

FIGHTING FOR GUT HEALTH IN FEMALES WITH FUNCTIONAL DIGESTIVE TROUBLES

Doina Georgescu(1), Corina Neanu(2), Daniel Lighezan(3)

(1) Ist Department of Internal Medicine, University of Medicine and Pharmacy “V Babes”, 2 Piata Eftimie Murgu, Timisoara, Romania, tel +40722595228, e mail: dgeorgescu@hotmail.com , corresponding author

(2) Medical Psychological Centre, 49 A Surorile Martir Caceu, Timisoara,Romania, tel+40724680136

(3) Ist Department of Internal Medicine, University of Medicine and Pharmacy “V Babes”, 2 Piata Eftimie Murgu, Timisoara, Romania, tel +40744558151

ABSTRACT: We wanted to assess how much would be the impact of a multilevel treatment with dietary supplements derived from purified natural nutrients and life style changes on symptoms related to constipation predominant irritable bowel syndrome(IBS). 21 naïve female patients, age=41,55±16,92 years, nonsmokers, non lactose intolerant, without proven food allergies, diagnosed with predominant constipation IBS according to Rome II criteria, joined a nonrandom open label pilot study. We assessed main symptoms using Mc Gill questionnaires part A and B and a Hydrogen expiratory test was performed before and after the treatment. After therapy differences were statistically significant for bowel habit, flatulence, bloating, incomplete evacuation and global status scores and not statistically significant for abdominal pain scoring. Hydrogen values measured at 15,30,60 and 120 minutes changed significantly after the treatment. In conclusion prebiotics, probiotics and activated charcoal associated to life style changes mitigated most of our female patients symptoms related to IBS.

KEY WORDS: Irritable bowel syndrome (IBS), multilevel treatment

1. Background Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain and altered bowel habits in the absence of specific and unique organic pathology, very often seen in modern, active woman.

IBS and so called modern life style are close related. Stress, alimentation with fast food type products and diet with over processed nutrients make us all candidates for intestinal disorders that could turn us into weak people, less energetic and less immune responsive. Apparently women are prone to this kind of disorder possibly as a consequence of specific reactivity patterns. More than half of ambulatory gastroenterological visits are related to functional disorders like those of IBS. Subsequently a lot of women having these complains have a low quality of life, professional and family malfunctions, require a lot of medical attention, also resulting in important social costs. This is why a lot of working have been done to understand the causes and the most efficient treatments of this disorder. Among many possible pathways, small bowel bacterial overgrowth and unbalanced gut microbiota, have been heralded as a unifying mechanism for the symptoms of bloating and distention common to patients with irritable bowel syndrome. This has led to proposed treatments with prebiotics, probiotics and antibiotics.

As seen in the table below there are a lot of bacterial species found in the human surfaces.

Table 1. Normally bacteria commonly found on the surfaces of the human body[7]

The gut is a huge, internal surface, where a lot of things occur when it comes for bacteria. Normally there is a balanced between different species as a result of a permanent underground fighting for taking over. Briefly, we could say that there is “good” and “bad” gut bacteria. There are studies demonstrating that stress, dietary particularities, traveling, orally antibiotics could influence this very sensitive balance and pushed the “bad” bacteria to overgrowth.

Among this, there is happily the “good Samaritan”, as Bifidobacteria, positive, non-sporeforming, lactic acid bacteria, that have been described as “friendly” bacteria in the intestine of humans. Bifidobacterium bifidum is the predominant bacterial species in the intestine of breast-fed infants, where it presumably prevents colonization by potential pathogens.

Figure 1 Gram stain for Lactobacilli. (Source Todar’s textbook of bacteriology. The Normal Bacterial Flora of Humans. Online Edition ; free access: page 1-5)[7]

These bacteria are sometimes used in the manufacture of yogurts and are frequently incorporated into probiotics.

Hydrogen breath tests are based on the physiological fact that healthy humans when fasting and at rest do not exhale hydrogen. As hydrogen is only generated during anaerobic metabolism and the human organism at rest does not have anaerobic metabolism, the hydrogen excreted with the exhaled air must originate from anaerobic bacteria[1].

