A STUDY OF THE ROLE OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the requirements
for the award of the degree of

DM (MEDICAL GASTROENTEROLOGY)

BRANCH – IV

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI

AUGUST 2011

DECLARATION

I solemnly declare that this dissertation titled "**THE ROLE OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME**" is done by me in the Department of Medical Gastroenterology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Professor & Head of the Department, Department of Medical Gastroenterology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of DM Medical Gastroenterology.

Place : Chennai
Date :

Dr.B.Vinoth
Postgraduate student,
Dept of Medical Gastroenterolgy,
Madras Medical College,
Chennai.

CERTIFICATE

This is to certify that the Dissertation entitled, **"THE ROLE OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME"** is the bonafide record work done by *Dr.B.Vinoth*, under our guidance and supervision in the Department of Medical Gastroenterology, Rajeev GandhiGovernment General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch IV MEDICAL GASTROENTEROLOGY, AUGUST 2011, under The Dr.M.G.R. Medical University, Chennai.

Dr. .Kanagasabai, M.D.,
THE DEAN,
MADRAS MEDICAL COLLEGE,
CHENNAI,

Dr.Mohammed Ali, M.D., D.M.,
PROFESSOR AND HEAD,
DEPT OF MEDICAL
GASTROENTEROLOGY,
MADRAS MEDICAL COLLEGE,
CHENNAI.

ACKNOWLEDGEMENT

I sincerely thank the Dean, ***Dr.KANAGASABAI M.D.,Ph.D.,*** for having permitted me to carry out this dissertation work at Government General Hospital, Madras Medical College, Chennai.

I have great pleasure in expressing my gratitude and respect to ***PROF. Dr.MOHAMMED ALI M.D., D.M.,*** Professor and Head, Department of Medical Gastroenterology, Madras Medical College, Chennai, for his valuable suggestions, kind guidance, constant supervision and moral support without which this study would not have been possible.

I have great pleasure in expressing my gratitude and respect to ***PROF. Dr.P.PADMANABHAN, M.D., D.M.,*** Additional Professor , Department of Medical Gastroenterology, Madras Medical College, Chennai, for his counseling and constructive suggestions.

I express my gratitude to assistant professors, Dr.K.Premkumar, Dr.Caroline Selvi, Dr.Kini and former assistant professer Dr.P.Ganesh for their support,interest and enthusiasm in completion of this study.

I thank my colleagues, Dr.Kani Shaikh Mohammed, Dr.M.Malarvizhi, Dr.R.Biggs Saravanan, Dr.T.Anand, Dr.Shafeeq, Dr.Radha, Dr.Senthil Kumar, Dr.Arvind, Dr.Hemamala for their help and assistance in successfully completing the study.

I thank my wife who stood by me and helped me a lot in successfully completing this study.

Last but not the least, my sincere thanks to the patients who co-operated for this study, without whom the study could not have been completed. This work would be complete if it had contributed, even in the smallest possible way, to alleviate their suffering.

INDEX

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS), the prototypical functional GI disorder, is common throughout the world and often requires care from primary care and specialist physicians. Because no etiology is found with routine treatment testing, IBS is a symptom-based diagnosis, requiring chronic abdominal discomfort / pain and abnormal bowel function; other Gastrointestinal (GI) symptoms are also common. Though it is considered as a functional bowel disorder the burden of the disease to the patient is very high and the quality of life in patients with IBS is miserable. Once an IBS sufferer has told “some of my earliest memories are sitting in the back of a car in excruciating pain during family trips and not telling anyone” and such is the quality of life in patients with IBS.

IBS appear to be part of a continuum of GI and CNS (Central nervous system) reactions to external and internal stimuli. At one end of this spectrum, many people have functional GI symptoms in response to emotional stress. Many such individuals do not seek health care for these symptoms, yet others have severe symptoms with or without stress that impair their quality of life. In the absence of a biological marker, defining abnormality on the spectrum ranging from occasional, stress related GI symptoms in people not seeking care to disabling symptoms in patients with refractory IBS is controversial.

Definition:

Various criteria's are used to define IBS which includes Manning criteria, Kruis criteria, Rome I criteria and the Rome II criteria.[1,2] The latest and the most widely used criteria at present is the Rome III criteria which defines IBS as shown in the Table 1.[3]

Rome III Criteria for Irritable bowel syndrome (IBS)
Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool * Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis ** "Discomfort" means an uncomfortable sensation not described as pain.

Table 1: Rome III criteria for IBS

Mechanism of disease :

A number of different mechanisms have been implicated in the pathogenesis of IBS, including abnormal motility, visceral hypersensitivity, low-grade inflammation, and stress. Genetic factors could modulate the processing of gastrointestinal signals centrally and the inflammatory and immune responses locally, possibly predisposing to IBS. It seems reasonable to postulate that for IBS to manifest, several abnormalities—multiple hits—might need to occur. The most prominent symptoms in IBS are pain, discomfort, and bloating, which involve interpretation at a cortical level of signals originating in the gut (Brain gut axis) (Fig1, 2). It seems likely that in IBS, an understanding of the individual, including his or her psychosocial nature and response to environmental factors, influences the expression of any biological determinants (Fig.3). [4]

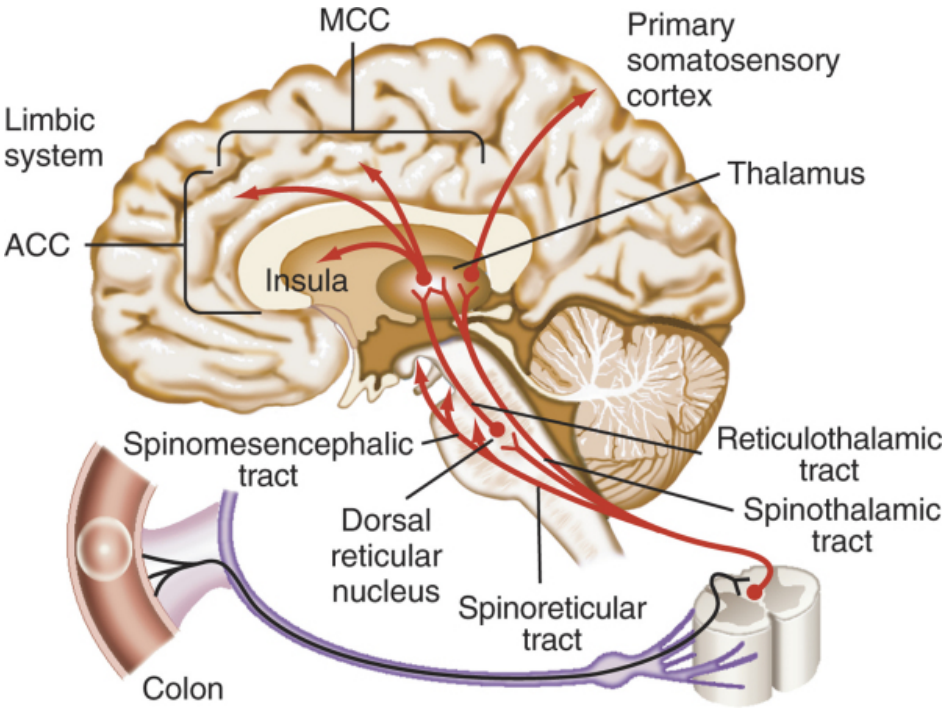

Figure 1: Afferent pathway of Brain gut axis

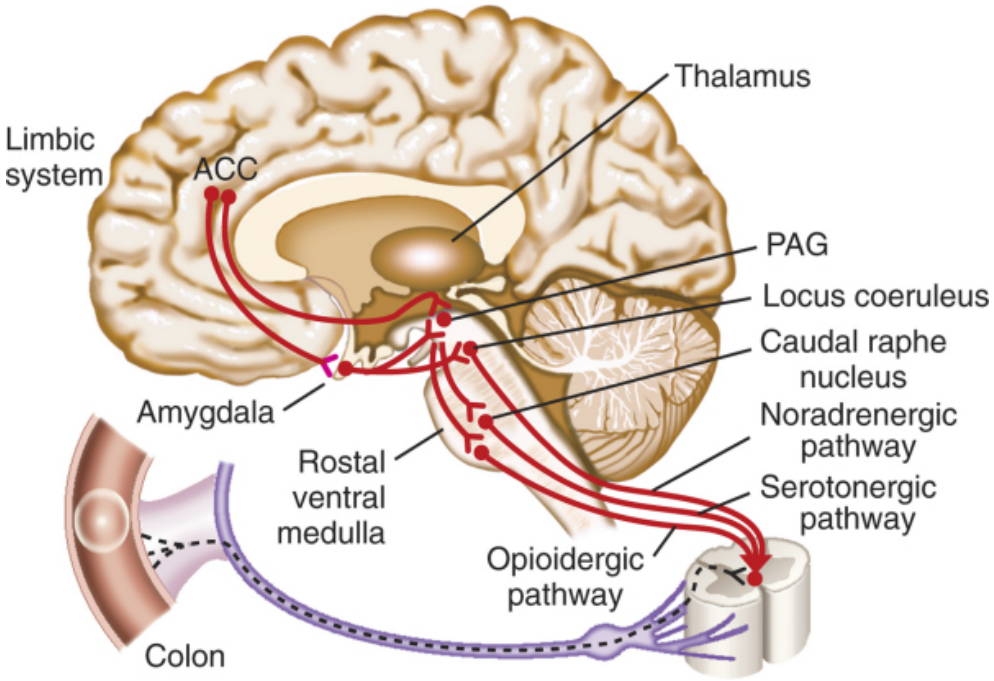

Figure 2: Efferent pathway of brain gut axis

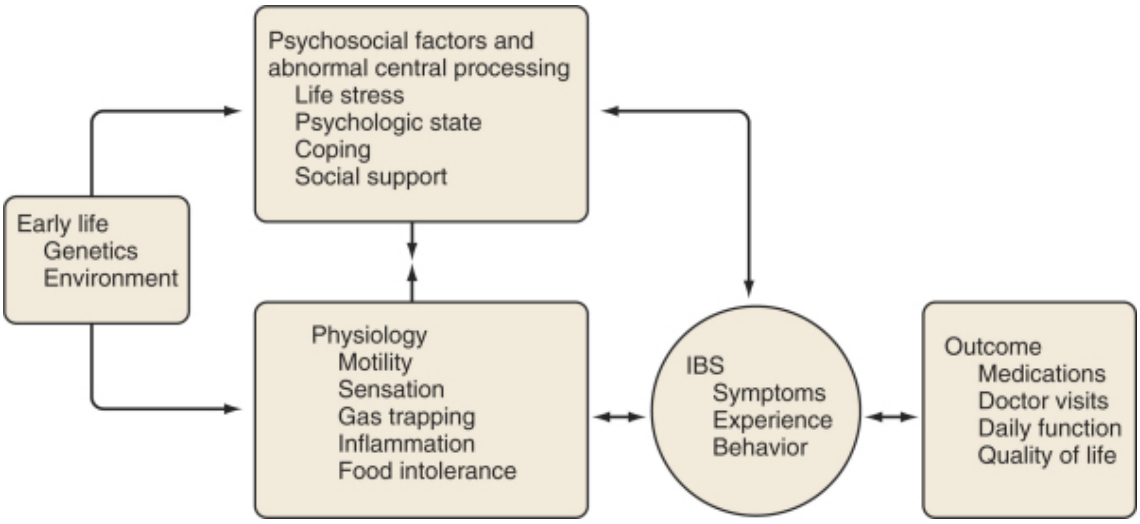

Figure 3: Pathogenesis of IBS

Mechanism and possible treatments therefore can be considered according to the level at which signaling becomes abnormal, starting at the level of the gut and finishing in the secondary association areas of the cerebral cortex (Box 1)

Box 1: Mechanisms & Treatment of IBS

Level	Mechanism	Possible treatments
Gut lumen	Physical / chemical stimulation by food, gas	Dietary, antibiotics, prebiotics
Gut mucosa	Inflammation, altered afferent signaling (enteroendocrine, mast cells)	Anti inflammatory, mast cell stabilizers ,probiotics
Spinal cord	Central sensitization	NMDA antagonists

Role of Probiotics :

It has been suggested that the colonic flora could be abnormal in a subset of patients with IBS, resulting in increased colonic fermentation, production of excess gas, and development of symptoms.[5] This has led to an interest in pre- and probiotic therapy for IBS. Probiotics are defined as preparation of alive microorganisms of specific genus and species in sufficient numbers to alter the microflora (by implantation or colonization) and by doing so exert beneficial effects in the host.

The clear delineation of a postinfective variety of IBS, and the description in numerous studies of evidence of low grade inflammation and immune activation in IBS, suggest a role of a dysfunctional relationship between the indigenous flora and the host in IBS. Accordingly, this provides a clear rationale for the use of probiotics in this disorder especially the post infectious variety of IBS. Other modes of action, including bacterial displacement and alterations in luminal contents, are also plausible. Clinical evidence of efficacy remains scanty, and a review of available trails, while providing some hints of efficacy and therapeutic promise, emphasizes the importance of clear definition of strain, selection, dose and viability. Therefore this study is undertaken to determine the role of probiotics in IBS.

