Original Article

Effects of symbiotic preparations on constipated irritable bowel syndrome symptoms

*Luca Dughera, Chiara Elia, Monica Navino, Fabio Cisarò and the ARMONIA Study Group**

Motility and Endoscopy Unit, Department of Gastroenterology and Clinical Nutrition, San Giovanni Battista Hospital, Torino, Italy

Abstract. *Background:* Prebiotic and probiotic therapies are new strategies that are being used to treat different gastrointestinal diseases, such as irritable bowel syndrome, diverticular disease and inflammatory bowel diseases. *Aims:* Evaluating the effects of a symbiotic preparation on symptoms and colonic transit in patients with irritable bowel syndrome and significant bloating. *Methods:* We carried out an open-label, prospective, uncontrolled, multicenter trial on 129 patients meeting Rome II criteria for irritable bowel syndrome who did not have lactose malabsorption, abdominal surgery, overt psychiatric disorders and ongoing psychotropic drug therapy or ethanol abuse. For three months, the patients were treated with a symbiotic preparation and were investigated trough questionnaires on symptoms. Data on bloating and abdominal pain were obtained using the McNemar-Bowker's test, while data on stool frequency were evaluated using the t-test. *Results:* The administration of a symbiotic preparation to these patients modified the clinical picture and intestinal function, with a significant increase of stool frequency. *Conclusions:* Our data, although the study had an open design, represent a further analysis of positive symbiotic effects on clinical manifestations and intestinal function in patients with irritable bowel syndrome.

Key words: Probiotics, Bifidobacteria, Irritable Bowel Syndrome

Introduction

Irritable bowel syndrome (IBS) is a common disorder throughout the world. Between 10% and 15% of the population living in North America reports IBS symptoms (1). Women are twice as likely to experience these symptoms than men (2). IBS prevalence varies minimally with the age (3). Although only 30% of subjects with IBS refers their symptoms to their physician, IBS accounts for approximately 12% of primary care visits and for approximately 28% of gastroenterologic visits (4). IBS patients have a lower quality of life, take more time off from work, and use more health care resources than those without IBS (5, 6).

Typical symptoms of IBS are abdominal discomfort or pain, usually located in the lower abdomen, associated with changes in frequency of bowel movements or in stool shape or appearance (7). Other symptoms associated with IBS include mucous stool, rectal urgency, bloating, and abdominal distention. Most commonly, Rome II criteria, established by an international group of IBS experts, are used for making a diagnosis. According to the Rome II criteria, symptoms of IBS must be present for at least 12 weeks or, either continuously or intermittently, over the previous 12 months (8, 9).

Luckey (1974) (10) popularized the idea that the gastrointestinal tract and organisms living in its lumen

* The Armonia Study Group: Gianpiero Aimo (Brescia); Anna Bertelè (Parma); Carlo Calabrese (Bologna); Isabella De Felici (Roma); Giuseppina Diligente (Aversa); Ingrid Febbraro (Roma), Angelo Franzè (Parma); Walter Fries (Messina), Marco Martorano (Sapri), Vincenzo Scifo (Augusta); Luigi Villardo (Cosenza)

constitute an ecologic unit. Metabolism and function of this ecologic unit affect the host. All the components of such ecologic unit are important and dependent among each other. If there is a major change in any of the components all the other ones are affected.

The human gut hosts different strains of bacteria, some of which play a key role in a correct physiological intestinal function (11). Intestinal anaerobic microflora represents an energy source for the host through the metabolism of non-digestible carbohydrates and the transformation of proteins into short chain fatty acids, which can then be absorbed (12). Intestinal microflora is able to synthesize vitamins as well as essential amino acids, and it also acts as an efficient barrier against pathogens. Bifidobacteria spp. are dominant in the intestinal microflora and they play antibacterial actions against non-dominant and potentially pathogenic species, such as Clostridia and *Escherichia coli* (13).

