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The efficacy of a mix of three probiotic strains in reducing abdominal pain and inflammatory biomarkers in acute uncomplicated diverticulitis

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Abstract. – OBJECTIVE: Acute Uncomplicated Diverticulitis (AUD) is defined as the inflammation of a colon diverticulum, often involving colic wall and pericolic fat. Conventional treatment of AUD includes antibiotics, usually ciprofloxacin and metronidazole, fasting, and fluid therapy. The aim of this study was to test the efficacy of a mix of three probiotic strains (*Bifidobacterium lactis* LA 304, *Lactobacillus salivarius* LA 302, *Lactobacillus acidophilus* LA 201; Lactibiane Iki®, Biocure [PiLeJe Groupe], Italy/PiLeJe Laboratoire, France) in association with conventional antibiotics in treating AUD compared to conventional antibiotics used alone.

PATIENTS AND METHODS: We enrolled 84 (25M/59F mean age 61.5 ± 11.5 years) consecutive patients who came to the Emergency Department of the Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy, with a diagnosis of AUD confirmed by CT scan. After routine blood test and dosage of C-reactive protein (C-RP), patients were randomly divided into two groups: Probiotic group (42 patients, 10M/32F mean age 32.23 ± 10.3 years) was treated with ciprofloxacin 400 mg twice a day and metronidazole 500 mg three times a day for one week and simultaneously supplemented with the probiotic mix, 1 sachet twice a day for 10 days. Control group (42 patients, 15M/27F mean age 59.01 ± 11.3 years) received the same antibiotic treatment without the probiotic mix. All patients filled a daily Visual Analog Scale (VAS) for assessment of abdominal pain, with a range value from 0 (asymptomatic) to 10, and CRP value was determined on admission and at discharge.

RESULTS: As regards abdominal pain, on Day 3, Group A showed a significant decrease of 4.06 points (51.4%) in VAS score compared to a decrease of 2.79 points (34.9%) in Group B. On Day 5 the decrease was of 6.3 points (80%) in Group A and of 4.85 points (61%) in Group B. VAS score was reduced by 7.59 points (96%) in Group A and 6.1 points (76%) in Group B on Day 7 +, and by 7.8 points (99%) in Group A and 7.2 points (90%) in Group B on Day 10. About inflammation, Group A showed a decrease in C-RP value of 64%, compared to a decrease of only 35% in Group B. We also observed that the duration of hospitalization was significantly shorter for patients in Group A: 89 h (3.7 days) in Group A vs. 101 h (4.2 days) in Group B (p=0.03).

CONCLUSIONS: Our results indicated showed that the supplement with the probiotic mix of *Bifidobacterium lactis* LA 304, *Lactobacillus salivarius* LA 302, and *Lactobacillus acidophilus* LA 201 in combination with the standard antibiotic therapy for AUD reduced abdominal pain and inflammation significantly more than antibiotic treatment used alone. These findings could be due to the anti-inflammatory activity of the probiotic mix. Larger studies are needed to validate its use in the clinical practice.

Key Words:
Acute diverticulitis, Probiotics, Inflammatory index

Introduction

Acute diverticulitis is a constantly increasing health problem all around the world[1]. It is a condition described as an inflammation of the diverticula, often localized in the left side of the colon (especially in the Western population). However, diverticula can be extended to the sigma and the trasversus, never involving the rectum[2].

The physiopathology of acute diverticulitis is an area of continuous research, and actually it seems that it is activated by the interactions of two elements: individual predisposition and environmental factors. The most important factors

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include colonic stasis, obstruction of the diverticula, alterations of the gut microbiota, and localized intestinal ischemia[3].

In particular, an altered gut microbiota can induce, through a state of inflammation, altered activation of nerve fibres, leading to muscular and neuronal dysfunction, which favours the development of abdominal symptoms[4].

The clinical presentation of acute diverticulitis covers a very wide range of symptoms, going from mild abdominal pain to fever, peritonitis, and septic shock[5]. Using the Hinchey Classification[6], currently the gold standard for the diagnosis of this condition, an imaging-based scoring with CT scan, acute diverticulitis is commonly divided into uncomplicated (Hinchey 0/Ia) and complicated (Hinchey IbIV) diverticulitis.