AIM

The aim of our study is to evaluate the role of probiotics in Irritable bowel syndrome.

REVIEW OF LITERATURE

IBS is a clinical syndrome in which chronic abdominal discomfort or pain occur with disturbed bowel habit not explained by an established organic or biochemical abnormality.[6]The definition of IBS has evolved from a diagnosis of exclusion to making a confident positive diagnosis based on standard criteria which at present is the Rome III criteria (Table). [3]

Manning Criteria* (BOX:2)
Abdominal pain eased after bowel movement Looser stools at onset of abdominal pain More frequent bowel movements at onset of abdominal pain Abdominal distension Mucus per rectum Feeling of incomplete emptying * Diagnostic cut-off: three or more of the six symptoms listed.

Kruis Criteria (BOX:3)
Patient's History
Abdominal pain Flatulence Irregularity of bowel movements Symptoms more than 2 years Mixed diarrhea and constipation Pellet-like stools or mucus
***Physician's Assessment*†**
Abnormal physical findings Erythrocyte sedimentation rate >20 mm/2 hr Leukocytosis (>10,000 cm^3) Haemoglobin (female <12 g/dL; male <14 g/dL) History of blood in stool † If any abnormal physical findings or any of the laboratory parameters assessed by the physician are present, IBS is *excluded*.

Previous criteria's includes Manning criteria, Kruis criteria, Rome I and Rome II criteria (Box 2, 3). [1, 2]

Epidemiology :

IBS is one of the most common occurrences in OP medicine and the most frequent reason for consultation with a gastroenterologist. [7] Because a limited proportion of subjects suffering from IBS seek medical for this condition, **only tip of the iceberg** is exposed and knowledge of IBS epidemiology depends on research in the general population to estimate the disease burden and to plan management and public health interventions. [7]

IBS affects approximately 3% - 15% of the general population based on various diagnostic criteria. There seem to be differences in disease epidemiology between the eastern and the western world. As data from larger Asian epidemiological studies begin to surface, however, such differences appear to be less marked. The proportion of IBS patients who consult a physician for their symptoms is around 50%. Psychological factors and the presence and duration of abdominal pain are all significant predictors for health care seeking.

Natural history and risk factors :

IBS is characterized by fluctuation of symptoms, sometimes between the different bowel subtypes, and by periods of symptom remission. [8] Unnecessary abdominal surgery is performed in a high proportion of IBS sufferers.

Risk factors :

IBS is a multifactorial condition in which GI motor and sensory dysfunction and psychological traits may contribute, in combination with a series of environmental factors such as acute GI infections and food intolerance. There also may be a background genetic predisposition. [9] Research on classical risk factors such as smoking and alcohol consumption has shown no association. [10] Along with the established role for psychosocial conditions in IBS, other risk factors are emerging. Evidence for post infectious IBS is mounting, but the clinical usefulness of characterizing such patients remains unclear. Food sensitivities are frequently present in IBS, but more well conducted trials of avoidance diets and desensitization are needed. Finally, genetic markers in IBS are an increasing focus of attention, but the amount of phenotypic variance explained by genetic variability remains to be established.

Pathophysiology :

The precise pathophysiology of IBS remains unknown. [11] For some time, pathophysiological and pharmacological research efforts have focused on 2 principal targets: dysmotility and altered visceral sensation. [12] There is no doubt that IBS is associated with several disturbances in motor function, not only in the colon, but throughout the GI tract, as reflected by the former use of such terms as spastic colon or spastic colitis to describe this syndrome and by the continued emphasis on the use of antispasmodics in its therapy. [13] Although it remains likely that dysmotility, or spasm, may play a role in the precipitation of symptoms, the specificity of any

proposed motor phenomenon for IBS has been questioned, and the primacy of dysmotility in the pathogenesis of IBS is now in doubt. Visceral hypersensitivity usually demonstrated by assessing the response to balloon inflation in the rectum or elsewhere, is a common phenomenon in IBS. and in all functional GI disorders, including functional dyspepsia and noncardiac chest pain. [14] Visceral hypersensitivity and related phenomena, such as visceral hyperalgesia and abnormal central perception, are so common in IBS that visual hypersensitivity, elicited by inflation of a rectal barostat balloon in the rectum, has been proposed as a diagnostic test for IBS. [14] Akin to the situation with dysmotility, the specificity of this phenomenon for IBS has been questioned; some experts in the field contend that visceral hypersensitivity reflects the impact of psychological traits associated with, or consequent upon, IBS and that it is not, therefore, a fundamental pathophysiological mechanism in IBS. [15]

More recently, roles for enteric infection and intestinal inflammation have been proposed. Thus, retrospective and prospective studies have documented the new onset of IBS following bacteriologically confirmed bacterial enteritis and others have provided evidence of low-grade mucosal inflammation and immune activation in patients who have IBS. [16, 17, 18, 19, 20)] The enteric flora also have been implicated; there has been a suggestion that some patients who have with IBS may harbor bacterial overgrowth and that their symptoms may be ameliorated by its eradication. [21] Despite these observations, the ever increasing understanding of gut flora-mucosa interaction and the existence of a significant body of basic research to support a role

for inflammatory and immune processes in contributing to enteric neuromuscular dysfunction, the role of lumen-mucosa interactions, in IBS, remains largely unexplored. It is in this content that probiotics have come to be evaluated in the management of IBS.

Why use probiotics in IBS?

Antibacterial and antivial effects :

Many probiotic organisms exert antibacterial and antiviral effects and could, therapy, prevent or modify the course of postinfective IBS. [22] Probiotics have been shown to be beneficial for preventing such human diarrheal conditions as toddlers `diarrhea and clostridium difficile-related, antibiotic associated diarrhea. [22]

These effects could be especially relevant to postinfectious IBS. Real data are beginning to emerge that directly support the concept of post infective or post dysenteric IBS. In a retrospective analysis, Mckendrick and Read reported on 12 patients (out of 38) who developed chronic bowel dysfunction within 12 months of documented salmonella gastroenteritis. [16] Taking advantage of the presence of centralized public health microbiology laboratories in the UK, Neal and colleagues performed a retrospective analysis on a large group of patients who had documented bacterial gastroenteritis. [23] When followed 6 months later, 7% had developed symptoms consistent with IBS. They went on to identify the following risk factors for post infectious IBS: being female and having a prolonged initial illness. Another study, also from UK, included 318 patients with gastroenteritis followed for 1 year. [24]

This study included a control population drawn from a national database. The rate of new diagnosis of IBS during the 12-months period of study was 4.4% for those with prior exposure to gastroenteritis and 0.3% for the control group, with a relative risk for developing IBS after gastroenteritis in excess of 10. Recent prospective studies have clarified the concept of post infectious IBS future. The first included 75 patients with acute gastroenteritis who were followed for at least 6 months. [25] At 3 months, 22 had developed IBS. Similar risk factors were identified female gender and a prolonged episode of gastroenteritis. In addition, they noted that the patients who developed IBS had higher scores for anxiety, depression, somatization and neurosis. They also provided some insights into the natural history of this disorder. At 6 months, 91% had persistent symptoms, at 9 months 79% had persistent symptoms and at 12 months 75% had persistent symptoms, suggesting that many of these individuals truly had developed chronic IBS. A second study from the same group evaluated 94 patients with acute gastroenteritis, and a control group, at the onset of the symptoms of GE and 3 months later with a questionnaire, psychometric testing, flexible sigmoidoscopy (with biopsy), whole gut transit study, and rectal distension. [26] They carefully excluded all patients with prior GI dysfunction, something that had not always been done in other studies. At 3 months, 23% of the gastroenteritis group had developed IBS.

Again 64% of those who developed postinfectious IBS were female. Psychological factors again proved predictive of IBS risks. Recent experience of a major life event and a high hypochondriasis score were especially predictive for

developing postinfectious IBS. For the first time, this study explored the possible role of inflammation. At the onset of gastroenteritis, 37% had evidence of microscopic colitis, regardless of whether they subsequently went on to develop IBS. At 3 months, in contrast, an increase in the number of chronic inflammatory cells was seen only among the patients who had developed IBS. In a very recent study, another group demonstrated a persisting increase in rectal mucosal enteroendocrine cells, T lymphocytes and in gut permeability in patients who had postdysenteric IBS. [27] Finally, an innovative, intriguing study surveyed individuals about to travel abroad to high-risk areas for enteric infections before travel, immediately on return, and at least 12 weeks later. [28] Forty-six percent developed traveler's diarrhea. At 12 weeks, 9.5% had new-onset IBS by Rome criteria, a relative risk of about 7, very consistent with other studies. Although probiotics have not been evaluated in the context of postinfectious IBS, the ability of probiotic preparations to influence the outcome of bacterial infections, such as Clostridium difficile colitis, and viral infections, such as rotavirus diarrhea, and the experimental demonstration of bactericidal, toxin-neutralizing and antiviral effects for specific probiotic strains, suggest that probiotics may have a role for preventing on treating postinfectious IBS.

Anti-inflammatory effects :

IBS also may be associated with inflammation or immune activation in the absence of an infectious trigger. That inflammation could lead to altered enteric nerve or muscle function had been demonstrated in the past in such disorders as Chagas' disease and postviral gastroparesis. IBS-type symptoms also have been associated

with inflammatory bowel disease (IBD) and celiac disease, even when in apparent remission. [29] More direct and compelling evidence recently was provided by Chadwick and colleagues, who evaluated 77 patients who had IBS, of whom 55% would be considered as diarrhea-predominant; none had a confirmed infectious origin for their IBS. [18] All had colonic biopsies taken for conventional histology and immunohistology. Thirty-eight had normal histology; 31 demonstrated microscopic inflammation, and eight fulfilled criteria for lymphocytic colitis. Among the group with normal histology, however, immunohistology revealed increased intraepithelial lymphocytes, and an increase in CD3 + and CD25 + cells in the lamina propria. All, therefore, showed evidence of immune activation. These features were even more evident in the microscopic inflammation group. These patients additionally revealed increased neutrophils, mast cells, and natural killer cells. All of these immunopathological abnormalities were most evident in the lymphocytic colitis group. These patients also demonstrated HLA-DR staining in crypts and increased CD8+cells in the lamina propria. Taking the group of IBS patients as a whole, CD3+ cell numbers were higher among those with diarrhea than among alternators or those with predominant constipation. In contrast, among the noninflamed IBS group, the presence of mast cells was a predictor of constipation. Surprisingly, given the described direct relationship between symptoms and chronic inflammation among patients who have postinfectious IBS, these authors did not find an association between the nature of disease onset or disease duration and immunological findings. That patients who have IBS may be predisposed to an inflammatory response to luminal triggers is also supported by the finding of a reduced frequency of the high-

producer phenotype for the anti-inflammatory cytokine interleukin (IL)-10 among patients who have IBS. [20] Most recently, among a group of 78 unselected IBS patients, the authors demonstrated in peripheral blood mononuclear cells an alteration in the ratio between the cytokines IL-10 and IL-12. this became skewed toward a Th1, proinflammatory profile. [19]

Although the inflammatory hypothesis in IBS is in its infancy, there is already some evidence for the extension of the inflammatory process beyond the confines of the mucosal compartment. Tornblom and colleagues addressed this issue in 10 patients who had severe IBS by examining full-thickness jejunal biopsies obtained at laparoscopy. [30] In nine patients, they found low-grade infiltration of lymphocytes in the myenteric plexus; four of these had an associated increase in intraepithelial lymphocytes, and six patients demonstrated evidence of neuronal degeneration. Nine patients had longitudinal muscle hypertrophy, and seven patients had abnormalities in the number and size of interstitial cells of Cajal. Three of their patients reported an acute onset of their IBS; in two patients, this possibly was precipitated by gastroenteritis. The finding of intraepithelial lymphocytosis is consistent with the reports of Chadwick and colleagues in the colon and of Wahnschaffe and colleagues in the duodenum. [18]

A direct linkage between immune activation and symptoms has been provided by the work of Barbara and colleagues, who demonstrated, not only an increased

prevalence of mast cell degranulation in the colon in IBS, but also a direct correlation between the proximity of mast cells to neuronal elements and pain severity. [31]

What is the pathogenesis of these inflammatory changes in IBS? With regard to postinfectious IBS, Spiller proposed that the development of chronic inflammation could represent a response to an initial bacterial infection among individuals rendered susceptible by a relative deficiency of anti-inflammatory cytokines. [32] A similar hypothesis has been advanced to explain inflammation and immune activation in IBS, in general, where a failure to adequately down-regulate a proinflammatory response following a precipitating event (eg, GI infection) may sustain the IBS state. [19, 20] Why than does this inflammatory response not progress to the state of florid inflammation so characteristic of IBD? In this regard, Collins suggests that the prominence of CD25+cells in the inflammatory infiltrate, as reported by Chadwick and colleagues, may act to prevent progression to a more florid inflammatory response. [17]

Laboratory experiments repeatedly have demonstrated the anti-inflammatory effects of certain probiotics. For example, oral administration of a Bifidobacterium exerted a profound anti-inflammatory effect in the IL-10 knock-out mouse, a potent model of IBD that was associated with suppression of the proinflammatory cytokines IFNγ, tumor necrosis factor (TNF)-α, and IL-12, while preserving activity of the anti-inflammatory cytokine TGFβ. [33] Others have demonstrated similar effects for the probiotic cocktail VSL #3 in another animal model of colitis; in this instance, the anti-

inflammatory effect was evident with bacterial DNA alone. In clinical practice, probiotics have been demonstrated to prevent development of pouchitis and reduce the relapse rate of this condition following successful antibiotic treatment. [34, 35] By reducing mucosal inflammation, probiotics could decrease immune mediated activation of enteric motor and sensory neurons and modify neural traffic between the gut and the central nervous system. [34, 35, 36] There is some preliminary evidence that probiotic administration may diminish visceral hypersensitivity in animal models. [36] Furthermore, effects on motility and perception could go some way toward explaining the beneficial effects of probiotics on bloating, given current concepts on the roles of altered gas transit and visceral hypersensitivity in the pathogenesis of this symptom.

