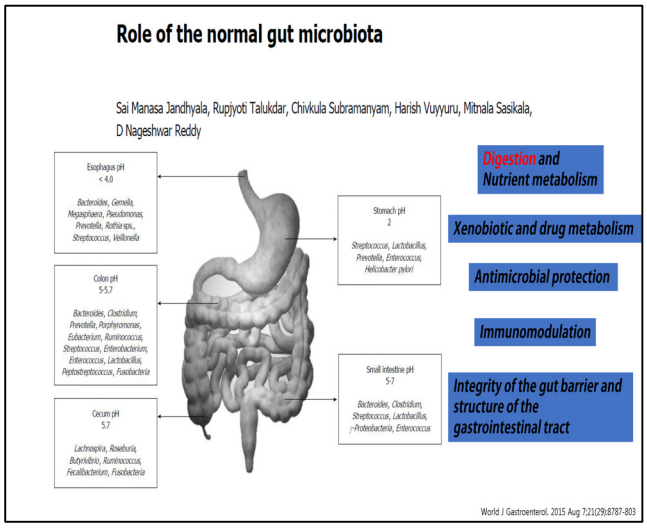
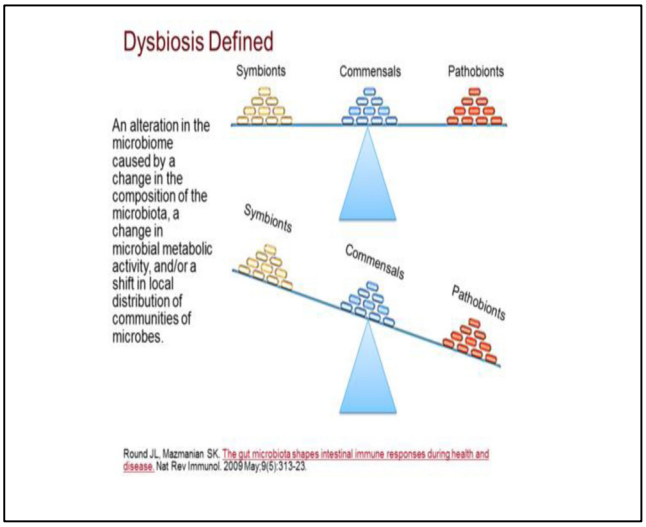
위장(기능성 소화기 질환) 치료의 기능의학적 접근 및 관리

김 규 남
아주대병원

연수강좌

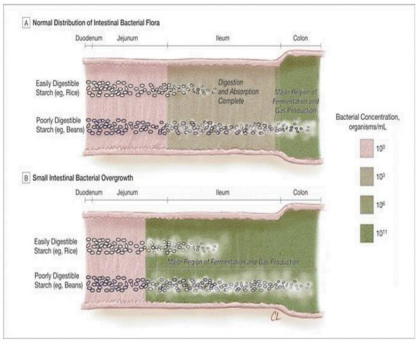




Dysbiosis 분류

- 1. Small Intestinal Bacterial Overgrowth
- 2. Colonic dysbiosis
- 3. Yeast Overgrowth in the Gut
- 4. Parasite in the Gut (rare)

The concept of small intestinal bacterial overgrowth



- SIBO : > 10^5 CFU/ml of intestinal aspirate
  and/or the presence of colonic-type species

Lim HC JAMA;18:852-858

EVALUATION OF SMALL INTESTINE BACTERIAL OVERGROWTH IN PATIENTS WITH FUNCTIONAL DYSPEPSIA THROUGH H_2 BREATH TEST

Michelle Bafutto Gomes **COSTA**[1], Itaciron Luiz **AZEREDO Jr.**[1], Ricardo Duarte **MARCIANO**[1], Luciana Morelli **CALDEIRA**[1] and Mauro **BAFUTTO**[2]

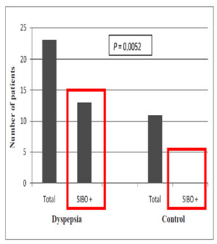


TABLE 3. Dyspepsia with PPI and control group, in relation to SIBO

	SIBO+	SIBO-	*P* value*
Dyspepsia with PPI	9	3	0.0011
Control group	0	11	
Total	9	14	

*chi-square test

FIGURE 1. Presence of SIBO in dyspeptic patients and control group

- Patients with functional dyspepsia presented SIBO, when they underwent to H2-lactulose breath test, compared to the non-dyspeptic.
- In addition, it was observed a higher prevalence of SIBO in dyspeptic patients that were using proton pump inhibitors, compared to control group.

