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**Is irritable bowel syndrome an infectious disease?**

Thompson JR.IBS: an infectious disease

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**Abstract**

Irritable bowel syndrome (IBS) is the most common of all gastroenterological diseases. While many mechanisms have been postulated to explain its etiology, no single mechanism entirely explains the heterogeneity of symptoms seen with the various phenotypes of the disease. Recent data from both basic and clinical sciences suggest that underlying infectious disease may provide a unifying hypothesis that better explains the overall symptomatology. The presence of small intestinal bowel overgrowth (SIBO) has been documented in patients with IBS and reductions in SIBO as determined by breath testing correlate with IBS symptom improvement in clinical trials. The incidence of new onset IBS symptoms following acute infectious gastroenteritis also suggests an infectious cause. Alterations in microbiota-host interactions may compromise epithelial barrier integrity, immune function, and the development and function of both central and enteric nervous systems explaining alterations in the brain-gut axis. Clinical evidence from treatment trials with both probiotics and antibiotics also support this etiology. Probiotics appear to restore the imbalance in the microflora and improve IBS-specific quality of life. Antibiotic trials with both neomycin and rifaximin show improvement in global IBS symptoms that correlates with breath test normalization in diarrhea-predominant patients. The treatment response to two weeks of rifaximin is sustained for up to ten weeks and comparable results are seen in symptom reduction with retreatment in patients who develop recurrent symptoms.

**Key words:** irritable bowel syndrome; pathopohysiology; etiology; Probiotics; antibiotics; infectious disease

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**Core tip:** Recent evidence from both basic and clinical science supports the hypothesis of infectious disease as an etiological agent in irritable bowel syndrome (IBS). The presence of small intestinal bowel overgrowth and its treatment as reflected in reductions of lactulose hydrogen breath tests correlates with improvement in IBS symptoms. Clinical trials with both probiotics and antibiotics also appear to relieve symptoms of IBS and have a sustained effect post-treatment. Recurrences of symptoms post-treatment appear to respond similarly with no loss of effect. An infectious disease etiology of IBS may explain the heterogeneous symptoms of the disease and varying responses seen with different symptom phenotypes.

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**INTRODUCTION**

Irritable bowel syndrome (IBS) is the most common gastroenterological disorder with a worldwide prevalence of 7%-21%[1]. Common symptoms include bloating with abdominal pain and altered bowel habits, with women experiencing more constipation and men experiencing more diarrhea. Difference in gender prevalence and phenotype vary geographically.

While many theories have been proposed in the past to explain the pathology of IBS, more recent evidence from both the basic and clinical sciences seems to point toward an infectious etiology. Our present situation with IBS may be analogous to that several years ago when Dr. Barry Marshall first suggested the cause of peptic ulcer disease to be *Helicobacter pylori*[2]. At that time most people believed excess gastric acid to be the source of the disease, but we now all accept the bacterial etiology of that disorder and our treatment has been directed toward it. Thus it is appropriate to examine the current evidence and ask if IBS might also be an infectious disease in origin.

**PATHOPHYSIOLOGY OF IBS**

Many things have been suggested to be the cause of IBS symptoms including abnormalities in motility, visceral sensation, brain-gut interaction, and psychosocial distress[1].Buckley recently proposed a convergence of neural, endocrine, and immune influences to explain the heterogenous symptoms of this disease[3]. Disordered neural signaling in IBS may be manifested as autonomic dysfunction, visceral hypersensitivity, sensitization of primary afferents, central pain amplification and enhanced central nervous system responses. Endocrine pathways may also contribute to the pathophysiology of IBS through the stress-induced production of corticotropin releasing factor (CRF), cortisol, and glucagon-like peptide 1. Immune dysregulation in IBS is evidenced by elevated mast cells in the mucosa, pro-inflammatory cytokines, and increased intestinal permeability. However, it is possible that the driver of all of these systems involved in the perpetuation of the disorder is infectious disease within the gut itself.

**RATIONALE FOR INFECTIOUS ETIOLOGY**

Small intestinal bacterial overgrowth (SIBO) has been found in patients with IBS at a frequency of 4%-78% versus 1%-40% in controls[4]. Since post-prandial bloating is a common symptom of IBS, abnormal fermentation and gas production by intestinal bacteria could provide a unifying hypothesis for the etiology of this disorder[5].Up to a four-fold greater rate of maximal gas excretion and greater total hydrogen excretion following ingestion of lactulose in patients with IBS has been documented compared with healthy volunteers[6,7]. The frequency of the diagnosis of SIBO also seems to be associated with the phenotype and the phenotype is associated with the type of gas produced. The frequency of SIBO by glucose hydrogen breath test was found to be substantially higher in patients with diarrhea-predominant IBS than in IBS patients without diarrhea or in healthy controls[8]. Excessive methane production has been associated with constipation[9]. Conversely, excessive hydrogen production has been associated with diarrhea-predominant IBS[10].