Most recently, a probiotic bacterium, lactobacillus paracasei, has been shown to reverse changes in intestinal muscle function induced by inflammation consequent upon infection of an animal model with Trichinella spiralis. [36] This latter finding indicates that a luminally administered probiotic can influence inflammatory processes beyond the mucosal surface.

In a recent study by Eammon Quigley , which compared the effects of two probiotics, a Lactobacillus and a Bifidobacterium, in IBS, efficacy was observed with the Bifidobacterium alone. Bifidobacterium, but not the Lactobacillus or placebo, normalized the disturbed cytokine ratio, providing, for the first time in people, evidence for an association between an effect on an inflammatory process and amelioration of symptoms. [19]

Altering the composition of the gut flora :

Although the status of the gut flora in IBS remains a source of some controversy, probiotic-related changes in the enteric flora could influence gut function either directly, through the augmentation of commensal lactobacilli or Bifidobacteria or the elimination of pathogens, or indirectly, through a reduction in pathogen-related inflammation or bacterial fermentation. [11] Whether IBS is accompanied by quantitative or qualitative changes in the bacterial flora of the small or large intestine remains a contentious issue. Although some have described bacterial over growth in the small intestine and qualitative alterations in the fecal flora and increased bacterial fermentation, others have failed to replicate these findings. [11, 38, 39] A reduction in bacterial fermentation by a modulation of the composition of the flora could contribute to the alleviation of the gas-related symptoms common in IBS and that appear to reflect a selective defect in intestinal gas transport. An effect on bloating may be the most consistent effect of probiotics across all studies.

Effects on luminal contents :

Probiotics could alter the volume or composition of stool and gas or increase intestinal mucus secretion. [40] These effects could influence intestinal handling and thus modulate such symptoms as constipation and diarrhea. Of these putative effects of probiotics, an effect on stool bulking would appear unlikely, given the findings of the Eammon Quigley study of a Bifidobacterium in IBS. [19] In contrast to the effects observed with two newly approved therapies for IBS, namely alosetron and tegaserod,

Eammon Quigley failed to observe any change in stool consistency or frequency. [41, 42] This apparent independence of the effects of Bifidobacterium from any change in stool frequency or form implies that this therapeutic approach may be applicable to all patients who have IBS, irrespective of stool pattern.

Effects on gut flora and luminal contents are not mutually exclusive and could interact with other factors known to influence symptom onset in IBS. Bacterial overgrowth or qualitative changes in the gut flora with a shift toward more gas-producing organisms could interact with unabsorbed carbohydrates (such as in the patient with lactase deficiency or fructose intolerance) to increase colonic fermentation, which could, not only increase intestinal gas-related symptoms, but also affect function in the proximal gut by promoting gastroesophageal reflux and modifying proximal gastric relaxation. These latter effects could contribute to the overlap between IBS and other functional GI disorders such as nonerosive gastroesophageal reflux disease and functional dyspepsia.

Metabonomic understanding of probiotic effects in humans with irritable bowel syndrome:

Systematic effect of probiotics on inflammatory bowel disease through metabonomics approach has been extensively studied to date and metabonomic characterization of the probiotics effect on IBS is also needed for better understanding the effect with respect to host metabolic mechanism. In a study done by Hong et al seventy-four IBS patients meeting Rome criteria were randomized to receive probiotics and placebo through a parallel-group, double-blind, randomized, placebo-controlled clinical study. [43] Probiotic fermented milk and placebo was administered 3 times daily for 8 weeks.

Fecal counts of the Lactobacilli, but not Bifidobacteria species, which included in the probiotic milk, were increased significantly in feces of IBS patients receiving treatment (P=0.014). Nuclear Magnetic resonance (NMR) data set coupled with multivariate statistical analysis identified intrinsically elevated serum levels of glucose (P=0.0265) and tyrosine (P=0.0016) in IBS patients. These levels normalized to those of healthy individuals in the probiotic administration group, but not the placebo group. They concluded that in a subset of IBS patients there exists a potential dysregulation in energy homeostasis (serum glucose) and liver function (serum tyrosine) that may be improved through probiotics supplementation

Studies of probiotics in irritable bowel syndrome:

Numerous studies have evaluated the response of IBS to probiotic preparations and, while results between studies are difficult to compare because of differences in study design, probiotic dose, and strain, there has been some evidence of symptom improvement. The overall impact of probiotics, in IBS, remains unclear. In a recent review, Hamilton-Miller, while drawing attention to the shortcomings of prior trails in terms of study design, concluded that there was overall sufficient evidence of efficacy to warrant further evaluation. [(44)] Most studies reviewed were small and almost certainly underpowered to demonstrate anything other than a very striking benefit. Several did not verify bacterial transit and survival by confirmatory stool studies. Many different organisms and strains were employed, and dosage varied from as little as 10^5 to 10^{13}. Furthermore, some, including a very recent study, employed probiotic cocktails rather than single isolates, rendering it impossible to induce wheat were the

active moieties. Nevertheless, some positive results were noted. Niedzielin reported resolution of abdominal pain in all 20 patients treated for 4 weeks with L plantarum 299V, in contrast to only 11 of 20 patients who received a placebo. [45] Halpern and colleagues noted a significant reduction in an IBS symptom index with a capsule containing $5x10^9$ heat-killed L acidophilus. [46] O'Sullivan and colleagues, while failing to detect an effect of L casei GG on overall symptomatology, did note a trend toward reduction in bloating. [47] Nobaek and colleagues, employing L plantarum, described a similar benefit in terms of relief of bloating, as did Kim and colleagues in their evaluation of VSL # 3. [48,49]

The effects of two probiotic strains on symptoms in patients who had IBS was done by O'Mahony et al and he demonstrated superiority for a B longum infantis over Lactobacillus or placebo for each of the cardinal symptoms of the IBS (abdominal pain/discomfort, distension/bloating, and difficult defection), and for a composite score. [50] For each individual symptom, with the notable exceptions of bowel movement frequency and consistency, the group randomized to B infantis experienced a greater reduction in symptom scores during the treatment period. These symptomatic benefits were associated with parallel trends in quality of life. Furthermore, this therapy was tolerated well and free of significant adverse events. As these benefits were observed independent of any change in stool frequency or form, they cannot be attributed to either a laxative or an antidiarrheal effect. Although this study did not involve a comparison with any other therapeutic modality, and the study design differed, in some aspects, from recent large trials of serotonergic agonists and antagonists, the therapeutic gain observed for Bifidobacterium over placebo (20% to

25%) was certainly no less than that reported for tegaserod and alosetron (10% to 20%). This study with B longum therefore provides clear evidence for a benefit, in IBS, for a clearly defined single-organism probiotic preparation and suggests that some strains may be more effective that others for this indication. This was a relatively small pilot study, and its findings must be interpreted with caution. Large, randomized controlled trials of this Bifidobacterium strain, however, are warranted in IBS, and detailed explorations of its mechanism(s) of action are indicated.

Saggiaro A et al in 2004 showed that combination strain of Lactobacillus plantarum and Lactobacillus acidophilus improved overall symptom score in ROME II criteria IBS patients. [51]

O`Mahony et al in 2005 showed that either Bifidobacterium infantis or Lactobacillus salivarius improved the quality of life assessment using an IBS specific questionnaire in ROME II criteria IBS patients. [50]

Kajender K et al in 2005 showed that Lactobacillus rhamnosus ,Bifidobacterium, Propionibacterium improved abdominal pain, distension, flatulence and borborygmi in ROME I&II criteria IBS patients.[52]

Bausserman M et al in 2005 showed that lactobacillus caused changes in abdominal pain severity in ROME II criteria IBS patients. [53]

Whorwell PJ et al in 2006 showed that Bifidobacterium .infantis caused improvement of abdominal pain/discomfort, bloating/distension in ROME II criteria IBS patients. [54]

Gawronska A et al in 2007 showed that Lactobacillus rhamnosus GG caused improvement of abdominal pain in children with ROME II criteria

IBS. [55]

Guyonnet et al in 2007 showed the beneficial effect of a probiotic food on discomfort health related quality of life score and bloating in IBS-C and on stool frequency in ROME II criteria constipation predominant IBS patients. [56]

Jong et al in October 2008 showed that treatment with probiotics significantly reduced the mean global IBS scores compared with baseline scores in IBS-D patients. [57]

Williams EA et al in Jan 2009 showed that multistrain probiotic preparation LAB4 caused statistically greater improvement in the symptom severity score of IBS and in the scores for quality of life days with pain and bowel habit in ROME II criteria IBS patients. [58]

Hong KS et al in June 2009 showed that probiotics caused significant decrease in abdominal pain, defecation discomfort, and sum of scores in ROME III criteria IBS patients. [59]

Dolin BJ in December 2009 showed that Bacillus coagulans significantly decreased average number of bowel movements per day in IBS patients. [60]

Hun L in March 2009 showed that Bacillus coagulans caused statistically significant improvement from baseline abdominal pain and bloating scores in IBS patients. [61]

Enck P et al in Feb 2009 showed that E.coli caused statistically significant improvement in general symptom score and abdominal pain in IBS patients when given for 8 weeks. [62]

Lyra et al in 2010 showed that probiotic supplement exert specific alterations in IBS associated microbiota. [63]

Guandalini S et al in 2010 showed that VSL#3 is superior to placebo in the subjective assessment of relief of symptoms, abdominal pain, bloating and family assessment of life disruption in IBS patients. [64]

Choi SC, Kim BJ et al in 2011 showed that probiotics had additive benefit for the symptoms of constipation in IBS-C group patients. They used a combination of Streptobacillus thermophilus,Lactobacillus acidophilus and Bifidobacterium infantis. [65]

Choi et al in 2011 showed that Sacch.boulardii given for 4 weeks in IBS-D/mixed type improved quality of life. [66]

Guglielmetti S et al in 2011 showed that probiotics alleviated global IBS and improved IBS symptoms simultaneously with an improvement of quality of life and Bifidobacterium bifidum was used as the probiotic. [67]

Sondergaard B et al in 2011 showed in IBS ROME II criteria patients that probiotics improved symptom score during the study period but no improvement was seen at the end of the study period. [68] A combination of Lactobacillus paracasei, Lactobacillus acidophilus and Bifidobacterium lactis was used as a probiotic in the above mentioned study

Indian scenario:

Only epidemiological studies are available from India and there are no studies regarding the effect of probiotics in IBS. A prospective multicentre study in which data was obtained from 30 centers from all over the country with many authors contributing to the study compiled by Udhay Ghosal et al showed that symptom

complex suggestive of IBS was seen in 4.2% of community subjects.[69] In that study, IBS-Indeterminate type (57.18%) was the most common followed by IBS-C (38.97%) and then followed by IBS-D (3.84%). IBS was common in middle aged male patients (39.4yrs) according to that study.

Need for Indian study on role of probiotics in IBS:

More than 18 Randomized controlled studies have evaluated the effect of probiotics on various symptoms in patients with IBS. Few studies have also evaluated the effect of probiotic on Quality of life of patients with IBS. The results are very much conflicting between each trial so that the exact role of probiotic in IBS patient is not known. Almost all of the studies are from outside India and there are no studies in Indian population. Considering the pathophysiology of IBS where the cultural, economic, religious and social activities plays a major role, there may be considerable difference between the disease profile between Indian population and foreign population. Hence a randomized controlled study in Indian population is required to confirm the role of probiotics in Indian patients with IBS

MATERIALS AND METHODS

Patients with Irritable bowel syndrome fulfilling the Rome III Criteria (Table: 2) attending the outpatient department of the Department of Medical Gastroenterology were included in the study. Patients with red flag signs (Table: 3), those who are already on probiotics and those who are not willing for the study are excluded from the study .Ethical clearance was obtained from the ethical committee. A written informed consent was obtained from all the patients entering the study. (See Appendix) The study is a prospective single blind randomized controlled study.

Rome III Criteria for Irritable bowel syndrome (IBS)
Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool * Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis ** "Discomfort" means an uncomfortable sensation not described as pain.