According to Horesh et al[7], the management of acute uncomplicated diverticulitis (AUD) is conservative. This is actually an area of great interest and the use of antibiotics for optimal treatment is being very debated. The guidelines of the American Gastroenterological Association Institute suggest the use of antibiotics, fasting and supporting infusion therapy (level of evidence III, recommendation B)[8]. However, two trials, conducted on over 1000 patients, concluded that using no antibiotics in AUD is safe. In particular, it does not increase the severity of the condition nor does it increase the recurrences and the surgery rate in the follow-up period[9]. It should be noted, however, that in patients with fever, comorbidities, severe inflammatory index and in the elderly, the administration of antibiotics is still recommended[10].

Nonetheless, new strategies for the management of AUD need to be found. Being the alteration of gut microbiota one of the major factors implicated in acute diverticulitis, probiotics able to positively modify the balance of the gut microbiota could be useful in the management of AUD.

The beneficial effect of a supplementation with probiotics has been widely demonstrated in conditions like the symptomatic uncomplicated diverticular disease (SUDD) and in the remission period after an acute diverticulitis[11], but the effects of probiotics in acute diverticulitis have been poorly investigated.

A recent randomized controlled trial (RCT) of our group, the first in this area, demonstrated the efficacy of supplementation with *Lactobacillus reuteri* (strain 4659) in patients affected by AUD, concluding that it significantly reduced abdominal pain and inflammatory markers compared to a placebo[12].

In view of these interesting results, we decided to perform another study using a different type of probiotics, a mix of three probiotic strains composed of *Lactobacillus acidophilus* LA201, *Lactobacillus salivarius* LA302 and *Bifidobacterium lactis* LA304, that we selected because of the potential anti-inflammatory and analgesic effects of the strains it contains[13].

Study Objective

The objective of the present study was to evaluate the efficacy of supplementation with a mix of three probiotic strains composed of *Lactobacillus acidophilus* LA201, *Lactobacillus salivarius* LA302, and *Bifidobacterium lactis* LA304 in addition to the standard antibiotic therapy in patients affected by AUD.

The primary end point was the reduction of abdominal pain (Visual Analog Scale [VAS] score) and the reduction of inflammation (C-Reactive Protein [CRP] level) compared to a control group.

The secondary end point was the reduction of the duration of hospitalization in the group that received the supplementation with the probiotic mix compared to a control group.

Patients and Methods

An open label controlled-trial was conducted in 84 consecutive adult patients (25M/59F; mean age 61.5 ± 11.5 years) with a diagnosis of AUD (Hinchey 0) admitted to the Emergency Department (ED) of Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy, between October 2017 and May 2018.

Inclusion criteria were:
- At least 18 years old;
- Diagnosis of AUD (Hinchey score grade 0) confirmed by CT scan;
- Body temperature more than 38°C;
- No allergies to antibiotics;
- Signed informed consent.

Exclusion criteria were:
- Age <18 years;
- Pregnant or breastfeeding women;
- Inclusion in another clinical trial ending less than 7-10 days before;
- Documented intake of probiotics or antibiotics in the last 7-15 days;

- Major comorbidities or inflammatory bowel disease (Crohn's disease, ulcerative colitis) or previous colonic surgery;
- Allergies to contrast agents or antibiotics;
- Mental illness or inability to join the protocols or sign the informed consent.

Patients could withdraw from the study at any time (according to a personal choice) or in case of side-effects related to the drugs administered.

At enrolment, a physician collected the medical history of the patients, performed a physical examination, blood tests (cell count, liver and kidney function, electrolytes levels, C-Reactive Protein [CRP]) and an abdominal CT scan to confirm the diagnosis of AUD.

All patients received a VAS ranging from 0 (asymptomatic) to 10 (the worst pain possible) for assessment of abdominal pain during the treatment period.