2. Aim The rationale of the study was to assess how much would be the impact of a particular treatment with dietary supplements derived from purified natural nutrients as friendly

environmental remedies associated to life style changes, on some symptoms related to intestinal disorders and further on the quality of life of female patients with constipation predominant IBS, viewing the bowel as a part of a giant, complex, ecological system.

3. Patients and methods: 21 naïve female patients, age=41,55±16,92 years, nonsmokers, non lactose intolerant, without proven food allergies, diagnosed with predominant constipation IBS according to Rome II criteria, at the First Department of Internal Medicine, University of Medicine and Pharmacy, “V Babes”, Timisoara, Romania, were enrolled in a nonrandom open label pilot study. We have studied main symptoms as: abdominal pain, alteration in bowel habit, incomplete evacuation sensation, bloating and flatulence with scoring assessment according to Mc Gill scale part A for global status from 0-10 points(0=very bad to 10=excellent condition),and B from 0-10 points(0 = symptom to 10= severe symptoms), as shown in figure below:

Figure 2 Mc Gill questionnaires part A and B[16]

Main symptoms were assessed as a self symptom evaluation, before and after the treatment, patients being assisted by a qualified psychologist.

An expiratory hydrogen test(Expirogrowth H₂ breath test), as an indirect assessment of an overgrowth bacterial gut IBS studied population, in fasting state and 15,30,60 and 120 minutes after ingestion of the test substance(10 grams lactulose solved in 100 ml water) was performed in 10 healthy female controls and patients before and 3 months after completing the treatment by the same analyst at the same device[1]. The H₂ curves were set.

Figure 3 Hydrogen test curves in controls

Dietary recommendation including non smoking on the day before and also lack of antibiotics, colonoscopy, laxatives within last month were strictly followed in order not to influence the accuracy of readings. The amount of H₂ in exhaled air was expressed in part per million(ppm). A cutoff value of 10 ppm was set, values between 10-20 ppm were considered borderline positive, and above 20 ppm pathological.

After the informal consent patients joined this multitarget, multilevel treatment consisting in: (1) probiotics as 2x60 mg living lactic bacteria(Lactobacillus acidophilus and Bifidobacterium infantis) conditioned as gastric resistant capsules, associated to (2) prebiotics like natural herbal fibers as 10 grams of a powder mixture dissolved in a cup of warm water at bedtime(for 5 grams of powder there were 2,5 gr extract of Plantago ovata,0,1 gr extract of Terminalia chebula ,as active substances, the rest excipients), and (3) gas absorbent, activated charcoal taken 2x100 g/day, conditioned as film tablets and (4) a special program with life style changes as part of behavioral therapy, being trained by a qualified psychologist how to cope with their personal issues.

This treatment lasted for 3 months.

4. Results

4.1 General aspects of patients are depicted below:

Tabel 2 General aspects of female IBS patients

As seen in the table above the vast majority of patients lived in urban locations(95,23% vs 4,76%), most of them had high instruction level(61,90% vs 38,09%),only 4,76% had regular dietary fiber intake, the rest 19,04% episodic and 76,19% no fiber and all the patients had conflict situations and stressful jobs.

4.2 Symptoms dynamic : before and after treatment

Figure 4. Life quality scores

Figure 5. Abdominal pain scores

Figure 6. Bowel habit alterations

Figure 7. Flatulence

Figure 8. Bloating

Figure 9. Incomplete evacuation

Analyzing data related to symptoms dynamic before and after therapy we can easy see the important differences in: alteration bowel habit score ($5,90 \pm 1,30$ vs. $3,29 \pm 1,15$; $p < 0,0001$, extremely statistically significant), flatulence($5,95 \pm 0,97$ vs. $3,05 \pm 0,74$; $p < 0,0001$, extremely statistically significant), bloating($6,00 \pm 0,84$ vs. $2,95 \pm 1,07$; $p < 0,0001$, extremely statistically significant), incomplete evacuation ($2,38 \pm 2,06$ vs. $1,05 \pm 1,20$; $p = 0,0143$, statistically significant) and global status($5,86 \pm 0,65$ vs. $6,38 \pm 0,80$; $p = 0,0259$, statistically significant).