Probiotics are live microbial feed supplements that benefit the host by improving the intestinal microbial balance. When they are assumed as yogurts, they fall into the functional foods class. Functional foods include probiotics, prebiotics, and, to a certain extent, dietary fiber. Prebiotics are non-digestible feed ingredients or supplements that alter the intestinal flora and stimulate the growth of beneficial bacteria (14, 15). It has been demonstrated that oral administration of probiotics modifies the fermentation mechanism in the large intestine, increasing the absolute count of Lactobacilli and Bifidobacteria in the stool (16, 17), whereas the association with a prebiotic facilitates the proliferation of Bifidobacteria and of other non pathogens (18).

A symbiotic drug (zir fos® Alfa Wassermann, Alanno Scalo, Pescara, Italy) has recently become available in the clinical practice; this preparation is constituted by a probiotic, *Bifidobacterium longum* W11 ($5x10^9$ cfu), which is known to antagonize the action of pathogens (19, 20) and by a prebiotic short-chain oligosaccharide, Fos-Actilight (2.5 g). The administration of high doses of a specific strain of Bifidobacteria and of its best nutrients favours the probiotic replication in the large intestine and the natural balance of gut microflora (21). Changes in fermentative activity of the intestinal bacteria lead to a normalization in gas production and to an acidification of the luminal pH with positive results for the whole body (22).

Although some very promising data have been recently published (23), an extensive review on literature concerning efficacy and safety of the probiotic administration in IBS patients reports very few studies with poor results (24).

In order to further investigate this issue, this trial was carried out to verify clinical efficacy and tolerability of a long-term treatment with a symbiotic preparation in patients with the constipation-predominant irritable bowel syndrome.

Patients and methods

Study design

This is an open-label, prospective, uncontrolled, multicenter study performed in 10 Italian gastroenterological centers. A written informed consent was obtained from each participant.

All subjects received the symbiotic preparation at breakfast time at the dose of 3 g (one bag) for three months. Patients were evaluated at the beginning of the study (T0), at one month (T1) and at the end of treatment (T3) through medical interview and physical examination. A Functional Bowel Disorder questionnaire was administered to all patients for the first, the second and the third month to investigate symptoms, stool frequency, concomitant treatments and/or comorbidity. The stool shape was evaluated daily by Bristol's classification and furthermore patients noted the number of passages.

Lower abdominal pain, bloating and tenesmus were evaluated as None = no symptoms; Slight = symptoms didn't influence daily activity; Moderate = symptoms could influence daily activity; Severe: symptoms influenced daily activity.

The well-being was evaluated as mediocre (influencing patient's daily activity), moderate (could have influenced patient's activity), excellent (patient was in perfect health, without symptoms). Lower abdominal pain and bloating were evaluated at each visit by the clinician through a Visual Analogic Scale (VAS). Furthermore, the questionnaire inquired about drug tolerability and the subjective impression regarding efficacy on symptoms.

Patients

All subjects were informed about the aims of the study and were free to participate or not. The ethics comitee approved the study.

A total of 129 patients were enrolled in the study: 38 males and 91 females, with a M/F ratio of 0.65; the mean age was 44±13 years and the mean weight was 65±12 kilograms. Table I reports the demographic and clinical characteristics of the study population: no difference was documented in terms of age, weight and history of constipation between males and females. No diets should be used during the treatment. At the entry in the study 29% of the subjects reported a regular intake of fiber, 17% reported a laxative abuse and 31% reported a consumption of antispasmodic agents more than three times per week. All patients had a diagnosis of constipation-predominant IBS, according to Roma II criteria. Therefore, each patient should have referred abdominal discomfort or pain for at least 12 weeks (not necessarily consecutive) in the previous 12 months; furthermore, pain should be usually relieved with defecation and/or associated with a change in stool frequency and/or shape. Moreover, at least one of the following conditions should have been present: stool frequency < 3 times per week, hard stools and forced evacuation.

Patients with organic constipation, psychiatric disorders or neoplastic diseases were excluded from the study, as well as those who seemed scarcely compliant to the treatment protocol or who denied to subscribe the informed consent form.

Statistical analysis

Descriptive statistical variables such as average, minimum and maximum standard deviation, absolute and relative ratio for quantitative variables were used.