Besides, they had to fill a diary for recording any adverse event occurring during the treatment, and every time they did not take the prescribed doses. At the end of the study, a physician analyzed all the diaries of the patients.

From October 2017 to May 2018, 109 patients obtained a confirmed diagnosis of AUD; 25 did not meet the inclusion criteria, specifically: 5 patients had a history of IBD, 4 patients had a history of previous colonic surgery, and 16 patients had an acute complicated diverticulitis (Hinchey > 0)[6] (Figure 1).

The remaining 84 patients were divided into two groups, using a randomized list in a 1:1 ratio provided by a statistical software:

- Probiotic group (n=42, 10M/32F mean age 32.23 ± 10.3 years): standard antibiotic therapy (ciprofloxacin 400 mg twice a day and metronidazole 500 mg three times a day for seven days) and supplementation with the probiotic mix twice a day for 10 days;
- Control group (n=42, 15M/27F mean age 59.01 ± 11.3 years): only standard antibiotic therapy (ciprofloxacin 400 mg twice a day and metronidazole 500 mg three times a day for seven days).

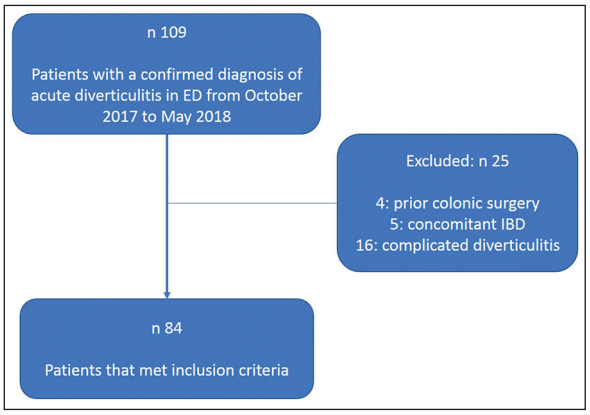

Figure 1. Study flowchart.

Blood tests and measure of the inflammatory marker C-RP were also performed 72 h after the start of the treatment.

All patients were instructed by the doctor that such a mix of probiotics could help in reducing the inflammation associated with diverticulitis.

The mix of probiotic strains contains 40×10^9 colony-forming units (CFU), specifically *Bifidobacterium lactis* LA 304 6×10^9 CFU, *Lactobacillus salivarius* LA 302 28×10^9 CFU, *Lactobacillus acidophilus* LA 6×10^9 CFU in a sachet form (Lactibiane® Iki, Biocure [PiLeJe Groupe], Italy/PiLeJe Laboratoire, France). One sachet was administered dissolved in water 30 min after meals twice a day. During the study period, patients were instructed to store the product at room temperature (25°C).

Protocol adherence was verified through sachet count in the boxes returned by patients on the day after finishing the treatment, and by directly asking patients about treatment accomplishment.

This investigation was approved by the independent Ethics Committee of the Catholic University of the Sacred Heart, Rome, Italy (ID 1520) and conducted according to the Declaration of Helsinki. Patients did not receive any grant for their participation in the study. Data were analyzed with intention to treat and per protocol analysis.

Statistical Analysis

A pilot study was used to calculate the sample size. Sample size ($\alpha = 0.05$, power 95%) resulted in a total of 84 patients divided in 42 patients per treatment. This number allowed to achieve statistical significance. We collected data in a database and analysed them using STATA 14 software for MAC; we expressed results as mean ± standard deviation (SD), with 95% confidence intervals. We used parametric and non-parametric statistical tests basing the choice on the type of variable examined and finally, we considered significant the value with a $p<0.05$.

Results

There were no statistically significant differences regarding age, gender, grade of initial inflammation (mean C-RP value), and mean VAS score at enrolment.

During the treatment period, none of the patients recorded adverse effect forcing them to interrupt their usual activity.

All patients were well informed of the importance of taking treatment and took more than 95% of the prescribed doses for the 10 days of treatment. No dropouts were observed (0/84patients).

As regards the extension of the diseases evaluated with abdominal CT scan, a majority of patients had an AUD in the left colon, with only 9 patients presenting an extension of the diverticula in the right colon.