Table 2

Red flag symptoms:
Unintentional weight loss Loss of appetite Short duration of symptoms Nocturnal symptoms Rectal bleeding Awareness of lump in the abdomen Perianal mass/ discharging sinuses Fever

Table 3

Detailed analysis of their symptoms were recorded including assigning a symptom score for each symptom.(See Proforma in the Appendix)

The symptom score is graded as follows:

Mild - No impairment of daily activities

Moderate – Impairment of daily activities but able to carry activities

Severe – Not able to carry daily activities (Absent to work/School)

Quality of life was also assessed with Health, wellness and quality of life questionnaire (See Appendix). Routine investigations which includes complete blood count, urine routine, motion routine, blood sugar were done in all patients.ECG was done in all older patients.

The patients were divided into 3 groups based on the type of IBS as follows,

Group 1: IBS-D (Diarrhea predominant IBS)

Group 2: IBS-C (Constipation predominant IBS)

Group 3: IBS-M (Mixed diarrhea and Constipation).

Each group was randomized to receive either Probiotic (Probiotic group) or placebo (Placebo group) for a period of 6 weeks. The Probiotic used and its composition is shown in Table 4.

Strain	**Strength**
Streptococcus faecalis JPC	30 million
Clostridium butyricum	2 million
Bacillus mesentericus JPC	1 million
Lactobacillus sporogenes	50 million

Table 4 : Composition of Probiotic used.

Probiotic was given in a twice a day dosage. The placebo used was vitamin capsule in the same twice a day dosage. At the end of 6 weeks the symptom score and Quality of life score were recorded again for both Probiotic and placebo groups and the data were analyzed to find out any statistical significance (Master chart in the Appendix)

Statistical analysis:

Unpaired t test was used to find out whether the age distribution and sex distribution was equally comparable between the probiotic group and the placebo group. Fischer exact test was used to calculate the p value for improvement in symptoms between the probiotic group and the placebo group

OBSERVATION AND RESULTS

Total of 113 patients entered the study.65 patients had IBS-D (57.5%), 43 patients had IBS-C (38%) and 5 patients had IBS-M (4.5%) (Figure: 4). There were 72 (64%) male patients and 41 (36%) female patients in the study. The mean age of patients in the study was 38.94 yrs (19-72yrs). (BOX: 4)

IBS-D: **BOX:4**

No of cases:	65(57.5%)
Mean age:	38.33
Males:	40(61.5%)
Females:	25(39.5%)

IBS-C

No of cases:	43(38%)
Mean age:	41.67
Males:	28(65%)
Females:	15(35%)

IBS-M:

No of cases:	5(4.5%)
Mean age:	29.2
Males:	4(80%)
Females:	1(20%)

IBS in general (IBS-D+IBS-C+IBS-M)

No of cases:	113
Mean age:	39.2
Males:	72(64%)
Females:	41(36%)

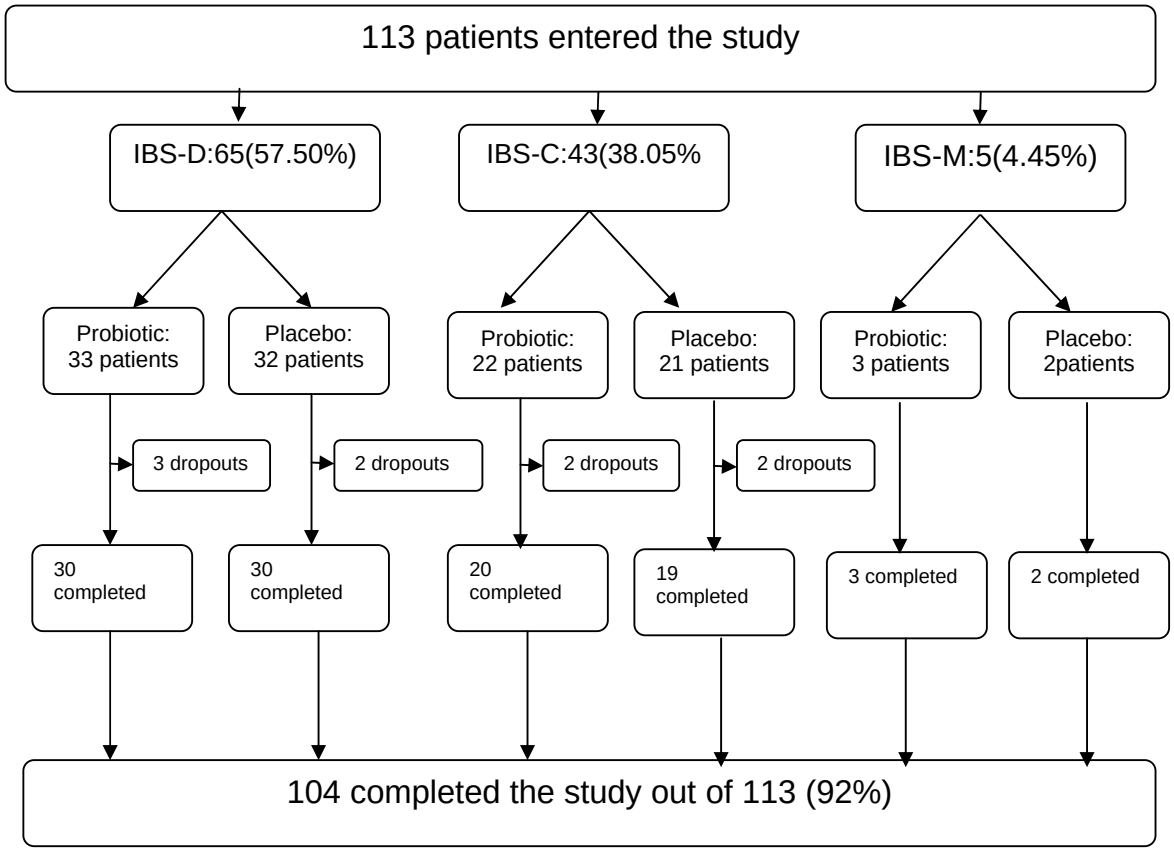

Figure: 4

In the IBS-D group there were 40 (61.5%) males and 25 (39.5%) females (Figure: 4). In the IBS-C group there were 28 (65%) males and 15 (35%) females (Figure: 4). In the IBS-M group there were 4 (80%) males and only one(20%) female though the incidence of this group is very low. There were 9 dropouts in the study, 5 in the IBS-D group and 4 in the IBS-C group. Out of 113 patients 104 (92%) completed the study. The compliance of the patients who completed the study was good.

IBS-D Group:

IBS-D was the most common form of IBS type in the study and constituted 57.5% (65 out of 113) of total cases. The frequency of stools in this group ranged from 2 to 15 times per day in the study, but most of the patients had 4-7 stools/day (51 pts out of 65 which constituted 78.5% of cases) (Table 5). 9 patients had less than 4 stools per day (13.8%) only 5 patients had more than 8 times per day (7.7%).The abdominal pain/discomfort was mild in 52 cases (80%) and moderate in 13 cases (20%) and none of the patient had severe pain/discomfort. Bloating was seen in 39 cases (60%), 24 patients in the probiotic group and 15 in the placebo group. Overall quality of life (QOL) assessment score was 2 (unhappy) in 14 cases (21.5%), 3 (mostly unsatisfied) in 45 cases (69.2%) and 4 (Mixed) in 6 cases(9.3%).Other associated symptoms like nausea, heartburn, regurgitation, feeling of indigestion, was seen in 11 patients (17%). Urinary symptoms were seen in one patient in the form of urgency and incontinence occasionally.

In this group 33 received probiotic and 32 received placebo out of which 30 in probiotic and 30 in placebo subgroup completed the study. The age and sex distribution between the probiotic and placebo group was statistically comparable. Frequency of stools improved in 16 out of 30 (53.33%) in the probiotic group and 7 out of 30 (23.33%) in the placebo group and the p value was significant (0.03) (Table 6 & Chart 1). The abdominal pain/discomfort improved in 15 out of 30 (50%) in probiotic group and 8 out of 30 (26.6%) in placebo group and the p value was not significant (0.11). (Table 6 & Chart 1). Bloating improved in 14 out of 24 (58.3%) in probiotic group and 5 out of 15 (33.3%) in placebo group and the p value was not

significant (0.19) (Table 7 and chart 2). The QOL improved in 15 out of 30 (50%) in probiotic and 8 out of 30 (26.67%) in placebo and the p value was not significant (0.11) (Table 6 & chart1)

Frequency of stools:

Frequency	No of patients	Percentage
4-7/day	51	78.50%
<4/day	9	13.80%
>8/day	5	7.70%

Abdominal pain/Discomfort:

Severity	No of patients	Percentage
Mild	52	80%
Moderate	13	20%
Severe	0	0

Bloating:

	No of cases	Percentage
Bloating	39	60%
No bloating	26	40%

Quality of Life (QOL):

Grade	No of patients	Percentage
2 (Unhappy)	14	21.50%
3 (Mostly dissatisfied)	45	69.20%
4 (Mixed)	6	9.30%

Table 5: Symptomatology of patients in IBS-D group

	Probiotic	Placebo	P value
No of cases	30	30	
Improvement in frequency of stools	16(53.33%)	7(23.33%)	0.03(significant)
Improvement in abdominal pain	15(50%)	8(26.67%)	0.11(Not significant)
Improvement in QOL	15(50%)	8(26.67%)	0.11(Not significant)

Table 6: Effect of probiotic vs placebo in IBS-D group.

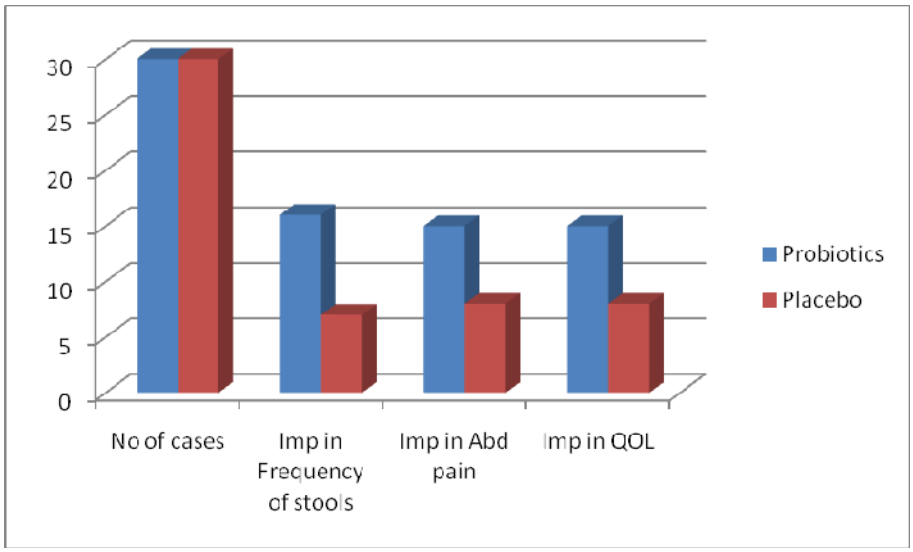

Chart 1 Effect of probiotic vs placebo in IBS-D pts

Key: Imp-Improvement

Bloating	Probiotic group	Placebo group
Improvement in bloating	14	5
No Improvement in bloating	10	10

Table 7: Improvement in bloating with probiotic vs placebo,

p value is 0.19

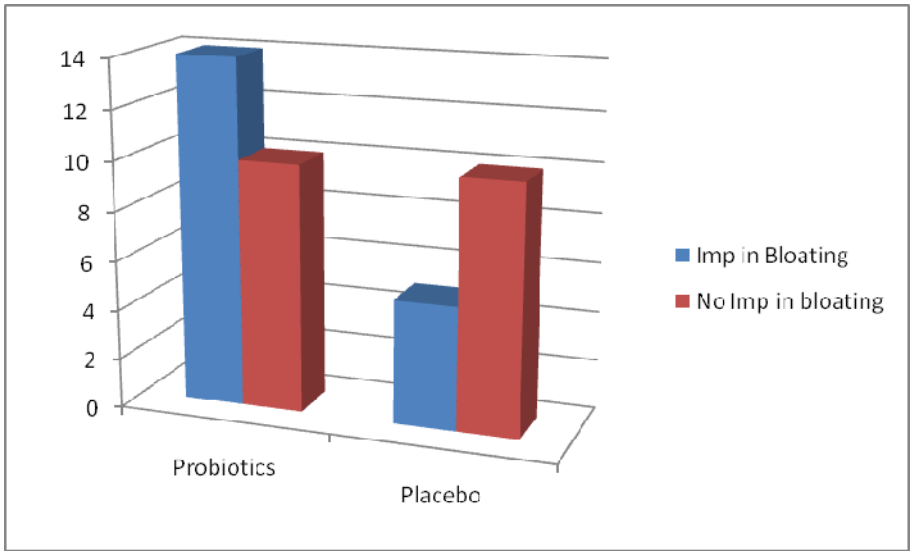

Chart 2 Effect of probiotic vs placebo on bloating in IBS-D pts

Key: Imp-Improvement

IBS-C group:

IBS-C constituted 38% of cases (43 cases out of 113). Patients with IBS passed stools mostly once in 2-3 days (40 out of 43 i.e. 93%).3 patients were passing stools once in 4-5 days (7%). Abdominal/Discomfort was mild in 35 pts (81.40%) and moderate in 8 patients (18.60%) and none of the patient had severe symptom. Bloating occurred in 31 patients (72%). The overall Quality of life assessment score was 2 (unhappy) in 8 patients (18.60%), 3 (Mostly dissatisfactory) in 34 patients (79%) and 4 (mixed) in 1 patient (2.40%) (Table 8). Associated symptoms like nausea, heartburn, belching, feeling of indigestion and regurgitation was seen in 7 patients (16.30%).

