placebo group ($p < 0.0001$; Fig. 4).

Hours of hospitalization

Analysis of total hours of hospitalization in BOU between the two groups revealed that the *L. reuteri* group had a mean hospital stay of 93 ± 17 h (3, 8 days), while the placebo group had a mean hospital stay of 113 ± 20 h (4, 8 days) ($p < 0.0001$; Fig. 5).

Discussion

There are currently no studies in the literature that evaluate the use, and any benefits, of inclusion of probiotic in the treatment of AUD, apart from a small open study carried out by our group and published as a conference paper in 2017 [18]. Thus, this is the first ever randomized double-blind placebo study using an anti-inflammatory probiotic as an adjuvant in the standard antibiotic therapy for AUD.

At birth, the intestine is sterile, but after a few hours, it undergoes slow and progressive colonization, influenced by the vaginal bacterial flora and by the type of feeding of the newborn. In a first phase, the flora consists of bifidobacteria, and then the lactobacilli are added [19].

The distribution of bacteria differs qualitatively and quantitatively in various parts of the intestine. The flora has trophic and protective functions, contributes to the regulation of intestinal permeability, is involved in the processes of immunomodulation, and influences the motility of the gastrointestinal tract. Among the 500–1000 species that make up the intestinal microbiota, there are useful bacteria that do not induce an inflammatory response and do not activate the signal

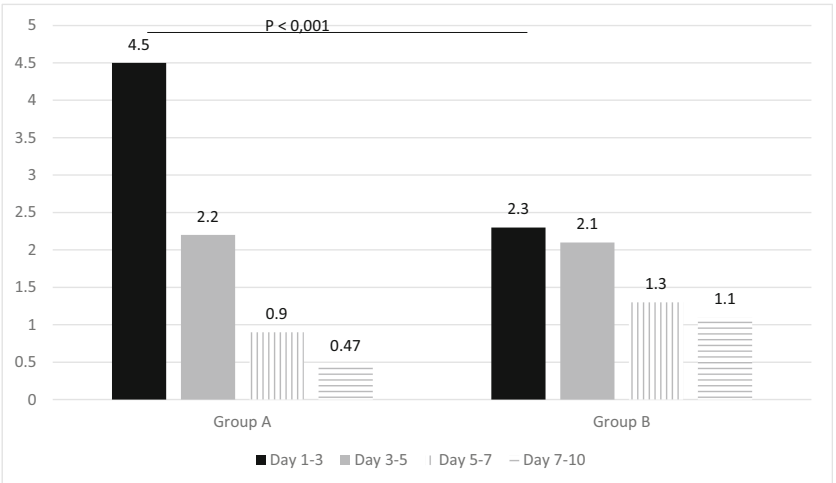

Fig. 3 Mean delta reduction of abdominal pain, as assessed by the visual analog scale (VAS) in subjects in groups A (*L. reuteri*) and B (placebo) for different subperiods during the study

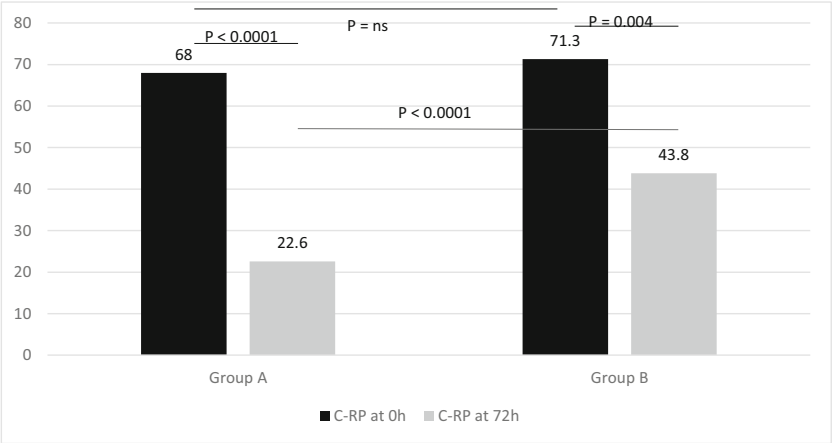

Fig. 4 Mean value of C-reactive protein (C-RP, mg/L) determined at enrollment and at 72 h, in subjects in groups A (*L. reuteri*) and B (placebo)

pathways that lead to the secretion of TNFα. There are also harmful bacteria which are able to bind to the toll-like receptors (TLR) on cell membranes and, through the MyD88 protein, dephosphorylate the inhibitor of NF-κB (IκB), allowing the latter to migrate into the nucleus and leading to overexpression of TNF-α and IL-8, generating pro-inflammatory effects [20]. In this way, an inflammatory response of type Th17 is activated. It is also able to influence the signal transmission pathways, and therefore pain, at the level of the submucosa.

Therefore, in the presence of a balanced flora and a healthy environment, there are no inflammatory reactions in the intestine and there is a state of well-being and health. If this balance is altered and a condition of dysbiosis or bacterial overgrowth develops, an inflammatory state that could be responsible for symptomatic diverticular disease is generated [21]. It follows that the intestinal microbiota should be a specific target of therapy in these pathological conditions.