Table 1. Demographic and clinical characteristics of the enrolled patients (mean ± SD)

	Males	Females	p
Patients (n)	38	91	
Age (years)	42±13	45±13	ns
Weight (kg)	77±12	61±8	ns
Constipation duration (average, years)	5.54±7.7	7.14±9.3	ns

The comparison between pre- and post-treatment variables (bloating and abdominal pain) as well as the end-study conclusions were accomplished by the McNemar-Bowker's symmetry test, a non-parametric test for two related dichotomous variables which tests for changes in responses using the chi-square distribution; this test is useful in detecting changes in responses due to experimental intervention in a "before-and-after" design (25). P value <0.05 is considered as significant. The variability between the average values of pre- and post-treatment variable "stool frequency" was evaluated using a t-test for paired data. P values <0.05 were considered as significant. The statistical analysis was performed using the SPSS Statistical Package, version 10.0.

Results

Effects of symbiotic administration on abdominal pain and bloating, as graded by VAS, are shown in Figure 1: a significant total symptom frequency reduction (p<0.0001) was observed at T1 and T3 versus T0. Mean values for abdominal pain were 13.8±20.2 at T0, 11.4±17.7 at T1 and 8.9±15.9 at T3, with a mean reduction rate of 2.36 (T1 vs T0) and 5.02 (T3 vs T0). Mean values for bloating were 14.8±20.3 at T0, 12.4±18.4 at T1 and 8.6±14.4 at T3, with a mean reduction rate of 2.38 (T1 vs T0) and 5.90 (T3 vs T0).

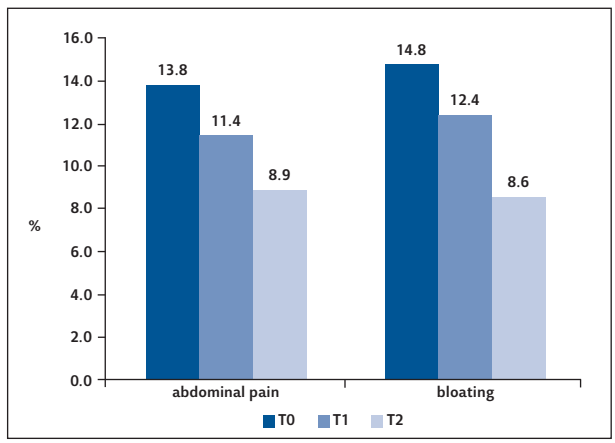

Figure 1. Symbiotic preparation effect on the severity of abdominal pain and bloating. The reduction rate is evaluated by the Visual Analogic Scale measurements recorded at each visit. T1 vs T0 and T3 vs T0, p <.0001, t-test for paired data

No differences were shown between males and females and between different ages.

The symbiotic preparation treatment had a strong positive effect on stool frequency: mean stool frequency before treatment was 12.8±7.1; indeed, a significant ($p<0.001$) increase of movements per month (14.7±8.7 during the first month, 15.8±7.8 during the second month and 16.96±7.8 at the end of treatment) was documented (Figure 2).

Furthermore, when symptoms have beeen stratified for severity on the basis of the reported VAS scales, the symbiotic preparation showed a significant effectiveness for moderate-to-severe "abdominal pain" and "bloating", as described by the symmetry test that was statistically significant ($p<0.0001$) when applied to variables as described by the patient at the beginning of the study and at the end of the treatment (Figures 3 and 4).

Treatment was very well tolerated: no significant side effects were observed and only mild and transient dyspepsia was recorded in one female subject.

Discussion

The results of the present study demonstrate that the administration of a symbiotic preparation for three months to patients with constipation-predominant IBS modifies not only the clinical picture, reducing predominant symptoms such as abdominal pain and bloating in patients with moderate to severe symptoms at the enrolment, but also modifies intestinal function significantly increasing stool frequency on a monthly basis.