Other evidence in support of an infectious etiology for this disorder includes the onset of new IBS symptoms following acute gastroenteritis, which has been reported in up to 40% of patients[11]. The clinical features of post-infectious IBS are consistent with the diarrhea-predominate phenotype. A recent meta-analysis of 18 studies showed an increased relative risk of 6.5 in patients developing IBS within one year of bacterial gastroenteritis and this risk remained elevated at 3.9 even 36 mo later[12]. Infective gastroenteritis has been shown to disrupt the commensal microbiota that normally inhibit pathogen colonization[13].

Hyland[14] has suggested that alterations in microbiota-host interactions in IBS may contribute to the pathogenesis of the disease in three ways. Altered commensal flora may compromise the integrity of the epithelial barrier and cause increases in permeability by altering tight junction protein expression, localization or function, changing the microbiota, and promoting pro-inflammatory cytokines and cell shedding. Similarly, alterations in microbiota-host interactions may interfere with the modulation of both local and systemic immune responses. Importantly, it has also been shown that the alterations in the microbiota can influence the development and function of the central and enteric nervous systems and neuromuscular function, thus explaining alterations in the brain-gut axis. Psychological stress in animal studies has been shown to change the bacterial composition of the gut and evoke cytokine responses with subsequent increased intestinal permeability[15]. Thus, the psychological morbidity associated with the disease could actually perpetrate the disorder through gastroenterological mechanisms.

**EVIDENCE FROM PROBIOTIC TRIALS**

Additional evidence in support of an infectious etiology for IBS comes from clinical trial results of both probiotics and antibiotics. Alternations in the microbiota of patients with IBS have been documented including increases in *Bacteroides* and *Clostridia* and a reduction in *Bifidobacterium*[16]. Two clinical trials in humans have demonstrated that supplementation with a *Bifidobacterium* probiotic reduces symptoms and improves overall well-being in patients with IBS[17,18]. Additionally, one multicenter, randomized, double-blind, placebo-controlled clinical intervention trial evaluating a three strain combination of lactic acid bacteria in IBS found improvement in IBS-specific quality of life and gut-specific anxiety in patients receiving the probiotic combination versus those receiving placebo[19].

**EVIDENCE FROM ANTIBIOTIC TRIALS**

Perhaps the most compelling data to date in support of the infectious disease hypothesis for the origin of IBS comes from clinical trials of antibiotic therapy for treatment of the disorder. Pimentel first studied neomycin treatment in IBS patients, in which 84% had an abnormal lactulose hydrogen breath test, suggestive of SIBO. Neomycin resulted in clinical symptom improvement in 35% of patients compared with 11% of patients receiving placebo[20]. The best outcomes were observed in patients in which neomycin normalized the lactulose hydrogen breath test.

More recently two large randomized, double-blind, placebo controlled trials (TARGET 1 and TARGET 2) evaluated the role of rifaximin 550 mg three times daily for two weeks in IBS patients without constipation[21].Significantly more patients in the rifaximin group had relief of global IBS symptoms during the first four weeks after treatment (40.7% *vs* 31.7%, *p* < 0.001 in both studies combined). There was also greater relief of bloating, daily ratings of IBS symptoms, abdominal pain, and stood consistency. Adverse effects were similar between the two groups. Interestingly, although the treatment period was only two weeks, patients were followed for an additional ten weeks and the improvement in percent of patients with adequate relief of global IBS symptoms was still statistically significant at the end of the ten weeks of observation, suggesting a durable response to the two week treatment course.

An additional phase 3 study was conducted to evaluate the safety and efficacy of retreatment with rifaximin in patients with diarrhea-predominant IBS who previously responded to rifaximin therapy[22]. During an 18-wk follow up period of open-label treatment with rifaximin, 636 patients had recurrent IBS symptoms and were randomized to retreatment with rifaximin 550 mg three times daily for two weeks or placebo. The proportion of responders with rifaximin retreatment was 33% *vs* 25% with placebo (*p* = 0.02). During a second double-blind retreatment phase, the percentage of responders with rifaximin was 37% *vs* 29% with placebo (*p* = 004). Adverse event rates were similar between groups and only one patient from each group discontinued therapy because of adverse events.

**CONCLUSION**

Irritable bowel syndrome is clearly a very heterogenous disease by symptom presentation and numerous mechanisms have been offered to explain its etiology. Current evidence from both basic and clinical science supports the role of infectious disease as a potential etiology and a unifying explanation of the multifaceted nature of the disease. Further work is needed in this regard to better understand the differences in organisms responsible and differing responses seen with varying phenotypes of the disorder.