Abdominal pain scoring assessment before and after therapy revealed that differences were not statistically significant ($8,05 \pm 13,09$ vs. $4,95 \pm 0,92$; $p = 0,2863$).

4.3 Evaluation of gut microbiota by Hydrogen breathing test

As seen in table below the dynamic of Hydrogen values measured at 15,30,60 and 120 minutes changed significantly after treatment.

Table 3 Hydrogen breathing test(values in ppm) before and after the treatment

5. Discussions: This study was designed as a multilevel, multitarget therapy trying to reach the ancient “men sana in corpore sano” idea. That mean that brain functioning regulation would probably improve the brain-gut connection on one side, making the gut more responsive on the other side, and all those together could complete the healing process. We took the opportunity to “relearn” their brains how to manage stress situation based on the fact that our patients were competent women, that already lived in urban location and had very good addressability and compliance to this behavioral therapy program. The gut addressing therapy envisaged improvement of intestinal function by different pathways: probiotics as balance microbiota gut

regulators, herbal fibers as improvers of the bowel habit and charcoal as gas absorbent in a cohort of patients that obviously lack the daily fibers intake.

The fecal microflora also differs among patients with irritable bowel syndrome versus controls. Sophisticated molecular analysis suggested an alteration in the patterns and the contents of gut bacteria[3,4].

The large bowel contains an enormous number of bacteria that are predominantly anaerobes and produce a large quantity of hydrogen. It is assumed that the large intestine contains around 10¹⁵ bacteria whilst there is only a very small quantity of anaerobic bacteria in the small intestine.

In theory speaking a nutrition with functional products (nutraceuticals) or a so called “functional alimentation”, that act as a physiologically proven remedy, could be a reasonable solution to IBS female problem[11].

On the other side, how much can we rely on the results of a study in which the standardisation and quantification of patient daily food intake is rather difficult, so that the hypothetical conclusions regarding the relation diet-symptom relief could be speculative ones? This is why we used products from dietary supplements and we validated their effectiveness on gut microflora by performing H₂ breathing test.

Traditional theories regarding pathophysiology may be visualized as a 3-part complex of altered GI motility, visceral hyperalgesia, and psychopathology.

Altered GI motility includes distinct aberrations in small and large bowel motility, is probably associated to a generalized smooth muscle hyperresponsiveness.

Visceral hyperalgesia characterizes irritable bowel syndrome by enhanced perception of normal motility and visceral pain. Rectosigmoid and small bowel balloon inflation produces pain at lower volumes in patients than in controls.

Sensitization of the intestinal afferent nociceptive pathways that synapse in the dorsal horn of the spinal cord provides a unifying mechanism for abdominal pain.

Psychopathology is the third aspect but associations between psychiatric disturbances and irritable bowel syndrome pathogenesis are not clearly defined and understood[13,15].

As a consequence until today no consensus regarding a treatment guide has been yet released so the clinicians should use in their practice[14]. Several studies based on several theories and observations didn't get to the same conclusions and are still subjects to debate. Some of long duration treatment could have many side-effects, causing dropout cases. That is why fighting irritable intestine is a very difficult task to reach.

However there are some promising studies, majority in children, regarding the beneficial effects of probiotics in the relief of IBS symptoms[8,9,10].

Pimentel and colleagues have proposed that small bowel bacterial overgrowth provides a unifying mechanism for the common symptoms of bloating and gaseous distention in patients with irritable bowel syndrome[5].