The role of intestinal microflora and its qualitative and quantitative variations in patients with IBS has been focused: Salminen (1998) (14) observed a reduction of Lactobacillus spp., E. coli spp. and Bifidobacteria in the stools of patients with IBS compared to healthy controls, whereas (26) a predominance of E. coli, Proteus spp. and Clostridium spp. was also reported. Moreover, microflora composition correlates with abnormal fermentation, leading to increased gas production, which may cause bloating (17) and it was also demonstrated that the administration of Lactobacillus strictly correlates with a reduction of abdominal pain and flatulence (9). The largest trial published to date

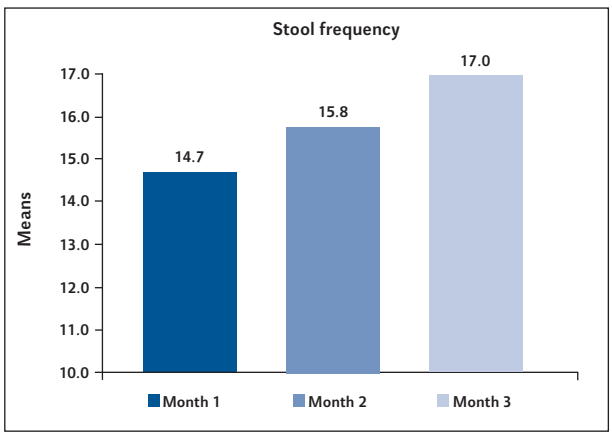

Figure 2. Symbiotic preparation effect on stool frequency. Results are expressed as mean increase of number of passages per month. Month 3 vs Month 1 p <.001, t-test for paired data.

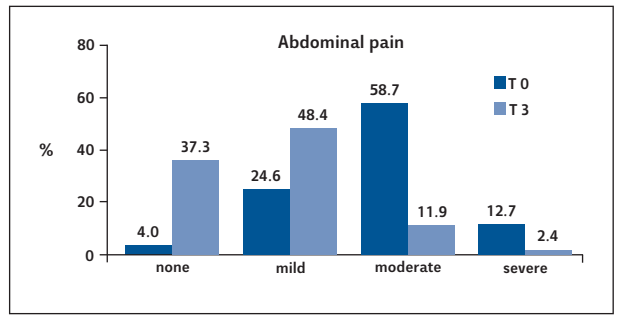

Figure 3. Comparison between abdominal pain characteristics at the beginning and at the end of the study. The variation rate is compared by the McNemar-Bowker's symmetry test, while the variability between the average values of pre- and post-treatment variables.T3 vs. T0 p<.0001

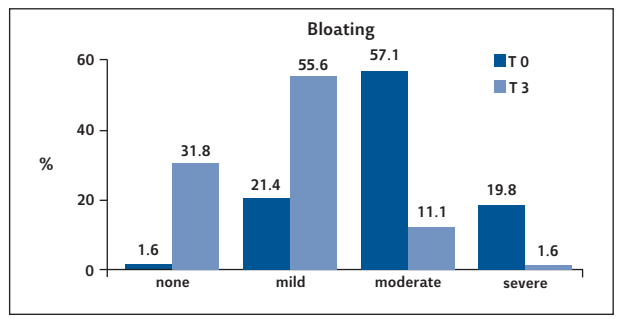

Figure 4. Comparison between bloating characteristics at the beginning and at the end of the study. The variation rate is compared by the McNemar-Bowker's symmetry test, while the variability between the average values of pre- and post-treatment variables. T3 vs. T0 p<.0001

(27) demonstrated a significant clinical improvement with the treatment with Bifidobacterium spp., but not with Lactobacillus spp. or placebo. This study also provided novel data about changes in inflammatory cytokines, which might help to explain the beneficial observed effect. There is currently great interest in how the balance between IL-10 and IL-12 in the gut mucosa determines T-cell responses. IL-10 derived from both regulatory T-cells and other immunocytes acts limiting the immune response and minimizing collateral damage in the mucosa (28) by the inhibition of tumor necrosis factor α, IL-6, and interferon γ secretion. IL-10 also inhibits antigen-presenting cell function by inhibiting MHCII and B7 expression and hence T-cell activation and IL-12 production. There are several recent reports on low-grade mucosal inflammation in IBS with increased mucosal T-lymphocytes in both unselected diarrhea-predominant IBS (29) and in IBS beginning with an acute episode of bacterial gastroenteritis (30). It has been also reported that IBS patients show an immune pro-inflammatory phenotype (Th-1) and that Bifidobacteria, but not Lactobacilli, exert an immunomodulating effect on dendritic cells, increasing IL-10 production and thus inhibiting Th-1 lymphocyte generation (31).