In IBS-C group 22 received probiotic and 21 received placebo out of which 20 in probiotic and 19 in placebo completed the study. The age and sex distribution between the probiotic and placebo group was statistically comparable. Improvement in frequency of stools was seen in 5 out of 20 patients (25%) in probiotic group and 4 out of 19 patients (21%) in the placebo group and p value was not significant (1.00)(Table 9 & Chart 3). The abdominal pain/Discomfort improved in 12 out of 20 patients (60%) in probiotic group and 5 out of 19 patients (26.30%) in placebo group and the p value was not significant (0.0536). (Table 9 & Chart 3) Improvement in bloating was seen in 11 out of 16 patients (68.75%) in the probiotic group and 4 out of 15 patients (26.67%) in placebo group and the p value was significant (0.03) (Table 10 & Chart 4). The overall QOL assessment score improvement was seen in 13 out of 20 patients (65%) in the probiotic group and 5 out of 19 patients (26.67%) in the placebo group and the p value was significant (0.02). (Table 9 & Chart 3).

Frequency of stools:

Frequency	No of patients	Percentage
1/2-3days	40	93%
1/4-5days	3	7%

Abdominal pain/Discomfort:

Severity	No of patients	Percentage
Mild	35	81.40%
Moderate	8	18.60%
Severe	0	0

Bloating:

	No of cases	Percentage
Bloating	31	72%
No bloating	12	28%

Quality of Life (QOL):

Grade	No of patients	Percentage
2 (Unhappy)	8	18.60%
3 (Mostly dissatisfied)	45	79%
4 (Mixed)	6	2.4%

Table 8: Symptomatology of IBS-C patients

	Probiotics	Placebo	P value
No of cases	20	19	
Improvement in frequency of stools	5(25%)	4(21%)	1.00 (Not Significant)
Improvement in abd pain	12(60%)	5(26.30%)	0.0536(Not Significant)
Improvement in QOL	13(65%)	5(26.30%)	0.02(Significant)

Table 9: Effect of probiotic vs placebo in IBS-C patients

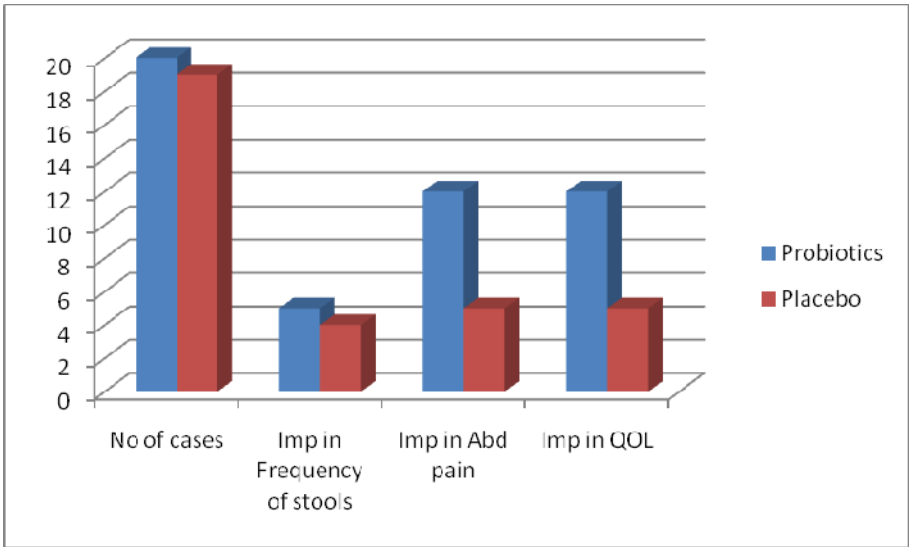

Chart 3 Effect of probiotic vs placebo in IBS-C patients

Key: Imp-Improvement

Bloating	Probiotic group	Placebo group
Improvement in bloating	11	4
No Improvement in bloating	5	11

Table 10: Improvement in bloating with probiotic vs placebo,

p value is 0.03

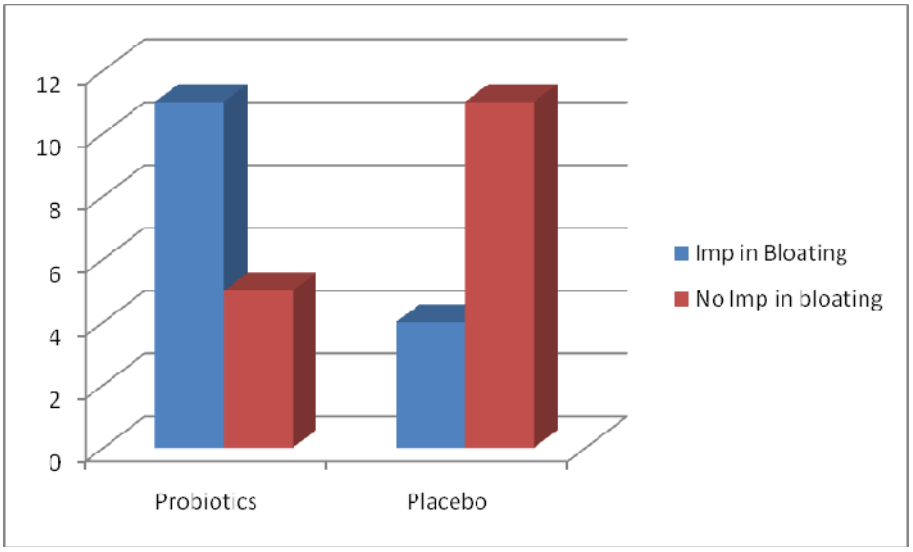

chart 4 Effect of probiotic vs placebo on bloating in IBS-C patients

Key: Imp-Improvement

IBS-M:

The IBS-M constituted only 4.45% of cases (5 out of 113). 3 patients received probiotic and 2 received placebo.2 out of 3 patients in the probiotic group showed improvement in symptoms while none of the patients in the placebo group showed any improvement in the symptoms; however statistical significance could not be calculated because of very small sample size.

DISCUSSION

EPIDEMIOLOGY AND CLINICAL PROFILE:

In our study IBS-D was the most common form of IBS which accounts for 57.5% of cases followed by IBS-C which accounts for 38% and then followed by IBS-M which accounted for only 4.5% of cases. In a study by Katsenilos et al in Greece, out of 373 patients with IBS 136 (36.5%) suffered from diarrhoea-predominant IBS, 165 (44.2%) suffered from IBS-C and 72 (19.3%) suffered from mixed type IBS.[70] This difference would probably be due to the fact that in even normal patients, the number of stools per week is less in the western population when compared to the east probably due to the difference in the dietary habits between the west and the east. Our data was also totally different from previously published Indian data on IBS done by the Task force of Indian society of Gastroenterology where IBS-Indeterminate type (57.18%) was the most commonest followed by IBS-C(38.97%)and then followed by IBS-D(3.84%).[68] The study was a prospective multicentre study in which data was obtained from 30 centers from all over the country with many authors contributing to the study compiled by Udhay Ghosal et al. In that study among indeterminate type constipation predominant was 53% and diarrhea predominant was 47%. Hence if we take that in to account again IBS-C was the most common type in that study which was again not found in our study. This difference might probably be due to difference in the clinical profile of IBS within different parts of the country. Population group in our study were only from southern part of India but the study by Udhay et al was from 30 centers all over the country, and in India we know that the diet, culture, religion, socioeconomic status are different in different parts of the country and they play an

important role in pathophysiology of IBS. We are continuing a larger study on this aspect and once the results are available we may be able to confirm our findings.
The incidence of IBS was more common in middle aged male patients in our study in contrast to the finding in other parts of the world where it is common in females. But this was also noted in the Indian study published by Udhay Ghosal et al where IBS was common in middle aged male patients (39.4yrs).In our study the mean age of presentation in male patients is 36.84 years and in female patients it is 43.34 years. Male to female ratio was 1.75: 1.00 in our study but in the Indian study by Udhay et al the ratio was 2.12:1.00.

Among the associated symptoms bloating was the most common symptom which was seen in 70 out of 113 patients (62%). Bloating was more common in IBS-C (72%) than IBS-D (60%) in our study. Other associated symptoms include nausea, heartburn, regurgitation, feeling of indigestion, urinary symptoms which were seen in 20 out of 113 cases (17.70%).This data was low when compared to the other previous studies (25-50%).

Effect of Probiotics on IBS:

More than 18 Randomized controlled studies has evaluated the effect of probiotics on various symptoms in patients with IBS. Few studies have also evaluated the effect of probiotic on Quality of life of patients with IBS. The results are very much conflicting between each trial so that the exact role of probiotic in IBS patient is not known. Almost all of the studies are from outside India and there are no studies in Indian population. Considering the pathophysiology of IBS where the cultural, economic, religious and social activities plays a major role, there may be considerable difference

between the disease profile between Indian population and foreign population. Hence a randomized controlled study in Indian population is required to confirm the role of probiotics in Indian patients with IBS. We selected frequency of stools, abdominal pain and bloating as main symptoms to be compared between probiotic and placebo since most of the studies have shown improvements with these symptoms. We also evaluated the improvement in quality of life in patients treated with probiotics which only very few studies have done.

IBS-D Population:

In our study the improvement with stool frequency was found to be statistically significant with probiotic when compared to placebo (p value is 0.03). This result was consistent with previous studies by O Sullivan et al (Lactobacillus GG 1×10^{10} cfu/day given two tablets twice a day for 20 week),Dolin BJ et al (Ganeden BC 30 bacillus coagulans given once a day for 8 weeks) and Guglielmetti S et al (Bifidobacterium bifidum MIMBb75 given once a day for 4 weeks).The studies done by Choi et al (Saccharomyces boulardii given for 4 wks) and Anwarul Kabir (*Lactobacillus* casei strain GG did not show any significant improvement in frequency of stools with probiotics when compared to placebo .

We also observed that improvement in frequency of stools was mostly seen in patients with more than 5 stools per day (p value is 0.02) showing that probiotics are more useful when stool frequency is more than 5 times per day. The cumulative reduction in stool frequency was atleast 2 stools/day.

The improvement in abdominal pain was not statistically significant with probiotics when compared to placebo in patients with IBS-C (p value was 0.11).This was also noted by the study done by Choei et al (Saccharomyces boulardii given for 4 wks).However the studies done by Guglielmetti S et al (Bifidobacterium bifidum MIMBb75 given once a day for 4 weeks),Jeng et al (Streptobacillus thermophilus, Lactobacillus bulgaricus, l.acidophilus, Bifidobacterium longus), Kim HJ et al (VSL # 3 mixture of bacteria **combination** One packet twice a day 8 wks), and O Sullivan et al (Lactobacillus GG 1×10^{10} cfu/day given two tablets twice a day for 20 week) showed that the improvement in abdominal pain was significant with probiotics when compared to placebo. Though many previous studies have shown that abdominal pain improves significantly with probiotics when compared to placebo our study failed to show any significant benefit.

The improvement in bloating was also not significant in probiotics when compared to placebo in patients with IBS-C. Similar result was seen in the study by Choi et al but most other studies (Guglielmetti S et al, Jeng et al, Kim HJ et al, O Sullivan et al) showed significant improvement with probiotics when compared to placebo).

In our study the overall QOL did not improve significantly with probiotics when compared to placebo (p value was 0.11) i patients with IBS-C. This was also seen in the study by Simren et al 2010 (L.Paracasei' L.acidophilus, Bifidobacterium lactis). Thus in our study though probiotic improved the frequency of stools significantly it failed to show any significant improvement in abdominal pain, bloating and overall Quality of life when compared to placebo.

IBS –C Population:

In our study 39 patients with IBS-C completed the study, 20 in the probiotic group and 19 in the placebo group. The improvement in the frequency of stool was not significant between probiotic and placebo group in our study (p value was 1.00). Similar result was also seen in the study by Sondergaard B et al (1.Lactobacillus paracasei ssp paracasei F19, 2.Lactobacillus acidophilus La5 and 3.Bifidobacterium lactis Bb12 given for 8 weeks). However Guandalini S et al jul 2010 in their study showed a significant improvement in stool frequency with probiotic (VSL# 3 given for 6 weeks) when compared to placebo. The probable reason for the improvement would be the strain used in that study and we need to confirm this by doing more stdies with VSL#3. In a study done by Chois et al, probiotics in combination with dietary fibre increased the frequency of stool in patients with IBS-C when compared to probiotic given alone. However the result of the above test has to be interpreted carefully as dietary fibre may itself independently increase the stool frequency even without the use of probiotic along with it. So there are conflicting results in the previous studies with regard to improvement in stool frequency and our study also failed to show any significant improvement with probiotics in patients with IBS-C.