Abdominal Pain Assessed on a VAS

All patients fulfilled the VAS until Day 10, with no dropouts.

On Day 1, the two groups showed a similar VAS score with a mean of 7.9 points for probiotic group and 8.0 for control group (p=0.74, ns; Figure 2).

On Day 3, probiotic group showed a mean VAS score of 3.84 points, meanwhile control group showed a value of 5.21 (p=0.0013), corresponding to a decrease of 4.06 points (51.4%) for probiotic group compared to a decrease of 2.79 points (34.9%) for control group.

On Day 5, mean VAS score was 1.6 points in probiotic group compared to 3.15 points in control group (p=0.0001). This corresponded to a decrease (from Day 1) of 6.3 points (80%) for probiotic group and of 4.85 points (61%) for control group.

On Day 7, probiotic group showed a mean VAS score of 0.64 points, whereas control group showed a mean VAS score of 1.9 points (p<0.0001), corresponding to a decrease (from Day 1) of 7.59 points (96%) for probiotic group and of 6.1 (76%) points for control group.

Finally, on Day 10, mean VAS score was of 0.1 point in probiotic group and of 0.8 points in control group (p=0.048). Therefore, between Day 1 and Day 10, mean VAS decreased by 7.8 points (99%) in probiotic group and by 7.2 points (90%) in control group.

C-Reactive Protein Level

At enrolment, C-RP level was not different between the two groups (76.44 mg/dl in probiotic group *vs.* 67.90 mg/dl in control group, p=0.48, ns; Figure 3).