**REFERENCES**

1 **Chey WD**, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015; **313**: 949-958 [PMID: 25734736 DOI: 10.1001/jama.2015.0954]

2 **Marshall BJ**. The discovery that *Helicobacter pylori*, a spiral bacterium, caused peptic ulcer disease. In: Marshall BJ. *Helicobacter* Pioneers: Firsthand Accounts from the Scientists who Discovered Helicobacters 1892-1982.Oxford: Blackwell. pp, 2002: 165–202

3 **Buckley MM**, O'Mahony SM, O'Malley D. Convergence of neuro-endocrine-immune pathways in the pathophysiology of irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 8846-8858 [PMID: 25083058 DOI: 10.3748/wjg.v20.i27.8846]

4 **Ghoshal UC**, Srivastava D. Irritable bowel syndrome and small intestinal bacterial overgrowth: meaningful association or unnecessary hype. *World J Gastroenterol* 2014; **20**: 2482-2491 [PMID: 24627585 DOI: 10.3748/wjg.v20.i10.2482]

5 **Lin HC**. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA* 2004; **292**: 852-858 [PMID: 15316000 DOI: 10.1001/jama.292.7.852]

6 **King TS**, Ekua M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. *Lancet* 1998; **352**: 1187-1189 [PMID 9777836 DOI: 10.1016/S0140-6736(98)02146-1]

7 **Sen S**, Dear KL, King TS, Hunter JO. Evaluation of hydrogen excretion after lactulose administration as a screening test for causes of irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2002; **14**: 753-756 [PMID 12169984 DOI: 10.1097/00042737-200207000-00007]

8 **Ghoshal UC**, Kumar S, Mehrotra M, Lakshmi C, Misra A. Frequency of small intestinal bacterial overgrowth in patients with irritable bowel syndrome and chronic non-specific diarrhea. *J Neurogastroenterol Motil* 2010; **16**: 40-46 [PMID 20535325 DOI: 10.5056/jnm.2010.16.1.40]

9 **Chatterjee S**, Park S, Low K, Kong Y, Pimentel M. The degree of breath methane production in IBS correlates with the severity of constipation. *Am J Gastroenterol* 2007; **102**: 837-841 [PMID: 17397408 DOI: 10.1111/j.1572-0241.2007.01072.x]

10 **Pimentel M**, Lezcano S. Irritable Bowel Syndrome: Bacterial Overgrowth--What's Known and What to Do. *Curr Treat Options Gastroenterol* 2007; **10**: 328-337 [PMID: 17761126 DOI: 10.1007/s11938-007-0076-1]

11 **Simrén M**, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 2013; **62**: 159-176 [PMID: 22730468 DOI: 10.1136/gutjnl-2012-302167]

12 **Thabane M**, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; **26**: 535-544 [PMID: 17661757 DOI: 10.1111/j.1365-2036.2007.03399.x]

13 **Lupp C**, Robertson ML, Wickham ME, Sekirov I, Champion OL, Gaynor EC, Finlay BB. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host Microbe* 2007; **2**: 204 [PMID: 18030708 DOI: 10.1016/j.chom.2007.08.002]

14 **Hyland NP**, Quigley EM, Brint E. Microbiota-host interactions in irritable bowel syndrome: epithelial barrier, immune regulation and brain-gut interactions. *World J Gastroenterol* 2014; **20**: 8859-8866 [PMID: 25083059 DOI: 10.3748/wjg.v20.i27.8859]

15 **Gareau MG**, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut* 2007; **56**: 1522-1528 [PMID: 17339238 DOI: 10.1136/gut.2006.117176]

16 **Tojo R**, Suárez A, Clemente MG, de los Reyes-Gavilán CG, Margolles A, Gueimonde M, Ruas-Madiedo P. Intestinal microbiota in health and disease: role of bifidobacteria in gut homeostasis. *World J Gastroenterol* 2014; **20**: 15163-15176 [PMID: 25386066 DOI: 10.3748/wjg.v20.i41.15163]

17 **Kajander K**, Myllyluoma E, Rajilić-Stojanović M, Kyrönpalo S, Rasmussen M, Järvenpää S, Zoetendal EG, de Vos WM, Vapaatalo H, Korpela R. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. *Aliment Pharmacol Ther* 2008; **27**: 48-57 [PMID: 17919270 DOI: 10.1111/j.1365-2036.2007.03542.x]

18 **Guyonnet D**, Chassany O, Ducrotte P, Picard C, Mouret M, Mercier CH, Matuchansky C. 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**: 475-486 [PMID: 17635382 DOI: 10.1111/j.1365-2036.2007.03362.x]

19 **Lorenzo-Zúñiga V**, Llop E, Suárez C, Alvarez B, Abreu L, Espadaler J, Serra J. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol* 2014; **20**: 8709-8716 [PMID: 25024629 DOI: 10.3748/wjg.v20.i26.8709]

20 **Pimentel M**, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003; **98**: 412-419 [PMID: 12591062]

21 **Pimentel M**, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; **364**: 22-32 [PMID: 21208106 DOI: 10.1056/NEJMoa1004409]

22 **Lembo A**, Pimentel M, Rao SS. Efficacy and safety of repeat treatment with rifaximin for diarrhea-predominant irritable bowel syndrome (IBS-D): Results of the TARGET 3 study. Presented at the American College of Gastroenterology Annual Meeting, Philadelphia, PA, [United](javascript:void(0);) [States](javascript:void(0);). 2014: 17-22

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