Many of patients complaints have as trigger the bowel distension very often associated to local bacterial imbalance as a result of dietary intake habits, stress, antibiotics intake, traveling[2,6]

Abdominal pain has many pathogenic pathways being a very complex symptom. The pain in IBS has many faces: visceral overreaction to colonic distension and sensitization, a particular perception

and sometimes twisted central processing of received information explaining why this symptom is in fact so difficult to eradicate[12]

Treatment with prebiotics, probiotics and activated charcoal addressed in the present study mainly to colonic distension by controlling intestinal gas resulting in decreasing of gas production and increasing the gas absorption and having also a carminative and anti-inflammatory effect at the intestinal mucosa by modifying the gut microflora. But still remained in some patients with functional intestinal movement disorders, a particular reaction and particular pain perception affecting the response to our treatment.

6. Conclusions The multilevel treatment with prebiotics, probiotics and activated charcoal, having in background the regulation of responsiveness by behavioral therapy acted successfully in mitigating symptoms like: bowel habit disturbances, bloating, incomplete evacuation and flatulence and only partially in alleviating abdominal pain. However the quality of patients life improved significantly. These results have a good correlation with Hydrogen respiratory test, and the high probability of resetting the gut microbiota pattern after our therapy. Just a minority of patients didn't reach the normally Hydrogen test curves, remaining in the borderline positive area after completing the therapy.

Reference:

1. Alexander Eisenmann, Anton Amann, Michael Said, Bettina Datta, Maximilian Ledochowski. Implementation and interpretation of hydrogen breath test. *J. Breath Res.* 2 (2008)
2. Azpiroz, F., and J. Serra. "Treatment of Excessive Intestinal Gas." *Current Treatment Options in Gastroenterology* 7 (August 2004): 299-305.
3. Amir Ata Saei, Abolfazl Barzegari, *Future Microbiol.* 2012;7(9):1037-1046. The Microbiome: The Forgotten Organ of the Astronaut's Body — Probiotics Beyond Terrestrial Limits.
4. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, Rinttilä T, Paulin L, Corander J, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology.* Jul 2007;133(1):24-33.
5. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol.* Feb 2003;98(2):412-9.
6. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol.* Jul 2008;6(7):765-71.
7. Todar's textbook of bacteriology. The Normal Bacterial Flora of Humans. Online Edition ; free access: page 1-5)

8. Hoveyda N, Heneghan C, Mahtani KR, Perera R, Roberts N, Glasziou P. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol.* 2009; 9: 15.
9. McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J. Gastroenterol.* 2008; 14: 2650–61
10. Ford AC, Talley NJ, Quigley EM, Moayyedi P. Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials. *Dis. Colon Rectum* 2009; 52: 1805; author reply 6.
11. Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. *Aliment. Pharmacol. Ther.* 2003; 17: 841–51.
12. Thompson WG, Longstreth GF, Drossman DA *et al.* Functional bowel disorders and functional abdominal pain. *Gut* 1999;45 (Suppl 2): II43–II47
13. Jerndal P, Ringstrom G, Agerforz P *et al.* Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. *Neurogastroenterol Motil* 2010;22:646 e179.
14. Torri A, Toda G. Management of irritable bowel syndrome. *Internal Med* 2004; 43: 353–9.
15. J. Labus, A. Gupta, H. K. Gill, I. Posserud, M. Mayer, H. Raen, R. Bolus, M. Simren, B. D. Naliboff, E. A. Maye. Randomised Clinical Trial: Symptoms of the Irritable Bowel Syndrome Are Improved by a Psycho-education Group Intervention. *Aliment Pharmacol Ther.* 2013;37(3):304-315.
16. McGill Pain Questionnaire: Appraisal and current status. Melzack, Ronald; Katz, Joel, Turk, Dennis C. (Ed); Melzack, Ronald (Ed), (2001). *Handbook of pain assessment* (2nd ed.). , (pp. 35-52). New York, NY, US: Guilford Press, xix, 760 pp.