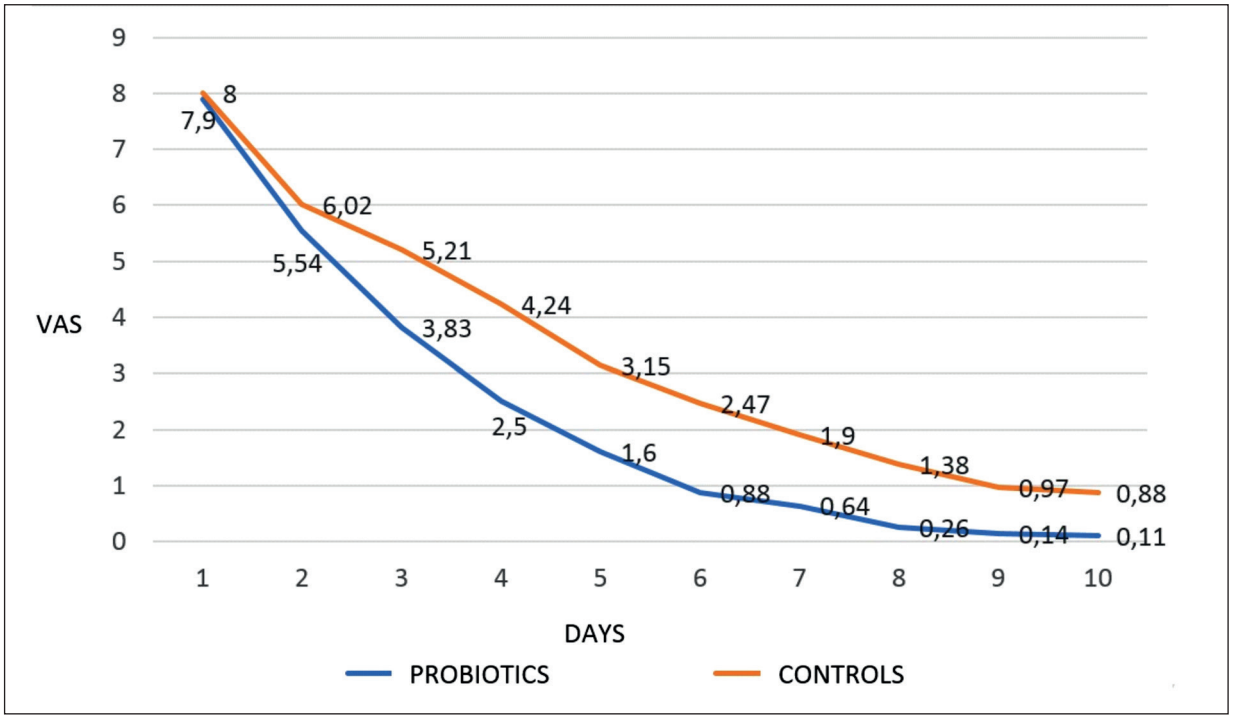

Figure 2. Comparison of abdominal pain assessed daily on a VAS by the patients

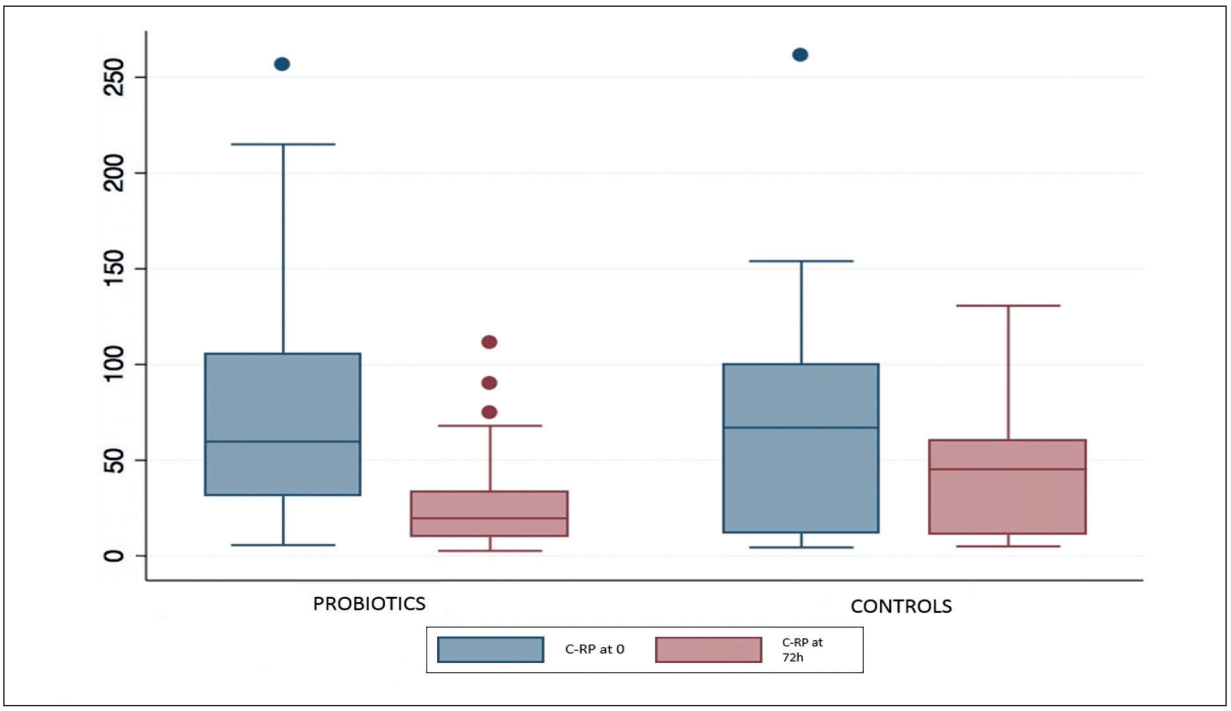

Figure 3. Comparison of mean C-reactive protein (C-RP) levels between the two groups at enrolment and at 72 h after the start of treatment.

At 72 h probiotic group showed a mean C-RP value of 27.46 mg/dl compared to a mean level of 46.16 mg/dl in control group (p=0.006). Therefore, the decrease in the inflammatory marker was of 64% in probiotic group and of only 35% in control group.

Duration of Hospitalization

Patients of probiotic group stayed in hospital for an average of 89 h (3.7 days), whereas mean duration of hospitalization of patients in control group was 101 h (4.2 days); there was a difference of 0.5 day between the two groups (p=0.03).