One of the main goals when treating patients with constipation-variant IBS is to increase stool frequency. An increase in fecal mass has to be reached with the administration of drugs other than probiotics, mainly acting on intestinal motility. Non-absorbable carbohydrates such as oligofructose and inulin (32) as well as FOS (33) induce an increase in stool frequency through an increase in fecal hydration and mass. Changes in intestinal transit are one of the mechanisms that might be responsible for symptoms in IBS patients: a reduction in the interdigestive motility phase III was demonstrated in patients with IBS and bacterial overgrowth, and the antibiotic treatment normalized intestinal motility (34). The use of a symbiotic product may cause an acceleration of intestinal transit as well as a modification of intestinal microflora, thus ameliorating symptoms better than probiotics alone. The increase in stool frequency documented in this study can be explained on the basis of the specific characteristics of the symbiotic tested. In fact, the symbiotic preparation included strains of *Bifidobacterium longum* W11, one of the most representative species of gut microbiota, and fructose oligosaccharides, which exert a positive effect on intestinal motility and favor the development of Bifidobacteria in the gut lumen.

To date, one previous trial described the positive effect of a symbiotic preparation in IBS patients, with a significant increase in Lactobacilla, Eubacteria and Bifidobacteria in the gut lumen, but this specific treatment needs to be given on a cyclic schedule because of the temporary modification of the fecal flora (35). Moreover, in a large italian multicenter open label trial, it was recently demonstraded that a symbiotic preparation can increase stool frequency in patients with constipation-variant IBS and reduce abdominal pain and bloating in those with moderate-severe symptoms (23).

Further studies are needed to confirm these results, particularly large and randomized clinical trials in order to define the clinical role of symbiotic administration in patients with IBS. However, this study, although performed with an open-label design and a limited number of patients, confirms recent data indicating that the administration of a symbiotic agent in patients with constipation-variant IBS improves intestinal function and ameliorates the clinical manifestations of the disease.

References

1. Saito YA, Schoenfeld P, Locke GR III. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol 2002; 97: 1910-5.
2. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders: prevalence, sociodemography, and health impact. Dig Dis Sci 1993; 38: 1569-80.
3. Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. J Intern Med 1994; 236: 23-30.
4. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterology 1997; 112: 2120-37.
5. Akehurst RL, Brazier JE, Mathers N, et al. Health-related quality of life and cost impact of irritable bowel syndrome in a UK primary care setting. Pharmacoeconomics 2002; 20: 455-62.