Tables and figures

Table 1. Normally bacteria commonly found on the surfaces of the human body

BACTERIUM	Skin Con- Nose Pharynx Mouth Lower Ant. Vagina							
	junc- tiva					GI	ure- thra	
Staphylococcus epidermidis	++	+	++	++	++	+	++	++
Staphylococcus aureus	+	+/-	+	+	+	++	+/-	+
Streptococcus mitis				+	++	+/-	+	+
Streptococcus salivarius				++	++			
Streptococcus mutans				+	++			
Enterococcus faecalis				+/-	+	++	+	+
Streptococcus pneumoniae		+/-	+/-	+	+			+/-
Streptococcus pyogenes	+/-	+/-		+	+	+/-		+/-
Neisseria sp.		+	+	++	+		+	+
Neisseria meningitidis			+	++	+			+
Enterobacteriaceae(Escherichia coli)		+/-	+/-	+/-	+	++	+	+
Proteus sp.		+/-	+	+	+	+	+	+
Pseudomonas aeruginosa				+/-	+/-	+		+/-
Haemophilus influenzae		+/-	+	+	+			
Bacteroides sp.						++	+	+/-
Bifidobacterium bifidum						++		
Lactobacillus sp.				+	++	++		++

Clostridium sp.					+/-	++		
Clostridium tetani						+/-		
Corynebacteria	++	+	++	+	+	+	+	+
Mycobacteria	+		+/-	+/-		+	+	
Actinomycetes				+	+			
Spirochetes				+	++	++		
Mycoplasmas				+	+	+	+/-	+

Table 2 General aspects of female IBS patients

Patient	Location	Instruction level	Regular alimentation with fibers	Conflict situation	Stressful jobs
1	Urban	Medium	-	+	+
2	Urban	High	-	+	+
3	Urban	Medium	-	+	+
4	Urban	Medium	-	+	+
5	Urban	High	-	+	+
6	Urban	High	Episodic	+	+
7	Urban	High	-	+	+
8	Urban	High	-	+	+
9	Urban	High	-	+	+

10	Rural	Medium	+	+	+
11	Urban	High	-	+	+
12	Urban	High	-	+	+
13	Urban	High	Episodic	+	+
14	Urban	High	-	+	+
15	Urban	Medium	-	+	+
16	Urban	Medium	-	+	+
17	Urban	High	Episodic	+	+
18	Urban	High	-	+	+
19	Urban	High	-	+	+
20	Urban	Medium	Episodic	+	+
21	Urban	Medium	-	+	+

Table 3 Hydrogen breathing test(values in ppm) before and after the treatment

Patient	0'	15 minutes		30 minutes		60 minutes		90 minutes		120 minutes	
		P=0,038		P<0,0001		p<0,0001		p<0,0001		p<0,0001	
		Before	After	Before	After	Before	After	Before	After	Before	After
		5,43±	4,67±	16,95±	5.81±	30,62±	8,55±	49,76±	9,00±	52,95±	9,19±
		0,75	0,86	2,64	1,81	9,13	4,85	11,81	5,06	9,89	5,04
1	5	5	5	9	6	40	8	51	8	62	8

2	7	7	6	14	6	38	6	58	6	58	6
3	6	6	5	18	6	35	6	59	7	61	7
4	4	4	3	18	4	18	4	20	5	50	5
5	5	5	4	17	4	29	5	50	5	55	6
6	6	6	4	18	5	31	6	59	6	60	6
7	5	6	5	19	12	35	18	50	20	61	20
8	5	5	5	17	8	29	16	58	17	60	17
9	5	6	5	21	6	39	17	55	17	55	17
10	5	5	5	18	6	37	6	54	7	54	7
11	6	6	6	19	6	28	7	46	8	40	8
12	5	6	5	18	5	20	5	50	6	50	6
13	6	6	5	17	5	28	15	38	16	52	17
14	5	5	4	16	5	25	5	56	6	58	7
15	5	6	6	19	6	36	7	60	8	61	8
16	5	5	5	16	8	29	17	60	18	60	18
17	4	4	4	18	5	21	6	50	6	50	6
18	5	5	4	15	4	20	5	35	5	40	5
19	5	5	3	13	4	17	4	18	5	18	6
20	6	6	4	20	6	38	6	51	7	51	7
21	5	5	5	16	5	30	6	46	6	48	6

Figure 1. Gram stain for Lactobacilli. (Source Todar's textbook of bacteriology. The Normal Bacterial Flora of Humans. Online Edition ; free access: page 1-5)