Discussion

This research shows that the supplementation with a mix of probiotics with an anti-inflammatory effect, during antibiotic treatment for AUD, is able to quickly reduce abdominal pain, inflammation, and duration of hospitalization.

Recently we published a randomized double-blind placebo controlled trial that evaluated the efficacy of *L. Reuteri* 4675 in addition to standard antibiotic therapy during an episode of AUD in ED in which similar results were reported. We observed a significant reduction of C-RP around 70% in probiotic group compared to less than 40% in placebo group (p<0.0001) after 72 h of treatment. Favorable results were also obtained in the management of abdominal pain with a reduction of 4.5 points on the VAS in interventional group compared to a reduction of only 2.3 points in placebo group after 3 days[12].

The pathogenesis of diverticulitis is still unknown. However, it seems to develop from obstruction of the diverticulum with bacterial overgrowth, local ischemia, and micro perforation. The luminal gut environment is colonized by microbiota that seems to play an important role in the pathogenesis of the disease[14].

Moreover, recently it has been observed that dysbiosis with a reduction of anti-inflammatory bacterial species may lead to mucosal inflammation. At the same time, the mucosal inflammation drives dysbiosis, hence creating a vicious cycle. Furthermore, both mucosal inflammation and dysbiosis could lead to dysmotility, which in turn predisposes to the translocation of bacteria from the diverticular lumen to the perivisceral area. At this level, an activation of receptors of innate immunity, namely Toll-like receptors, may occur with a consequent inflammatory response in the surrounding tissues[15].

Diverticulitis and IBD have common clinical manifestations, such as abdominal pain and rise of inflammatory markers, and share pathophysiological mechanisms; the latter, in particular, regard an imbalance between pro-inflammatory and anti-inflammatory cytokines.

It is well known that one of the current treatment options for IBD is immune modulation with probiotics. However, not all the probiotics show the same effects: specific strains may inhibit pro-inflammatory cytokines and influence the induction of T-reg cells, thus restoring intestinal homeostasis, whilst many others have not been proven to do the same[16]. This leads the clinician to carefully select the possible strain or combination of strains to be administered in the management of this disease.

L. salivarius Ls33 and *L. acidophilus* NCF have been proven to be, among the 13 strains considered by Foligne et al[16], two of the three best-performing probiotics in terms of increased induction of the anti-inflammatory IL-10 and reduced induction of the pro-inflammatory IL-12 in IBD patients.

Both *in vitro* and *in vivo* investigations suggested that the administration of *L. salivarius* Ls33 could improve the recovery of inflamed tissues in a rat colitis model[16,17]. Recently, Li et al[18] examined the potential anti-inflammatory effects of *lactobacillus acidophilus* and *biphidobacterium lactis* administered separately or in combination in IBD patients. Results showed that the combination of the two strains had better properties than the strains taken separately when it comes to modulating TLR2-mediated NF-κB and MAPK signalling pathways involved in IBD-related inflammation[18].

In our study, we clearly showed in the group supplemented with the mix of *Bifidobacterium lactis* LA 304, *Lactobacillus salivarius* LA 302, and *Lactobacillus acidophilus* LA 201 an important anti-inflammatory effect after 72 h of treatment with a C-RP decrease of 64% compared to a decrease of 35% in the control group treated only with antibiotics.

Another important data is the reduction of abdominal pain we observed. At enrolment the mean VAS score was very high (around 8) in the two groups. There was a significantly higher reduction in abdominal pain in probiotic group compared to control group throughout the study already from the third day of treatment. Abdominal pain is frequently observed in patients with AUD referred to ED and it seems to be related to visceral hypersensitivity. Recent reports indicate that the gut microbiota influences visceral perception of pain, thus suggesting a new approach for the treatment of this condition. It has been speculated that some probiotics may have an impact on the gut epithelial cells' expression of receptors that locally modulate the transmission of nociception to the intestinal nervous system.