Costa MB et al. Evaluation of small intestine bacterial overgrowth in patients with functional dyspepsia through H2 breath test. Arq Gastroenterol. 2012 Dec;49(4):279-83.

REVIEW

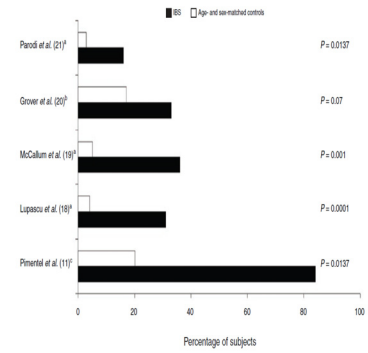
Functional dyspepsia

Gerald Holtmann[a,b,c] *and Nicholas J. Talley*[d]

- In recent years, treatment targeting H. pylori
  → not result in an improvement of symptoms in a substantial proportion of patients when peptic ulcers are not present,
- In new research, inflammation and in particular microscopic inflammation of the duodenumand intestine
  → emerged as important associations with functional dyspepsia.
- Interestingly, antibiotic therapy targeting H. pylori
  → more effective with regard to symptom improvement in patients with microscopic duodenal inflammation,
  ☞ suggesting that the effects are not simply mediated by eradication of H. pylori, but other antibacterial effects (e.g., on the duodenal microbiome) might be equally important.
- The observation of increased duodenal eosinophilia, impaired permeability, and immune activation
  → represent as a functional dyspepsia.

Curr Opin Gastroenterol. 2015 Nov;31(6):492–8.

Irritable Bowel Syndrome



- Breath-test findings in IBS subjects using age- and sex-matched healthy controls.

a : Glucose breath testing. b : Lactulose breath testing. c : Sucrose breath testing.

Mark Pimentel, Am J Gastroenterol 2010;105:718–721

MECHANISM OF IBS SYMPTOMS IN PATIENTS WITH DYSBIOSIS (GI motility)

Digestive Diseases and Sciences, Vol. 49, No. 1 (January 2004), pp. 84–87 (© 2004)

IBS Subjects with Methane on Lactulose Breath Test Have Lower Postprandial Serotonin Levels Than Subjects with Hydrogen

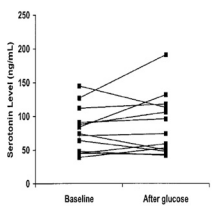


Fig 2. Individual serotonin responses after a glucose meal among IBS subjects producing only hydrogen.

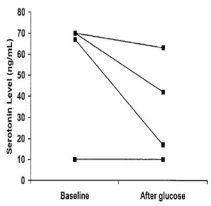
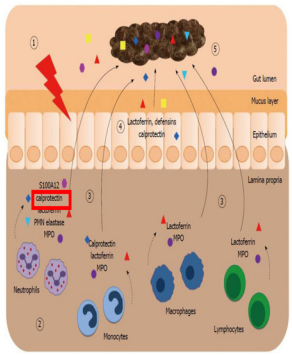


Fig 3. Individual serotonin responses after a glucose meal among IBS subjects producing only methane.

Fecal calprotectin (FC) for colonic dysbiosis dx



- Derived predominantly from neutrophils and monocytes.
- FC : 대장 염증의 지표
- Being resistant to enzymatic degradation
  → easily measured in stools with a commercially available ELISA immunoassay.

Däbritz J et al. Diagnostic utility of faecal biomarkers in patients with irritable bowel syndrome. World J Gastroenterol. 2014 Jan 14;20(2):363–75.

MOLECULAR MEDICINE REPORTS 10: 522-526, 2014

Faecal calprotectin as a novel biomarker for differentiating between inflammatory bowel disease and irritable bowel syndrome

MING-HUI CHANG[1,2*], JEN-WEI CHOU[3,4*], SHAN-MING CHEN[5,6], MING-CHANG TSAI[1,2], YU-SHU SUN[7], CHUN-CHE LIN[1,8] and CHING-PIN LIN[1,9]

Table II. Clinical and biochemical data of the IBD and IBS patients.

	IBD (n=58)		IBS (n=26)		
Parameter	Mean ± SD	Range	Mean ± SD	Range	P-value
CRP (mg/dl)	0.851±1.200	0.014-4.900	0.16±0.23	0.010-1.040	<0.0001
ESR (mm/h)	18.14±21.16	2-104	9.11±4.02	5-22	0.220
Faecal calprotectin (μg/g)	694.8±685.0	30-1810	85.8±136.1	30-622	<0.0001

IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation.