The improvement in abdominal pain was also not significant with probiotics when compared to placebo (p value was 0.056) in our study but p value was almost very close to being significant (<0.05 when compared to 0.056).However many of the previous studies showed significant improvement in abdominal pain with probiotics when compared to placebo. Only in the study by Gayonet et al there was no significant improvement in the abdominal pain. Hence even though many studies

showed that the abdominal pain improves significantly with probiotics, our study did not show any statistical significance.

Probiotics improved bloating significantly in patients with IBS-C when compared to placebo in our study (p value was 0.03). Previous studies done by Guyonnet et al,Whorewell et al, Kajander K et al, Kim et al 2003, Kim et al 2005, Niedzelin K et al, Nobaeks et al, O Sullivan et al, Gade et al and many others also showed clearly the benefit of probiotic in IBS-C patients with bloating when compared to placebo. Hence our study is also consistent with the observations of the previous studies that probiotics are useful in IBS-C patients with bloating when compared to placebo.

The Quality of life in patients also improved with probiotics in our study when compared to placebo (p value was 0.02). Previous studies which showed similar results include the one done by Guyonnet et al, O Mahony et al, Niv et al and Guglielmetti et al. The quality of life improvement was more in patients with bloating mainly due to the improvement of their bloating symptom which was more troublesome to the patients.

IBS-M Population:

There were only 5 patients with IBS-M (Mixed) in our study. It constituted only 4.5% of patients with IBS when compared to 19% in a study by Katsenilos et al in Greece and 57.18% (IBS-Indeterminate variety) in a study by Uday et al from India. Three patients received probiotics and two patients received placebo in this group. 2 out of 3 patients in the probiotic group showed improvement in symptoms while none of the patients in the placebo group showed any improvement in the symptoms. However because of the very small sample size we were not able to compare the results. Not

many studies have concentrated on this group of IBS patients. With more understanding of Irritable bowel syndrome and with formation and subsequent modification of guidelines (Recently Rome III) we are able to categories IBS patients in to either diarrhoea predominant (IBS-D) or constipation predominant most of the time and only few patients are left with indeterminate variety which are categorized as IBS-M (Mixed).

Limitations of the study:

The strains used in our study were not used by any of the previous studies mentioned above and hence it is difficult for us to compare the effect of the strains used in our study with the results of other studies since the strains were different.

Since we know that IBS mainly depends on the psychosocial, economical, cultural, and religious, dietary aspects of the population under study, it is very difficult for us to compare our results with other studies because all of them are outside India and the population is totally different. We need Indian studies for comparison as well as for confirmation our results.

The effect of probiotics is mainly assessed based on the subjective improvement of the patient which again can be considered one of the limitations of our study.

CONCLUSION

In patients with constipation predominant IBS (IBS-C), probiotics improves bloating and quality of life (QOL) when compared to placebo, however the improvement in abdominal pain and frequency of stools was not significant.

In patients with diarrhea predominant IBS (IBS-D), probiotics improves the frequency of stools when compared to placebo but the improvement in abdominal pain, bloating and quality of life was not significant.

Hence from our study we conclude that probiotic treatment have a definitive role in the constipation predominant IBS patients with bloating and in reducing the stool frequency in diarrhea predominant IBS with high frequency of stool passage (>5 stools/day).

BIBLIOGRAPHY

1. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. BMJ 1978; 2:653-4.
2. Kruis W, Thieme C, Weinzierl M, et al. A diagnostic score for the irritable bowel syndrome. Its value in the exclusion of organic disease. Gastroenterology 1984; 87:1-7.
3. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. In: Drossman DA, editor. Rome III: The Functional Gastrointestinal Disorders. 3rd edition. McLean, VA: Dagnon Associates. 2006, pg 491
4. Drossman D, Camilleri M, Mayer E, Whitehead W. AGA technical review on irritable bowel syndrome. Gastroenterology 2002; 123;2108
5. Madden JA, Hunter JO: A review of the role of the gut microflora in irritable bowel syndrome and the effects of probiotics. Br J Nutr 2002; 88:S67-72.
6. Thompson WG,Dotevall DA, Drossman D et al. Irritable bowel syndrome: Guidelines for the diagnosis. Gastroenterology International 1989,2(2):92-5.
7. Drossman DA, Whitehead WE,Camilleri M, Irritable bowel syndrome: Technical review for practice guideline development. Gastroenterology 1997; 112(6):2120-37.
8. Agreus L, Svardsudd K, Tally NJ, et al. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population based study. Am J Gastroenterology 2001; 96(10):2905-14.
9. Tally NJ, Spiller R. Irritable bowel syndrome: A little understood organic bowel disease? Lancet 2002; 360(9322): 555-64.

10. Tally NJ, Zinsmeister AR, Melton LJ 111. Irritable bowel syndrome in a community: Symptom subgroups, risk factors and health care utilization. Am J Epidemiology 1995;142(1):76-83.
11. Quigley Emm. Current concepts of the irritable bowel syndrome. Scan J Gastroenterology 2002;38 (suppl237):1-8
12. Mayer EA, Collins SM, Evolving pathophysiological models of functional GI disorders. Gastroenterology 2002;122:2032-48
13. Poynard T, Navean S, Mary B et al. Meta analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 1994;8:499-510.
14. Bouin m, Plourde V, Boivin M et al. Rectal distension testing in patients with irritable bowel syndrome: sensitivity and false positive values of pain sensory thresholds. Gastroenterology 2002;122:1771-7.
15. Whiehead WE, Palsson OS, Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychosocial influences on pain perception. Gastroenterology 1998;115:1263-71.
16. Mc Kendrick MW, Read MW. Irritable bowel syndrome-post salmonella infection. J Infec 1994;29:1-3.
17. Collins SM. A case for an immunological basis for irritable bowel syndrome. Gastroenterology 2002;122:2078-80.
18. Chadwick V, Chen W, Shu D et al. Activation of the mucosal immune system. Gastroenterology 2002;122:1778-83.

19. O'Mahony L, Mc Carthy J, Kelly et al. Lactobacillus and Bifidobacterium in irritable bowel syndrome: Symptom responses and relationship to cytokine profiles. Gastroenterology 2005;128:541-51.
20. Gonsalkorale WM, Perrey C, Pravica V, et al. Interlukin 10 genotypes in irritable syndrome: Evidence for an inflammatory component? Gut 2003;52:91-3.
21. Pimentel M, Chow EJ, Lin HC. Eradication of small bowel bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 2000;95:3503-6.
22. Isolauri E, Kirjavainen PV, Salminen S. Probiotics: a role in the treatment of intestinal infec tion and inflammation? Gut 2002;50: 54-9.
23. Neal KR, Hebdon J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome BMJ 1997; 314:779-82.
24. Gacia Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: Cohort study. BMJ 1999;318:565-6.
25. Gwee KA, Graham JC, MC Kendrick MW, et al. Psychometric scores and persistence of irritable bowel after infectious diarrhea. Lancet 1996;347:150-3.
26. Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. Gut 1999;44:400-6.
27. Spiller RC, Jenkins D, Thorney JP et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following

acute Campylobacter enteritis and in Post-infectious irritable bowel syndrome. Gut 2000;47:804-11.

28. Illynckyi A, Balachandra B, Ellioh L, et al. Post- traveller's diarrhea irritable bowel syndrome: Prospective study. Am J Gastroenterol 2003;98:596-9.
29. Simren M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission. The impact of IBS- like symptoms associated psychological factors. Am J Gastro enterol 2002;97:389-96.
30. Torblom H, Lindberg G, Nyberg B, et al. Full thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. Gastroenterology 2002;123:1973-9.
31. Barbara G, Stanghellini V, De Giorgio R et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastro enterology 2004;126:693-702.
32. Spiller RC. Role of nerves in enteric infection. Gut 2001;51:759-62.
33. O'Mahony L, Feeney M, O'Halloran S;et al. Probiotic impact on microbial flora, inflammation and tumour development in IL-10 knockout mice. Aliment pharmacol Ther 2001;15:1219-25.
34. Gionchetti P, Rizzello F, Helwig U,et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo controlled trial.Gastroenterology 2003;124:1202-09.
35. Gionchetti P, Rizzello F, Venturi A et al. Oral bacteriotherapy as maintainence treatment in patients with chronic pouchitis: a double blind, placebo-controlled trial. Gastroenterology 2000;119:305-9.

36. Greenwood-Van, Meervald B, Johnson AC, et al. Probiotic bacteria normalize post-inflammatory visceral hyperalgesia in rats. Gastroenterology 2004;126:1358-73.
37. Verdu EF, Bercik P, Bergonzelli GE,et al. Lactobacillus paracasei normalizes muscle hypercontractility in a murine model of post infective gut dysfunction. Gastroenterology 2004;127:826-37.
38. Pimentel M, Ehow E, Lin H. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. AM J Gastroenterology 2003;98:412-9.
39. Tursi A, Brandimarte G, Giorgetti GM. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastro intestinal symptoms after gluten withdrawal. Am J Gastro enterol 2003;98:839-43.
40. Ouwehand AC, Lagstrom H, Suomalainen T et al. Effect of probiotic on constipation,fecal azoreductase activity and fecal mucin content in the elderly. Ann Nutr Metab 2002;15:159-62.
41. Cremonini F, Delgado Aros S, Camelleri M. Efficacy of allosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. Neurogastroenterol Motil 2003;15:79-86.
42. Muller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5 HT receptor partial agonist relieves symptoms in irritable bowel syndrome patients abdominal pain, bloating and constipation. Aliment pharmacol Ther 2001;15:1655-66.

43. Hong YS, Hong KS, Park MH,et al. Metabonomic understanding of probiotic effects in humans with irritable bowel syndrome.J Clin Gastroenterol. 2011 May-Jun;45(5):415-25.
44. Hamilton-Miller JMT. Probiotics in the management of irritable bowel syndrome: a review of clinical trials. Microb Ecol Health Dis 2001;13:212-6.
45. Niedzielin K, Kordecki H, Birkenfeld B: A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum299V in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2001, 13(10)**:**1143-7
46. Halpern GM, Prindiville T, Blackenberg M et al. Treatment of irritable bowel syndrome with lacteal fort: a randomized, double blind, cross-over trial. Am J Gastroenterol 1996;91:1579-85
47. O'Sullivan MA, O'Morain CA: : Bacterial supplementation in the irritable bowel syndrome. A randomised double-blind placebo-controlled crossover study. Dig Liver Dis 2000, 32(4)**:**294-301.
48. Nobaek S, Johansson ML, Molin G, Ahrne S, Jeppsson B: Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 2000, 95(5):1231-8.
49. Kim HJ, Camilleri M, McKinzie S, Lempke MB, Burton DD, Thomforde GM, Zinsmeister AR. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2003**;**17:895–904

50. O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 2005, 128(3):541-51.
51. Saggioro A: Probiotics in the treatment of irritable bowel syndrome. J Clin Gastroenterol 2004, 38(6 Suppl):S104-S106
52. Kajandar K, Myllyluoma E, Rajlic-Stojanovic M, Kyronpalo SS, Rasmussen M, Jarvenpaa SS, Zoetendal EG, Vos WM, de Vapaatalo H, Korpela R: Clinical trial: multispecies probiotic supplementation alleviates alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment Pharmacol Ther 2008, 27(1):48-57.
53. Bausserman M, Michail S: The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. J Pediatr 2005, 147(2):197-201.
54. Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, et al.: Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 2006, 101(7):1581-90.
55. Gawronska A, Dziechciarz P, Horvath A, Szajewska H: A randomized double-blind placebo-controlled trial of Lactobacillus GG for for abdominal pain disorders in children. Aliment Pharmacol Ther 2007, 25(2):177-84.
56. Guyonnet D, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier CH, et al.: Effect of a fermented milk containing Bifidobacterium animalis DN-173 010

on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther 2007, 26(3):475-86.

57. Kyoung Sup Hong,* Hyoun Woo Kang,* Jong Pil Im, et al. Effect of Probiotics on Symptoms in Korean Adults with Irritable Bowel Syndrome. Gut Liver. 2009 June; 3(2): 101–107

58. Williams EA, Stimpson J, Wang D et al. Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. Aliment Pharmacol Ther. 2009 Jan;29(1):97-103

59. Hong KS, Kang HW, Im JP et al. Effect of probiotics on symptoms in korean adults with irritable bowel syndrome. Gut Liver. 2009 Jun;3(2):101-7

60. Dolin BJ. Effects of a proprietary Bacillus coagulans preparation on symptoms of diarrhea- predominant irritable bowel syndrome. Methods Find Exp Clin Pharmacol. 2009 Dec;31(10):655-9.

61. Hun L. Bacillus coagulans significantly improved abdominal pain and bloating in patients with IBS. Postgrad Med. 2009 Mar;121(2):119-24.

62. Enck P, Menke G, Zimmermann K, Martens U, Klosterhalfen S. Effective probiotic therapy of the irritable bowel syndrome (IBS): A multi-center clinical trial with primary care physicians. Gastroenterology. 2007;132 Suppl 2:A79.