Rousseaux et al[13] evaluated the efficacy of specific lactobacillus strains in pain control. *L. acidophilus* and *L. salivarius* strains induced a higher *in vitro* expression of opioid and cannabinoid receptors on gut epithelial cells. Moreover, in a murine model these strains showed an analgesic effect similar to that of morphine. Our choice of the combination of three strains tested was based on these immune modulatory effects and potentially analgesic properties.

Duration of hospital stay is an important factor to be considered. Recent data made available by two Italian groups have both shown an increasing hospitalization rate for acute diverticulitis over the past years. Binda et al[19] found 174,436 admissions from 2008 to 2015 by searching through the Italian Hospital Information System of the National Healthcare System. Between the first and the last year analyzed, an increasing rate from 39 to 48 per 100,000 inhabitants was observed. This is in line with Cammarota et al[20] that focused on the hospitalization rate for acute diverticulitis in the Abruzzo region during the last 10 years. They found an increment of 28.8% with a high impact on national costs.

Bollom et al[21], aimed at highlighting the national cost of ED visits in the US associated to acute diverticulitis from 2006 to 2013+, reported an increase of 105% in terms of economic burden.

Furthermore, the reduction of hospital beds has lately been one of the measures adopted by governments in different countries in order to face increasing expenditures. Our research shows that the use of probiotics by having a positive impact on both clinical symptoms and inflammation, reduces the length of stay (LOS): with an earlier decrease in inflammation and associated reduction of pain, patients were discharged sooner. This is expected to have a positive effect both in terms of cost-reduction for the health system and psychological impact for the patients.

To our knowledge, there are no other investigations in the literature that evaluated the beneficial effects of probiotics during an acute attack of AUD. While the efficacy of probiotics in prevention of recurrent diverticulitis is still under debate

and the evidence does not support it so far[22], the current study and our previous published trial provide evidence of their positive effect in the acute setting, thus enabling the clinician to manage AUD patients directly in the Brief Observation Unit of the ED and avoiding unnecessary hospitalizations into the hospital.

Limitations of our study are the open label design and the lack of a placebo control group. Howeover, it is well known that the degree of abdominal pain is affected by a placebo results; hence, part of the effect observed in this study could be due to such an effect. However, the reduction of C-RP, an objective parameter, shows that there is a modification of the gut microbiota with reduction of inflammatory cytokines by the specific strains we used.

Taking into account the increasing evidence advocating for non-antibiotic treatment strategies in AUD, following the application of new European guidelines and of the American Gastroenterological Association Institute Guidelines[14], it would be interesting to assess the efficacy of the use of specific probiotics used alone *vs.* placebo, with the possibility to confirm these results.