•Significantly higher stool FC levels in IBS patients than serum CRP levels.

Gastroenterol Hepatol. 2017 Mar;40(3):125-131. doi: 10.1016/j.gastrohep.2016.04.009. Epub 2016 May 31.

Faecal calprotectin, an useful marker in discriminating between inflammatory bowel disease and functional gastrointestinal disorders.

[Article in English, Spanish]
Lozoya Angulo ME[1], de Las Heras Gómez J[2], Martínez Villanueva M[2], Noguera Velasco JA[2], Avilés Plaza F[2].

Author information

Abstract

INTRODUCTION: Diagnostic discrimination between inflammatory bowel disease (IBD) and functional gastrointestinal disorders is complex, as they cause similar signs and symptoms. Faecal calprotectin (FC) is a useful marker in this context, and can be used to select patients who will most benefit from colonoscopy. The aim of this study was to evaluate the utility of FC in discriminating between organic disease and functional disorders.

MATERIAL AND METHODS: The study included 264 patients presenting with gastrointestinal complaints consistent with an organic pathology. FC levels were determined and diagnostic accuracy was assessed using the area under the curve obtained from the final diagnosis.

RESULTS: Calprotectin levels in organic bowel disease patients were significantly higher (median 254μg/g; 95% confidence interval [CI], interquartile range 105-588.5) than in functional disease patients (95μg/g; 95% CI, 47.25-243.92) (P<.0001). Similarly, in patients with IBD, the values obtained were higher (270.85μg/g; 95% CI, 96.85-674.00) than in those with irritable bowel syndrome (79.70μg/g; 95% CI, 36.50-117.25) (P<.0001). For a cut-off of 150μg/g, FC had an area under the ROC curve to discriminate between organic and functional disease of 0.718, and 0.872 to discriminate between irritable bowel syndrome and IBD.

CONCLUSION: Our study supports the importance of FC as a marker in the evaluation of patients with IBD. The best diagnostic accuracy is obtained at a cut-off value of 150μg/g.

Contents lists available at ScienceDirect

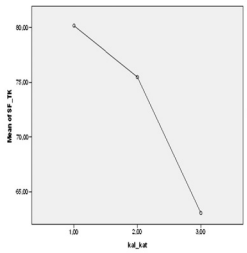
Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Fecal Calprotectin and serum chromogranin A as potential biomarkers of irritable bowel syndrome symptom severity ☆

Sanda Pletikosic[a], Ivana Plavsic[b], Goran Hauser[b,c,*], Mladenka Tkalcic[a]

[a] Department of Psychology, Faculty of Humanities and Social Sciences, University of Rijeka, Croatia
[b] Centre for Emergency Medicine, Clinical Hospital Centre, Rijeka, Croatia
[c] Department of Internal Medicine, Division of Gastroenterology, Clinical Hospital Centre, Rijeka, Croatia



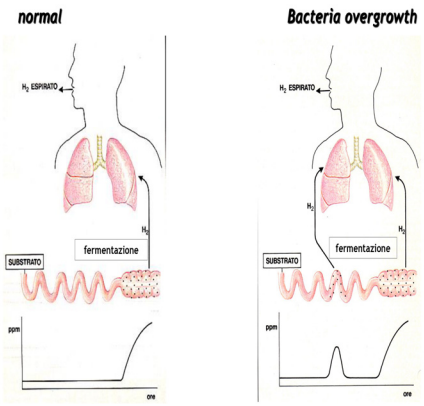
- The patient' s FC status (less than 30 lg/g, from 31 to 50 lg/g, more than 51 lg/g).
- FC levels significantly correlated with the physical component of health related quality of life (HRQoL).

Med Hypotheses. 2015 Sep;85(3):339-42

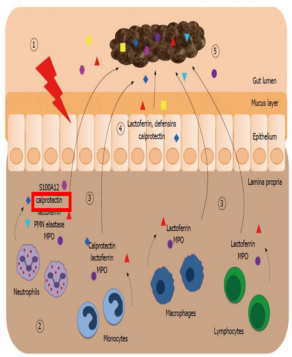
Evaluation of SIBO

수소/메탄 호기 검사 기구

Lactulose or glucose H_2/CH_4 BREATH TEST



Fecal calprotectin (FC) for colonic dysbiosis dx



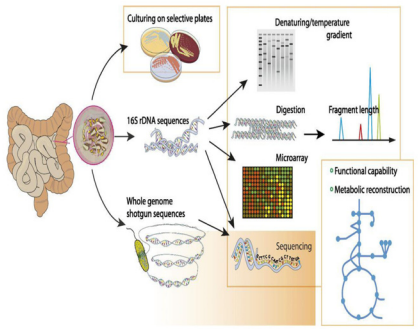
- Derived predominantly from neutrophils and monocytes.
- FC : 대장 염증의 지표
- Being resistant to enzymatic degradation
  → easily measured in stools with a commercially available ELISA immunoassay.