63. Lyra A, Krogius-Kurikka L, Nikkilä J, et al. Effect of a multispecies probiotic supplement on quantity of irritable bowel syndrome-related intestinal microbial phylotypes. BMC Gastroenterol. 2010 Sep 19;10:110

64. Guandalini S, Magazzù G, Chiaro A, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010 Jul;51(1):24-30.

65. Choi SC, Kim BJ, Rhee PL, et al. Probiotic Fermented Milk Containing Dietary Fiber Has Additive Effects in IBS with Constipation Compared to Plain Probiotic Fermented Milk. Gut Liver. 2011 Mar;5(1):22-8.

66. Choi CH, Jo SY, Park HJ, et al. A Randomized, Double-blind, Placebo-controlled Multicenter Trial of Saccharomyces boulardii in IrritableBowel Syndrome: Effect on Quality of Life. J Clin Gastroenterol. 2011 Feb 4. [Epub ahead of print]

67. Guglielmetti S, Mora D, Gschwender M, Popp K. Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life--a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011 May;33(10):1123-32

68. Søndergaard B, Olsson J, Ohlson K, et al. Effects of probiotic fermented milk on symptoms and intestinal flora in patients with irritable bowel syndrome: A randomized, placebo-controlled trial. Scand J Gastroenterol. 2011 Jun;46(6):663-72

69. Uday et al, Epidemiological and clinical profile of Irritable bowel syndrome in india: Report of the Indian Society of Gastroenterology Task Force. Indian journal of Gastroenterology 2008 volume 27, number1.
70. Katsinelos P, Lazaraki G, Kountouras J, et al. Prevalence, bowel habit subtypes and medical care-seeking behaviour of patients with irritable bowel syndrome in Northern Greece. Eur J Gastroenterol Hepatol. 2009 Feb; 21(2):183-9.

APPENDIX I

CONSENT FORM AND
PATIENT INFORMATION FORM

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

இரிட்டபுள் பவல் சின்ட்ரோம் எனும் நோயில்
புரோபயாடிக் எனும் மாத்திரையின் பங்கு

ஆராய்ச்சி நிலையம் : குடல் பிரிவு
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக்கல்லூரி,
சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :
பங்கு பெறுபவரின் எண் :

பங்கு பெறுவர் இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டஏாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

ஆராய்ச்சி தகவல் தாள்

சென்னை அரசு பொது மருத்துவமனையில் இரிட்டபுள் பவல் சின்ட்ரோம் எனும் நோயில் புரோபயாடிக் எனும் மருந்தின் பங்கு பற்றிய ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

இவ்வாராய்ச்சியின் நோக்கம் யாதெனில் இரிட்டபுள் பவல் சின்ட்ரோம் நோயினால் பாதிக்கப்பட்டவர்களுக்கு பிரோபயாடிக் மாத்திரை அல்லது வெற்று மருந்து ஆறு வாரங்களுக்கு ஒரு நாளைக்கு இருமுறை கொடுக்கப்பட்டு ஆறு வாரங்களின் முடிவில் அந்த மாத்திரையினால் நோயில் பாதிப்புகள் குறைந்ததா என்று ஆராய்ந்து ஒரு முடிவு எடுக்கப்பவதே ஆகும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு உள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

தேதி

PATIENT CONSENT FORM

Study Details : **Role of Probiotics in Irritable Bowel Syndrome**

Study Centre : Department of Gastroenterology,
Madras Medical College, Chennai.

Patient may check (✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study. ☐

Signature/ Thumb Impression:
Patient Name and Address: Place Date

Signature of Investigator
Study Investigator's Name: Place Date

INFORMATION SHEET

- We are conducting an randomized double blined controlled study on “The role of probiotics in Irritable Bowel Syndrome” at Department of Gastroenterology, Madras Medical College and Government General Hospital, Chennai.
- The purpose of the study is to evaluate the the role of probiotics in Irritable Bowel Syndrome.
- Irritable Bowel Syndrome patients will be divided into two groups. One group will received probiotics and other goup will receive placebo twice a day for six weeks. At the end of six weeks the effect of both the drugs on each of the symptoms will be analysed and compared.
- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator ***Signature of participant***

Date:

APPENDIX II

PROFORMA

APPENDIX: II

PROFORMA

Name : MGE NO:

Age/ Sex: IP NO:

Ocupation:

Address:

Chief complaints:

History of presenting illness:

Onset: SUDDEN (Following an AGE) / GRADUAL

Symptoms	**symptom scorebefore trt**	**Symp score after trt**
1.Abd pain/ Abd discomfort		
2.Bloating/ Abd distension		
3.constipation:		
a.straining		
b.Incomplete evacuation		
c.frequency		
d.digital evacuation		
4.Loose stools:		
a.Frequency		
b.mucus		
c.Urgency		

d.incontinence

5.flatulence:

6.Borborygmi:

7.nausea

8.dyspepsia

9.heartburn

10. Regurgitation

Other Non GI symptoms:

Headache, Backache, Myalgia YES/NO

Urinary symptoms,Insomnia YES/NO

History of red flag symptoms:

Unintentional weight loss YES/NO

Loss of appetite YES/NO

Short duration of symptoms YES/NO

Nocturnal symptoms YES/NO

Rectal bleeding YES/NO

Recent use of antibiotics YES/NO

Awareness of lump in the abdomen YES/NO

Perianal mass/ discharging sinuses YES/NO

fever YES/NO

Other relevant history:

Relation to food : milk/ alcohol/ wheat etc..

Recent travel history

Abnormal eating habits

PAST HISTORY:

History of DM/ HTN /TB/ BA/ IHD/ CVA/ EPILEPSY

h/o similar illness in the past

h/o surgery/ Jaundice/ transfusion/ Tatooing

Personal history:

H/o alcohol intake

h/o smoking

h/o psychiatric illness

Family history:

h/o GI cancers/ Inflammatory bowel disease/ celiac disease

Examination:

Pallor/ cyanosis/ Clubbing / Pedal edema/ Raised JVP/ Icterus/ Lymphadenopathy

Ht: Wt: BMI:

Oral cavity:

AbdomenExamination:

Inspection:

Palpation:

Percussion:

Auscultation:

Per rectal Examination:

INVESTIGATIONS

CBC:

Hb:

TC:

DC:

ESR:

PLT:

Peripheral smear:

RFT: Urea:

Creatinine:

Urine routine:

Motion routine:

CXR:

ECG:

USG ABDOMEN:

FOS/COLONOSCOPY:

APPENDIX III

QUALITY OF LIFE QUESTIONNAIRE

APPENDIX : III

Health, Wellness & Quality of Life Questionnaire

Answer each of the questions below by putting a circle around the number that **best** represents you at this time.

Case Number: _____

I. Physical State

Date: _____

Rate the following questions with respect to frequency:

	Never	Rarely	Occasionally	Regularly	Constantly
1. Presence of physical pain (neck/back ache, sore arms/legs, etc.).	1	2	3	4	5
2. Feeling of tension or stiffness or lack of flexibility in your spine.	1	2	3	4	5
3. Incidence of fatigue or low energy.	1	2	3	4	5
4. Incidence of colds and flu.	1	2	3	4	5
5. Incidence of headaches (of any kind).	1	2	3	4	5
6. Incidence of nausea or constipation.	1	2	3	4	5
7. Incidence of menstrual discomfort.	1	2	3	4	5
8. Incidence of allergies or skin rashes.	1	2	3	4	5
9. Incidence of dizziness or light-headedness.	1	2	3	4	5
10. Incidence of accidents or near accidents or falling or tripping.	1	2	3	4	5

II. Mental/Emotional State

Rate the following questions with respect to frequency:

	Never	Rarely	Occasionally	Regularly	Constantly
1. If pain is present, how distressed are you about it?	1	2	3	4	5
2. Presence of negative or critical feelings about your self.	1	2	3	4	5
3. Experience of moodiness or temper or angry outbursts.	1	2	3	4	5
4. Experience of depression or lack of interest.	1	2	3	4	5
5. Being overly worried about small things.	1	2	3	4	5
6. Difficulty thinking or concentrating or indecisiveness.	1	2	3	4	5
7. Experience of vague fears or anxiety.	1	2	3	4	5
8. Being fidgety or restless; difficulty sitting still.	1	2	3	4	5
9. Difficulty falling or staying asleep.	1	2	3	4	5
10. Experience of recurring thoughts or dreams.	1	2	3	4	5

III. Stress Evaluation

Evaluate your stress relative to the following:

	None	Slight	Moderate	Pronounced	Extensive
1. Family.	1	2	3	4	5
2. Significant Relationship.	1	2	3	4	5
3. Health.	1	2	3	4	5
4. Finances.	1	2	3	4	5
5. Sex Life.	1	2	3	4	5
6. Work.	1	2	3	4	5
7. School.	1	2	3	4	5
8. General well-being.	1	2	3	4	5
9. Emotional well-being.	1	2	3	4	5
10. Coping with daily problems.	1	2	3	4	5

IV. Life Enjoyment

Rate the following on a degree scale of 1-5:

	Not at all	Slight	Moderate	Considerable	Extensive
1. Openness to guidance to your "inner voice/feelings."	1	2	3	4	5
2. Experience of relaxation or ease or well-being.	1	2	3	4	5
3. Presence of positive feelings about yourself.	1	2	3	4	5
4. Interest in maintaining a healthy lifestyle (e.g., diet, fitness, etc).	1	2	3	4	5
5. Feeling of being open and aware/connected when relating to others.	1	2	3	4	5
6. Level of confidence in your ability to deal with adversity.	1	2	3	4	5
7. Level of compassion for, and acceptance of, others.	1	2	3	4	5
8. Satisfaction with the level of recreation in your life.	1	2	3	4	5
9. Incidence of feelings of joy or happiness.	1	2	3	4	5
10. Level of satisfaction with your sex life.	1	2	3	4	5
11. Time devoted to things you enjoy.	1	2	3	4	5

V. Overall Quality of Life

Evaluate your feelings relative to the quality of life:

	Terrible	Unhappy	Mostly Dissatisfied	Mixed	Mostly Satisfied	Pleased	Delighted
1. Your personal life.	1	2	3	4	5	6	7
2. Your wife/husband or "significant other".	1	2	3	4	5	6	7
3. Your romantic life.	1	2	3	4	5	6	7
4. Your job.	1	2	3	4	5	6	7
5. Your co-workers.	1	2	3	4	5	6	7
6. The actual work you do.	1	2	3	4	5	6	7
7. The handling of problems in your life.	1	2	3	4	5	6	7
8. What you are actually accomplishing in your life.	1	2	3	4	5	6	7
9. Your physical appearance - the way you look to others.	1	2	3	4	5	6	7
10. Your self.	1	2	3	4	5	6	7
11. Your ability to adjust to change in your life.	1	2	3	4	5	6	7
12. Your life as a whole.	1	2	3	4	5	6	7
13. Overall contentment with your life.	1	2	3	4	5	6	7
14. The extent to which your life has been as you want it.	1	2	3	4	5	6	7

VI. Overall Impressions

Answer each of the questions with respect to when you first came to this office:

	Better	Same	Worse
1. Overall my physical well-being is:	1	2	3
2. Overall my mental/emotional state is:	1	2	3
3. Overall my ability to handle stress is:	1	2	3
4. Overall my enjoyment of life is:	1	2	3
5. Overall my quality of life is:	1	2	3

APPENDIX IV

ETHICAL COMMITTEE CLEARANCE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. B. Vinoth
PG in DM Medical Gstroenterology
Madras Medical College, Chennai -3

Dear Dr. B. Vinoth

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trail entitled " The role of Probiotics in Irritable bowel syndrome " No. 14102010.