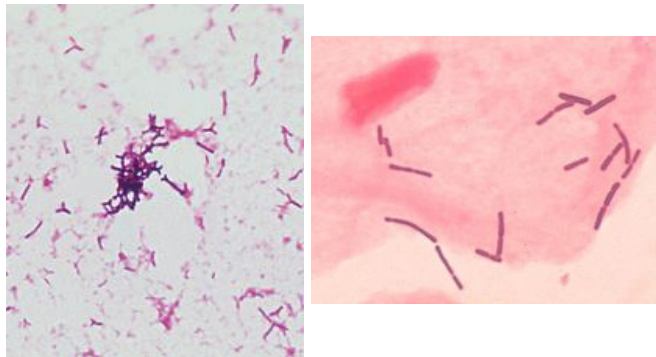


Figure 2. Mc Gill questionnaires part A and B

Very bad	0	1	2	3	4	5	6	7	8	9	10	Excellent
----------	---	---	---	---	---	---	---	---	---	---	----	-----------

No problem	0	1	2	3	4	5	6	7	8	9	10	tremendous problem
------------	---	---	---	---	---	---	---	---	---	---	----	--------------------

Figure 3. Hydrogen test curves in controls

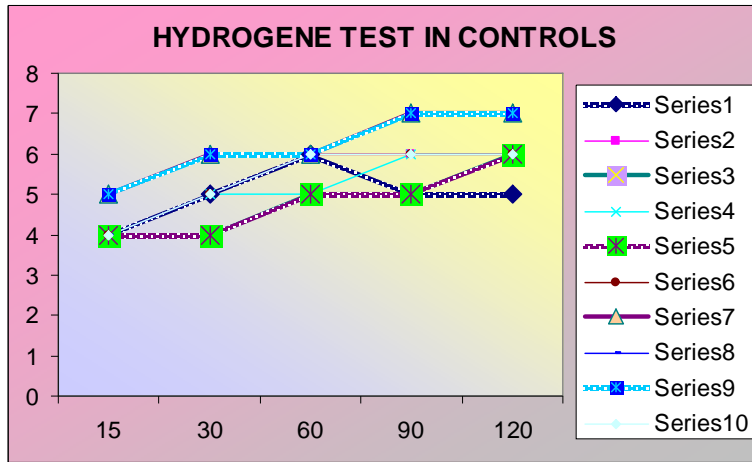