Dabritz J et al. Diagnostic utility of faecal biomarkers in patients with irritable bowel syndrome. World J Gastroenterol. 2014 Jan 14;20(2):363-75.

분류번호	코드	분 류
		[분변 검사]
나-75		분변 칼프로텍틴 Fecal Calprotectin
	B0751	가. 정성[간이검사] Qualitative[Handy Test]
	B0752	나. 정량 Quantitative
	B0753	주 : 간이검사로 실시한 경우 226.50점을 산정한다.

- 보건복지부 고시 제2017 - 37호
- 염증성 장질환과 과민성 대장 증후군 감별 진단 및 치료 효과 판정, 추적 검사로 이용

Methods for studying the microbiota using stool for dysbiosis dx



Karlsson F et al. Diabetes 2013;62:3341-3349

American Diabetes Association.

Treatment

The 5R Program

1. Remove
2. Replace
3. Reinoculate
4. Repair
5. Rebalance

AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: rifaximin versus placebo for the treatment of functional dyspepsia

V. P. Y. Tan, K. S. H. Liu, F. Y. F. Lam, I. F. N. Hung, M. F. Yuen & W. K. Leung

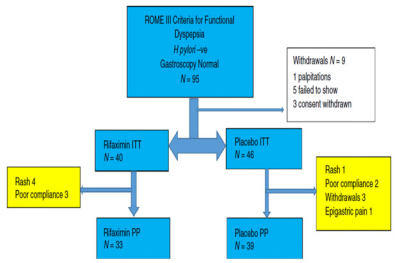
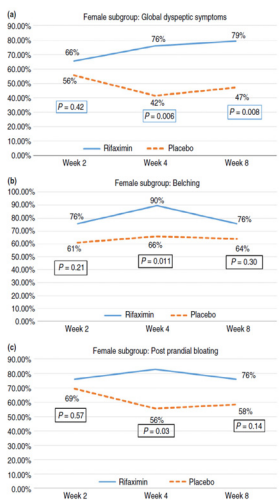


Figure 1 | Trial profile. ITT, intention-to-treat; PP, per-protocol analysis.

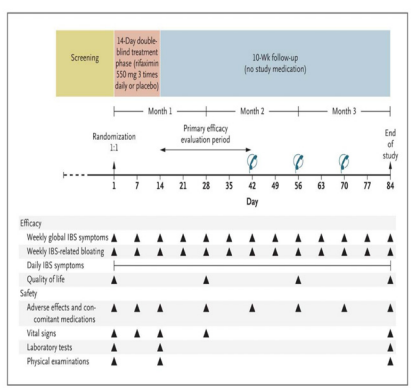
1200 mg given at 400 mg three times per day for 14 days.

Aliment Pharmacol Ther. 2017 Mar;45(6):767–776

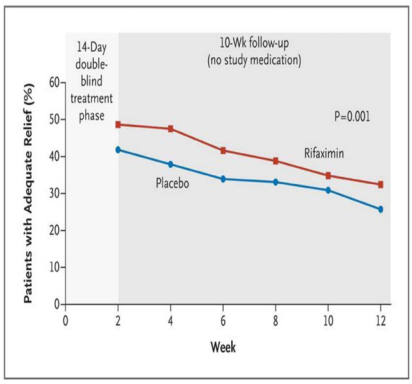


- Treatment with 2 weeks of rifaximin
  → led to adequate relief of global dyspeptic symptoms, belching and post-prandial fullness/bloating in subjects with functional dyspepsia.

Aliment Pharmacol Ther. 2017 Mar;45(6):767–776



The NEW ENGLAND JOURNAL of MEDICINE



The NEW ENGLAND JOURNAL of MEDICINE

A Combination of Rifaximin and Neomycin Is Most Effective in Treating Irritable Bowel Syndrome Patients With Methane on Lactulose Breath Test

Kimberly Low, BA, Laura Hwang, BS, Johnson Hua, MD, Amy Zhu, MD, Walter Morales, BS, and Mark Pimentel, MD

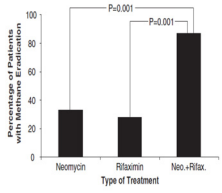


FIGURE 2. Comparision of the three treatment approaches in their ability, to eradicate methane based on postantibiotic breath test.