The following members of Ethics Committee were present in the meeting held on 22.10.2010 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD	-- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3. Prof. A. Sundaram, MD Vice Principal , MMC, Chennai -3	-- Member Secretary
4. Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
5. Prof. Pregna B. Dolia , MD Director, Institute of Biochemistry, MMC, Ch-3	-- Member
6. Prof. C. Rajendran , MD Director, Institute of Internal Medicine, MMC, Ch-3	-- Member
7. Prof. Md. Ali, MD, DM Professor & Head ,,Dept. of MGE, MMC, Ch-3	-- Member
8. Thiru. S. Govindasamy BA.BL	-- Lawyer
9. Tmt. Arnold Soulina	-- Social Scientist

We approve the Proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

APPENDIX V

MASTER CHART

Name	Age	sex	Hosp No	Type of IBS	Frequency of stool	Abd pain	Bloating	associated symptoms	QOL	Drug	Frequency o	Abd pain	Bloating	Other symp	QOL	Phone No
Saraswathy	55	F	326/99	D	7-8/day	2+	-	Y, epigastric discomfort	2	probiotic	Y	Y	NA	N	Y	
Sarala	47	F	4589/04	D	4-5/day	1+	+	no	3	probiotic	N	N	N	N	N	9444627109
Rani 2	55	F	1083/08	D	4-5/day	2+	+	no	2	probiotic	N	N	Y	N	N	9787948481
Sekar	34	M	6414/08	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Muthammal	30	F	1632/09	D	4-5/day	1+	+	no	3	probiotic	N	N	N	N	N	
Shanthi	36	F	2217/09	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Manohar	40	M	2969/09	D	5-6/day	1+	-	no	3	probiotic	D	D	D	D	D	
Uma farooq	24	M	5285/09	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Puzal mannan	32	M	5867/09	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Nagoor meera	39	M	6610/09	D	4-5/day	1+	+	no	3	Probiotic	N	N	N	N	N	
Chinnaraj	24	M	397/10	D	4-5/day	1+	+	no	3	probiotic	N	N	N	N	N	
Arul	20	M	1178/10	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Jayakumar	29	M	1753/10	D	6-7/day	1+	+	Y, epigastric discomfort	3	probiotic	N	N	N	N	N	
Jallal	40	M	1999/10	D	6-7/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Vishwanathan	48	M	2243/10	D	3-4/day	2+	-	no	3	probiotics	Y	Y	NA	N	Y	9884389841
Vijaya	30	F	3283/10	D	6-7/day	1+	+	no	3	probiotic	N	N	N	N	N	
Devi	70	F	3588/10	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	9884584690
Karthikeyan	29	M	3690/10	D	5-6/day	1+	+	no	3	probiotic	N	N	N	N	N	9840814558
Rajagopal	40	M	4190/10	D	5-6/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Sathiya	24	F	4293/10	D	10-12/day	2+	+	Y, Nausea, Regurgitation	2	probiotic	Y	Y	Y	N	Y	
Karthick 2	28	M	4473/10	D	5-6/day	1+	-	no	3	probiotic	D	D	D	D	D	9841784212
Shanmugam	21	M	4698/10	D	3-4/day	1+	-	no	3	probiotic	D	D	D	D	D	
Dillibabu	34	M	4858/10	D	6-7/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	9786293727
Babu 1	32	M	4997/10	D	6-7/day	1+	+	Y,Heartburn,regurgitation	3	probiotic	N	N	N	N	N	
Siranjivi	26	M	5367/10	D	4-6/day	1+	+	Y,Indigestion, urinary	2	probiotic	Y	N	N	N	N	9840696446
Suddamuthu	50	M	5441/10	D	5-6/day	1+	-	no	4	probiotic	N	N	NA	N	N	
Jothi	40	F	5766/10	D	4-5/day	1+	+	yes, heartburn, dysp	4	probiotic	N	N	N	N	N	
Karthick 1	28	M	6088/10	D	4-5/day	1+	-	no	3	probiotic	N	N	NA	N	N	
Janibasha	36	M	6491/10	D	5-6/day	1+	+	no	4	probiotic	Y	Y	Y	N	Y	
Lakshmi	50	F	6726/10	D	3-4/day	2+	-	no	2	probiotic	N	N	NA	N	N	9787527288
Napoleon	30	M	6867/10	D	4-5/day	1+	+	no	3	probiotic	Y	Y	Y	N	Y	9790712791
Vasantha	45	F	124/11	D	4-5/day	2+	+	no	2	probiotic	Y	Y	Y	N	Y	
Bharanitharan	19	M	2369/11	D	5-6/day	2+	-	no	2	probiotic	N	N	NA	N	N	
Susheela	47	F	4556/04	D	5-6/day	2+	+	no	2	placebo	y	Y	Y	N	Y	
Selvi	46	F	1000/08	D	4-5/day	1+	-	no	3	placebo	N	N	NA	N	N	9180122171
Rani	55	F	3836/08	D	4-5/day	1+	-	no	3	placebo	D	D	D	D	D	
Kumar	46	M	878/09	D	5-6/day	1+	+	no	3	placebo	N	N	N	N	N	
Venu	56	M	2011/09	D	6-7/day	2+	-	no	2	placebo	N	N	NA	N	N	9840341876
Vishwanathan	55	M	2243/09	D	2/day	1+	+	no	3	placebo	N	N	N	N	N	
Sundarajan	46	M	3545/09	D	5-6/day	1+	+	no	3	placebo	Y	Y	Y	N	Y	

Satyabagam	37	F	5365/09	D	4-5/day	1+	+	Y,Heartburn	3	placebo	N	N	N	N	N	
srinivasan 2	31	M	5920/09	D	5-6/day	1+	+	no	3	placebo	N	N	N	N	N	
Vadamalai	45	M	7032/09	D	7-8/day	2+	-	no	2	placebo	N	Y	NA	N	Y	
Venkatesan 1	35	M	1135/10	D	5-6/day	1+	+	no	3	placebo	N	N	N	N	N	
Jayalakshmi	30	F	1718/10	D	4-5/day	2+	+	Y,indigestion	2	placebo	D	D	D	D	D	
Ramani	30	F	1871/10	D	3-4/day	1+	-	no	3	placebo	Y	Y	NA	N	Y	
Vadivu	25	M	2028/10	D	5-6/day	1+	+	no	3	placebo	N	N	N	N	N	
Masilamani	30	M	3068/10	D	5-6/day	1+	-	no	3	placebo	N	N	NA	N	N	
Srinivasan 1	33	M	3385/10	D	12-15/day	1+	-	no	2	placebo	Y	Y	NA	N	Y	9940552893
Selvaraj	46	M	3625/10	D	4-5/day	2+	+	Y,Dysp,Heartburn	2	placebo	N	N	N	N	N	9750713441
Revathy	40	F	3721/10	D	4-5/day	1+	-	no	3	placebo	N	N	NA	N	N	
Andal	53	F	4252/10	D	5-6/day	1+	+	Y, Indigestion	3	placebo	N	N	N	N	N	
Chandrika	46	F	4452/10	D	5-6/day	1+	+	no	3	placebo	N	N	N	N	N	
Bhavani	22	F	4567/10	D	7-8/day	2+	+	no	2	placebo	y	y	y	N	y	
Kala	53	F	4834/10	D	5-6/day	1+	-	no	4	placebo	N	N	NA	N	N	
Dilli 2	52	M	4892/10	D	5-6/day	1+	-	no	4	placebo	N	N	NA	N	N	
Babu 2	35	M	5108/10	D	6-7/day	1+	-	no	3	placebo	N	N	NA	N	N	9840764792
Saroja	49	F	5369/10	D	5-6/day	1+	+	no	3	placebo	y	y	y	N	y	
Komagan	27	M	5489/10	D	4-5/day	1+	-	Y,epigastric discomfort	3	placebo	N	N	NA	N	N	
Raja	40	M	6015/10	D	3-4/day	1+	-	no	3	placebo	N	N	NA	N	N	
Poongothai	47	F	6447/10	D	5-6/day	1+	-	no	3	placebo	N	N	NA	N	N	
Logeswari	50	F	6607/10	D	3-4/day	1+	-	no	3	placebo	N	N	NA	N	N	
Manikandan	21	M	6814/10	D	2-3/day	1+	-	no	4	placebo	N	N	NA	N	N	
Venkatathiri	25	M	6937/10	D	6-7/day	1+	-	no	3	placebo	N	N	NA	N	N	9500904091
Solaiman	54	M	361/11	D	3/day	1+	+	no	3	placebo	Y	Y	Y	N	Y	9965683758
Ramasamy	70	M	5621/07	C	1/2days	1+	+	no	3	probiotic	N	Y	Y	N	Y	
Panchavarnam	45	F	1218/09	C	1/2-3days	1+	+	no	3	probiotic	Y	Y	Y	N	Y	
Nagendran	50	M	1495/09	C	1/2-3day	1+	+	no	3	probiotic	N	N	N	N	N	
Nagappan	72	M	5861/09	C	1/2-3day	2+	+	Y, Nausea	2	probiotic	Y	Y	Y	N	Y	
Vanitha 2	30	F	77/10	C	1/2-3days	1+	+	yes, indigestion	3	probiotic	N	Y	Y	N	Y	9600169592
Shanmugam	50	M	1119/10	C	1/2-3days	2+	+	no	3	probiotic	N	N	N	N	N	
Renubee	32	F	1180/10	C	1/2-3day	2+	+	no	2	probiotic	Y	Y	Y	N	Y	9841177058
Patciappan	22	M	1669/10	C	1/2-3day	1+	+	no	3	probiotic	N	N	N	N	N	
Kumar	39	m	3459/10	c	1/2-3day	1+	+	no	3	probiotic	N	Y	Y	N	Y	
Dilli	32	M	3622/10	C	1/2-3day	1+	+	no	3	probiotic	N	Y	Y	N	Y	9688685986
Ganesan	36	M	4053/10	C	1/2-3day	1+	+	no	3	probiotic	N	N	N	N	N	9994664974
Padma	55	F	4462/10	C	1/2-3days	1+	-	no	3	probiotic	D	D	D	D	D	
Vatsala	35	F	4481/10	C	1/2-3days	1+	+	no	3	probiotic	N	Y	Y	N	Y	
Timitro	20	M	4595/10	C	1/2-3days	1+	+	no	3	probiotic	N	N	y	N	y	9940282430
Vanitha 1	22	F	4805/10	C	1/2days	1+	+	no	3	probiotic	Y	Y	Y	N	Y	9688595317
Abdulbariq	45	M	4954/10	C	1/2-3days	1+	+	no	3	probiotic	N	Y	Y	N	Y	
Moses	32	M	5055/10	C	1/2-3days	1+	-	no	3	probiotic	N	Y	NA	N	Y	

Girija	37	F	5717/10	C	1/2-3days	1+	-	no	3	probiotic	D	D	D	D	D	
Karnan	45	M	6376/10	C	1/2-3day	2+	-	no	2	probiotic	N	N	NA	N	N	9380772394
Krishnan	55	M	520/11	C	1/2-3days	1+	-	no	3	probiotic	N	N	NA	N	N	9042783694
Subramani	40	M	721/11	C	1/3-4days	1+	+	no	3	probiotic	Y	Y	Y	N	Y	9943313157
Pushpavathy	55	F	1018/11	C	1/2-3days	1+	-	no	3	probiotic	N	N	NA	N	N	
Baby	60	F	909/09	C	1/2-3day	1+	+	Y,epigastric discount	2	placebo	Y	Y	Y	N	Y	
Mangalamary	55	F	1431/09	C	1/2-3day	2+	+	no	2	placebo	N	N	N	N	N	
Sivakumar	34	M	5702/09	C	1/2-3day	1+	-	no	3	placebo	N	N	N	N	N	
Sampoorna	55	F	7201/09	C	1/2-3day	2+	+	Y, Indigestion	2	placebo	N	N	N	N	N	
Rajakumari	46	F	1025/10	C	1/4days	1+	+	no	3	placebo	Y	Y	Y	N	Y	
Mani	26	M	1172/10	C	1/2-3day	1+	+	no	3	placebo	N	N	N	N	N	
Machalingam	40	M	1545/10	C	1/2-3day	1+	+	no	3	placebo	N	N	N	N	N	
Yogalakhsmi	45	M	1940/10	C	1/2-3day	1+	-	no	3	placebo	N	Y	N	N	Y	
Malathy	45	F	3572/10	C	1/2-3day	2+	+	no	2	placebo	N	N	N	N	N	9176599405
Anand	47	M	3699/10	C	1/2-3 days	1+	+	Y, heart burn	3	placebo	N	N	N	N	N	
Karthiraj	53	M	4061/10	C	1/2-3day	1+	-	no	3	placebo	D	D	D	D	D	9976080165
Venkatesan 2	41	M	4463/10	C	4-5/day	1+	+	yes, Regurgitation, belch	3	placebo	Y	Y	Y	N	Y	9382302228
Anandaraj	34	M	4488/10	C	1/2-3day	1+	+	no	3	placebo	N	N	N	N	N	
Mahalakshmi	40	F	4641/10	C	1/2-3days	2+	-	no	2	placebo	N	N	N	N	N	9285955751
Gowri	50	F	4932/10	C	1/2-3days	1+	+	no	3	placebo	N	N	N	N	N	
Anandaraj	34	M	4998/10	C	1/2-3days	1+	+	no	4	placebo	Y	Y	Y	N	Y	
Sakthivel	33	M	5348/10	C	1/2-3days	1+	-	no	3	placebo	N	N	N	N	N	9940140174
Gopal	35	M	5842/10	C	1/2-3days	1+	+	no	3	placebo	N	N	N	N	N	9444141427
Ramdoss	20	M	6476/10	C	1/2-3days	1+	+	no	3	placebo	N	N	N	N	N	9003472660
Subramani	48	M	720/11	C	1/2-3days	1+	+	Y,nausea,regurgitation	3	placebo	N	N	N	N	N	
Venkatesan	32	M	998/11	C	1/2-3days	1+	-	no	3	placebo	D	D	D	D	D	
kotteswaran	30	M	7104/09	M	2-3/day	1+	-	Y, epigastric discomfort	3	probiotic	N	N	NA	N	N	
Prakash	20	M	6005/10	M	5-6/day	1+	-	no	4	probiotic	Y	Y	NA	N	Y	9840333198
Kavitha	28	F	734/11	M	3-4/day	1+	-	no	3	probiotic	Y	Y	NA	N	Y	9884159909
Narasimhan	33	M	1851/10	M	4-5/day	2+	+	Y,Heartburn	2	placebo	N	N	N	N	N	
Kumar	35	M	325/11	M	1/2-3days	1+	-	no	3	placebo	N	N	NA	N	N	