Figure 4. Life quality scores

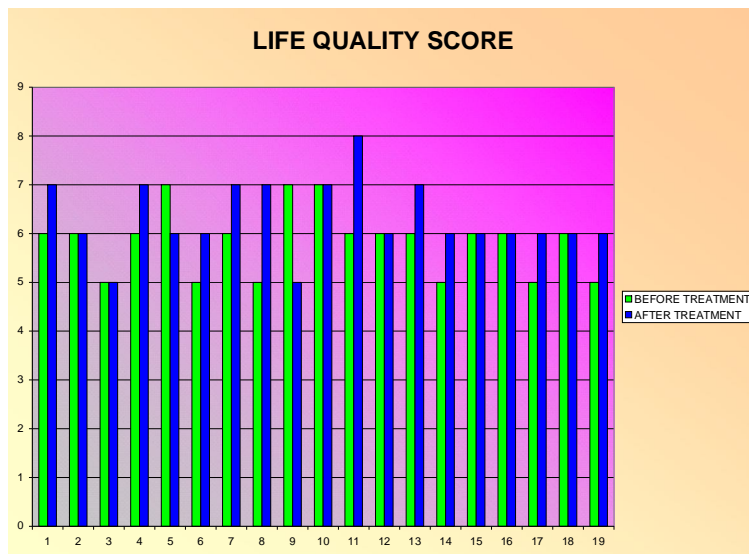


Figure 5. Abdominal pain scores

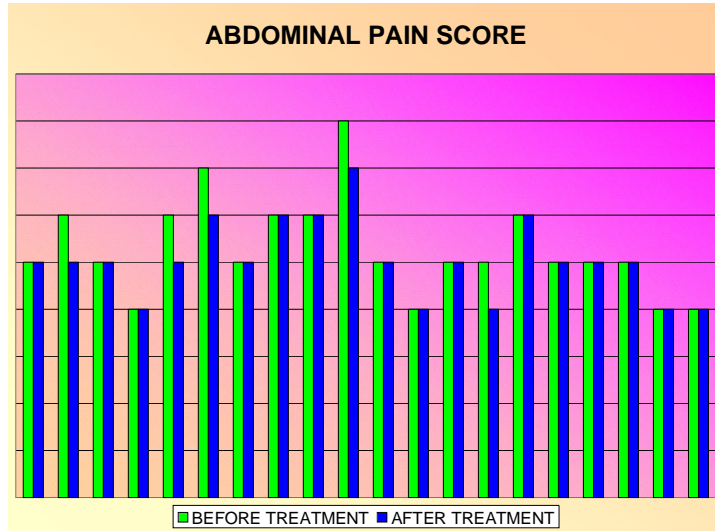


Figure 6. Bowel habit alterations

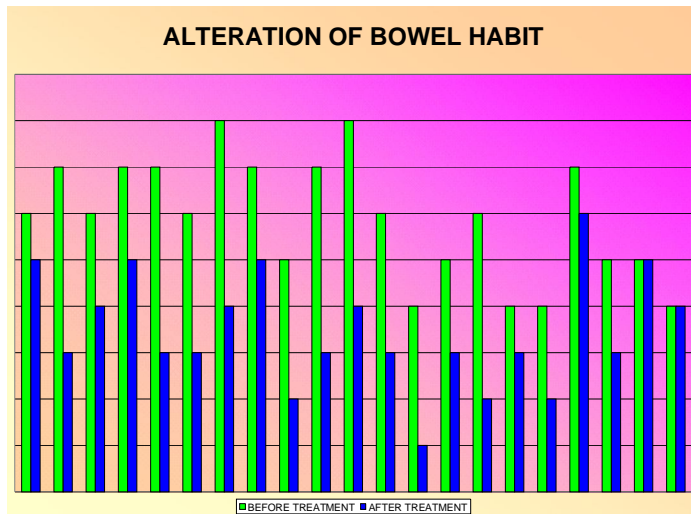


Figure 7. Flatulence

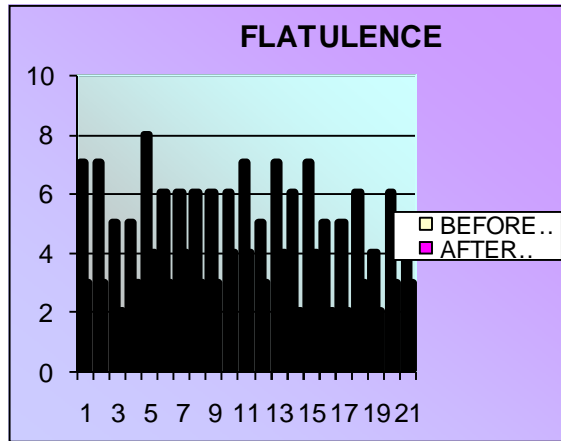


Figure 8. Bloating

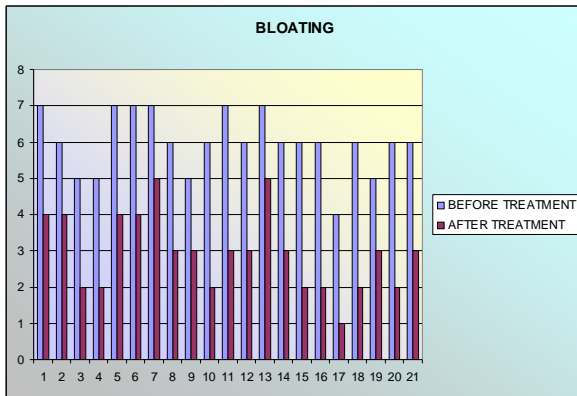


Figure 9. Incomplete evacuation