6. Shih YC, Barghout VE, Sandler RS, et al. Resource utilization associated with irritable bowel syndrome in the United States 1987-1997. Dig Dis Sci 2002; 47: 1705-15.
7. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. Gut 1999; 45(Suppl II): II43-II47.
8. American Gastroenterological Association medical position statement: irritable bowel syndrome. Gastroenterology 2002, 123: 2105-7.
9. De Giorgio R, Barbara G, Stanghellini V, Cremon C, Salvioli B, De Ponti F, Corinaldesi R. Diagnosis and therapy of irritable bowel syndrome. Aliment Pharmacol Ther 2004; 20 (Suppl. 2): 10-22.
10. Luckey TD. The villus in chemostat man. Am J Clin Nutr 1974, 27:1266-76.
11. Guarner F, Malagelada JR. Gut flora in health and disease Lancet 2003; 360: 512-9.
12. Cummings JH, Macfarlane GT. A review. The control and the consequence of bacteria fermentation in the human colon. J Appl Bacteriol 1991; 70: 443-59.
13. Gibson GR,Wang X. Regulatory effects of bifidobacteria on growth of other colonic bacteria. J Appl Bacteriol 1994; 77: 412-20.
14. Salminen S, Bouley C, Boutron-Routron MC, Cummings JH, Franck A, Gibson GR, Isolauri E, Moreau MC, Robertfroid M, Rowland I. Functional food science and gastrointestinal physiology and function. Br J Nutr 1998; 80, Suppl. 1, S147-S171.
15. Floch MH, Hong-Curtiss JA. Probiotics and functional foods in gastrointestinal disorders. Curr Opin Gastroenterol 2001; 3: 343-50.
16. Roberfroid MB. Prebiotics and probiotics: are they functional foods? Am J Clin Nutr 2000;71(suppl):1682S-7S.
17. King TS, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. Lancet 1998; 352: 1187-9.
18. Gibson GR, Ottaway PB, Rastall RA. Prebiotics: new developments in functional foods. Oxford: Chandos Publishing ltd. 2000.
19. Shi-Shun Zhong, Zhen-Shu Zhang, Ji-De Wang, Zhuo-Sheng Lai, Qun-Ying Wang, Ling-Jia Pan, Yue-Xin Ren. Competitive inhibition of adherence of enterotoxigenic Escherichia coli, enteropathogenic Escherichia coli and Clostridium difficile to intestinal epithelial cell line Lovo by purified adhesin of Bifidobacterium adolescentis 1027. World J Gastroenterol 2004 June 1; 10 (11):1630-3.
20. Gibson GR, Wang X. Regulatory effects of bifidobacteria on the growth of other colonic bacteria. J Appl Bacteriol 1994; 77(4): 412-20.
21. Van Loo JAE. Prebiotics promote good health. The basis, the potential, and the emerging evidence. J Clin Gastroenterol 2004; 38: Suppl. 3, S70- S-75.
22. Fabrizis Suarez L, Levitt MD. An understanding of excessive intestinal gas. Curr Gastroenterol Report, 2005; 2: 413-419.
23. Colecchia A, Vestito A, La Rocca A, Pasqui F, Nikiforaki A, Festi D. Effetto di una preparazione simbiotica sulle manifestazioni cliniche della sindrome dell'intestino irritabile variante stipsi. Minerva Gastroenterol Dietol 2006;52, 349-58.
24. Floch MH. Use of diet therapy in the irritable bowel syndrome. Analysis of the literature. J Clin Gastroenterol 2005; 39(Suppl 3): S243-S246.
25. May, WL, Johnson, WD. Symmetry in square contingency tables: tests of hypotheses and confidence interval construction. J Biopharm Stat 2001; 11(1-2): 23-33.
26. Drossman DA. The functional gastrointestinal disorders: Diagnosis, pathophysiology and treatment. A multinational consensus. Boston: Little Brown, 1994.
27. O'Mahoney L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, Quigley EM. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology. 2005;128(3):541-51.
28. O'Garra A, Vieira PL, Vieira P, Goldfeld AE. IL-10-producing and naturally occurring CD4+ Tregs (limiting collateral damage). J Clin Invest. 2004;114:1372–8.
29. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, et al. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology, 2002; 122: 1778–83.
30. Wang LH, Fang XC, Pan GZ. Bacillary dysentery as a causative factor of irritable bowel syndrome and its pathogenesis. Gut, 2004; 53: 1096–101.
31. Hart AL. Modulation of human dendritic cell phenotype and function by probiotic bacteria. Gut, 2004; 53: 1602-9.
32. Gibson GR, Beatty ER, Wang X, Cunnings J. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. Gastroenterology 1995; 108: 975-82.
33. Hidaka H, Tashiro Y, Eida T. Proliferation of bifidobacteria by oligosaccharides and their useful effect on human health. Bifidobacteria. Microflora 1991; 10: 65-79.
34. Pimentel M, Soffer EE, Chow EJ, Kong Y, Lin HC. Lower frequency of MMC is found in IBS subjects with abnormal lactulose breath test, suggesting bacterial overgrowth. Dig Dis Sci 2002; 47: 2639-43.
35. Tsuchiya J, Barreto R, Okura R, Kawakita S, Fesce E, Marotta F. Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome. Chin J Dig Dis 2004; 5(4): 169-74.

Accepted: 16th July 2007
Correspondence: Luca Dughera, MD
S.S. Motilità ed Endoscopia Digestiva A.O. S. Giovanni Battista
Via Genova, 3
10123 Torino, Italy
E-mail: luca.dughera@libero.it, www.actabiomedica.it