Conclusions

Supplementation with the probiotic mix of *Bifidobacterium lactis LA 304, Lactobacillus salivarius LA 302, and Lactobacillus acidophilus LA 201* in combination with the standard antibiotic therapy for AUD reduced abdominal pain and inflammation significantly more than antibiotic treatment alone. Moreover, we observed a reduction in the length of stay in the group treated with the probiotic mix.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Strate LL, Morris AM. Epidemiology, pathophysiology, and treatment of diverticulitis. Gastroenterology 2019; 156: 1282-1298.
2) Schieffer KM, Kline BP, Yochum GS, Koltun WA. Pathophysiology of diverticular disease. Expert Rev Gastroenterol Hepatol 2018; 12: 683-692.
3) Fagenholz PJ, de Moya MA. Acute inflammatory surgical disease. Surg Clin North Am 2014; 94: 1-30.
4) Wedel T, Böttner M. Anatomy and pathogenesis of diverticular disease. Chirurg 2014; 85: 281-288.
5) Meara MP, Alexander CM. Emergency presentations of diverticulitis. Surg Clin North Am 2018; 98: 1025-1046.
6) Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg 1979; 12: 85-109.
7) Horesh N, Wasserberg N, Zbar AP, Gravetz A, Berger Y, Gutman M, Rosin D, Zmora O. Changing paradigms in the management of diverticulitis. Int J Surg 2016; 33: 146-150.
8) Stollman N, Smalley W, Hirano I. AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the management of acute diverticulitis. Gastroenterology 2015; 149: 1944-1949.
9) van Dijk ST, Daniels L, Ünlü Ç, de Korte N, van Dieren S, Stockmann HB, Vrouenraets BC, Consten EC, van der Hoeven JA, Eijsbouts QA, Faneyte IF, Bemelman WA, Dijkgraaf MG, Boermeester MA; Dutch Diverticular Disease (3D) Collaborative Study Group. Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis. Am J Gastroenterol 2018; 113: 1045-1052.
10) Regenbogen SE, Hardiman KM, Hendren S, Morris AM. Surgery for diverticulitis in the 21st century: a systematic review. JAMA Surg 2014; 149: 292-303.
11) Ojetti V, Petruzziello C, Cardone S, Saviano L, Migneco A, Santarelli L, Gabrielli M, Zaccaria R, Lopetuso L, Covino M, Candelli M, Gasbarrini A, Franceschi F. The use of probiotics in different phases of diverticular disease. Rev Recent Clin Trials 2018; 13: 89-96.
12) Petruzziello C, Migneco A, Cardone S, Covino M, Saviano A, Franceschi F, Ojetti V. Supplementation with Lactobacillus reuteri ATCC PTA 4659 in patients affected by acute uncomplicated diverticulitis: a randomized double-blind placebo controlled trial. Int J Colorectal Dis 2019; 34: 1087-1094.
13) Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel J, Ardid D, Desreumaux P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. Nat Med 2007; 13: 35-37.
14) Rezapuour M, Stollman N. Antibiotics in acute uncomplicated diverticulitis: to give or not to give? Inflamm Intest Dis 2018; 3: 75-79.
15) Severi C, Carabotti M, Cicenia A, Pallotta L, Annibale B. Recent advances in understanding and managing diverticulitis. F1000Res 2018; 7. pii: F1000 Faculty Rev-971.
16) Foligne B, Nutten S, Grangette C, Dennin V, Goudercourt D, Poiret S, Dewulf J, Brassart D, Mercenier A, Pot B. Correlation between in vitro and in vivo immunomodulatory properties

of lactic acid bacteria. World J Gastroenterol 2007; 13: 236-243.

17) Peran L, Camuesco D, Comalada M, Nieto A, Concha A, Diaz-Ropero MP, Olivares M, Xaus J, Zarzuelo A, Galvez J. Preventive effects of a probiotic, Lactobacillus salivarius ssp. salivarius, in the TNBS model of rat colitis. World J Gastroenterol 2005; 11: 5185-5192.

18) Li SC, Hsu WF, Chang JS, Shih CK. Combination of lactobacillus acidophilus and Bifidobacterium animalis subsp. Lactis shows a stronger anti-inflammatory effect than individual strains in HT-29 cells. Nutrients 2019; 11. pii: E969.

19) Binda GA, Mataloni F, Bruzzone M, Carabotti M, Cirocchi R, Nascimbeni R, Gambassi G, Amato A, Vettoretto N, Pinnarelli L, Cuomo R, Annibale B. Trends in hospital admission for acute diverticulitis in Italy from 2008 to 2015. Tech Coloproctol 2018; 22: 597-604.

20) Cammarota S, Cargiolli M, Andreozzi P, Toraldo B, Citarella A, Flacco ME, Binda GA, Annibale B, Manzoli L, Cuomo R. Increasing trend in admission rates and costs for acute diverticulitis during 2005-2015: real-life data from the Abruzzo region. Therap Adv Gastroenterol 2018; 11: 1756284818791502.

21) Bollom A, Austrie J, Hirsch W, Nee J, Friedlander D, Ellingson K, Cheng V, Lembo A. Emergency Department burden of diverticulitis in the USA, 2006-2013. Dig Dis Sci 2017; 62: 2694-2703.

22) van Dijk ST, Rottier SJ, Van Geloven AAW, Boermeester MA. Conservative treatment of acute colonic diverticulitis. Curr Infect Dis Rep 2017; 19: 44.