In particular, an imbalance of gut microbiota, with bacterial overgrowth, is not only able to cause abdominal symptoms, but is also able to trigger a process which, over time, can lead to symptomatic diverticular disease and acute diverticulitis. Recent data on the clinical and natural history of the disease have highlighted many points in common with inflammatory bowel disease (IBD). In particular, in both diseases, there is an increase in pro-inflammatory cytokines, with a reduction in anti-inflammatory cytokines.

In a prospective study by Fric and Zarovral, in which 15 patients with a previous episode of AUD were treated with *Escherichia coli* strain Nissle 1917 [22], a longer period of clinical remission and improvement of gastrointestinal symptoms were observed. In a prospective randomized study by Tursi et al. [23] on 90 patients with AUD in remission, patients were randomized into three groups: treated with mesalazine, treated with probiotic (*L. casei*), and treated with a combination of probiotic and mesalazine. At the end of the study, the group treated with the combination of mesalazine and *L. casei* showed a total absence of symptoms, unlike the other two groups [23].

Recently, Kvasnovsky et al. performed a randomized double-blind placebo-controlled trial on the use of a multistrain probiotic composed by *Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175, and *Enterococcus*

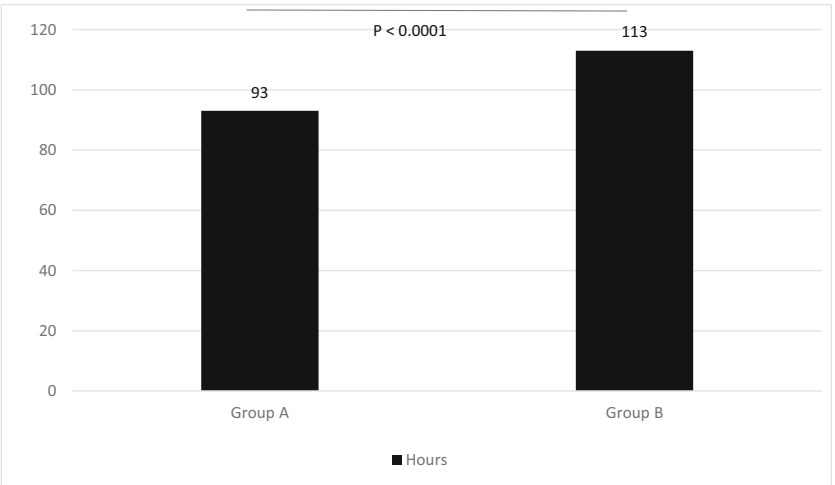

Fig. 5 Mean hours of hospitalization in the brief observation unit (BOU) in subjects in groups A (*L. reuteri*) and B (placebo)

faecium NCIMB 30176, in patients affected by SUDD. They concluded that the supplementation with probiotics do not improve the severity of abdominal pain, but it reduces the inflammatory markers [24].

A very interesting study was published in 2014 by Krokowicz et al. They evaluated the role of microencapsulated sodium butyrate (MSB) in patients with diverticulosis, analyzing its potential for reduction of diverticulitis episodes and in diverticulitis prevention in a randomized study. That concluded that MSB reduced the frequency of AUD and improved the quality of life of the patients [25].

However, these studies examined the remission period following an acute attack of diverticulitis, and not in the acute phase.

In our study, we used a particular strain of *L. reuteri* (strain 4659), which expresses mucus adhesins that exert immunoregulatory effects in the gut through modulating the Th1-promoting capacity of dendritic cells upon interaction with C-type lectins. These mucus adhesins also mediate anti- and pro-inflammatory effects by induction of interleukin-10 (IL-10), TNF-α, IL-1β, IL-6, and IL-12 cytokines [26].

Our study, showed for the first time, real-life use of this particular strain of *L. reuteri* in significantly reducing C-RP values compared with a placebo ($p < 0.0001$) in the first 3 days of treatment. This led also to a significant reduction in abdominal pain compared with the placebo ($p < 0.0001$). In fact, we confirmed that the degree of histological inflammation and the level of C-RP seems to correlate with the severity of disease, as in IBD. With the early reduction in inflammatory index, and consequently the reduction in abdominal pain suffered by the patients, we were able to discharge these patients faster (93 h compared with 113 h for the placebo group; $p < 0.0001$).

In conclusion, based on the results of this randomized placebo-controlled study, we suggest supplementation with *Lactobacillus reuteri* strain 4659 for patients with acute uncomplicated acute diverticulitis, because of its anti-inflammatory action, which allows more rapid healing. It also allows a treatment directly in the emergency department and faster discharge from hospital, providing economic benefits.

Compliance with ethical standards All patients gave written informed consent. The study was approved by the independent Ethics Committee of the Catholic University of Rome (ID 1398) and conducted in accordance with the Declaration of Helsinki. Subjects did not receive any payment for their participation in the study. Intention to treat and per protocol analysis was performed.

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