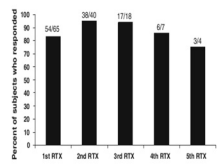
- Patients with methane on their lactulose breath test (>3 ppm of methane)
- Tx group
  1. 500mg b.i.d. for 10 days of neomycin
  2. 400mg t.i.d. for 10 days of rifaximin
  3. both

⇒ The combination of rifaximin and neomycin is more effective in treating methane-producing subjects

J Clin Gastroenterol 2010;44:547–550

Effects of Rifaximin Treatment and Retreatment in Nonconstipated IBS Subjects

Mark Pimentel · Walter Morales · Kathleen Chua · Gillian Barlow · Stacy Weitsman · Gene Kim · Meridythe M. Amichai · Venkata Pokkunuri · Emily Rook · Ruchi Mathur · Zachary Marsh



Success rate of each retreatment with rifaximin

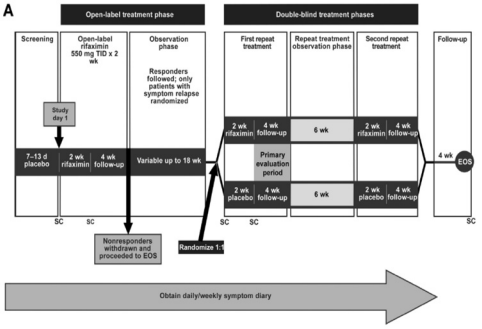
- Retreatment with rifaximin is highly likely to improve IBS, even when used up to five times
  - ☞ suggest a lack of development of clinical resistance to rifaximin

26

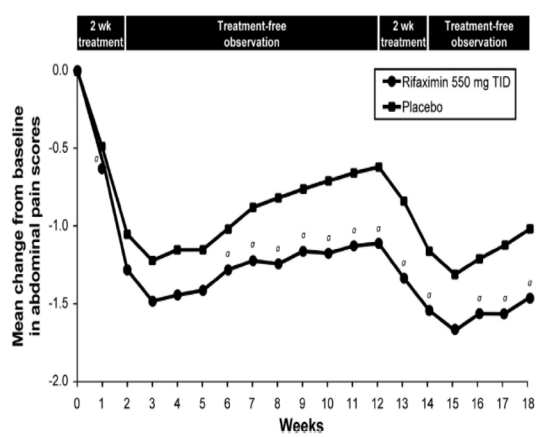
Dig Dis Sci. 2011 Jul;56(7):2067–72

Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome

Anthony Lembo,[1] Mark Pimentel,[2] Satish S. Rao,[3] Philip Schoenfeld,[4] Brooks Cash,[5] Leonard B. Weinstock,[6] Craig Paterson,[7] Enoch Bortey,[7] and William P. Forbes[7]



Gastroenterology. 2016 Dec;151(6):1113-1121



Gastroenterology. 2016 Dec;151(6):1113-1121

Table 3. Summary of Adverse Events During Open-label (n = 2579) and Double-blind (n = 636) Phases[a]

	Open-label population	Double-blind population	
AE, n (%)	Rifaximin, 550 mg TID (n = 2579)	Rifaximin 550 mg TID (n = 328)	Placebo (n = 308)
Any AE	822 (31.9)	140 (42.7)	140 (45.5)
Drug-related AE	85 (3.3)	6 (1.8)	8 (2.6)
Serious AE	28 (1.1)	4 (1.2)[b]	4 (1.3)[c]
Most common AEs[d]			
Nausea	52 (2.0)	12 (3.7)	7 (2.3)
Upper respiratory tract infection	41 (1.6)	12 (3.7)	8 (2.6)
Urinary tract infection	35 (1.4)	11 (3.4)	15 (4.9)
Nasopharyngitis	36 (1.4)	10 (3.0)	9 (2.9)
Alanine aminotransferase increased	24 (0.9)	9 (2.7)	4 (1.3)
Blood creatinine phosphokinase increased	31 (1.2)	9 (2.7)	3 (1.0)
Bronchitis	15 (0.6)	9 (2.7)	5 (1.6)
Aspartate aminotransferase increased	24 (0.9)	7 (2.1)	4 (1.3)
Diarrhea	20 (0.8)	7 (2.1)	3 (1.0)
Influenza	33 (1.3)	7 (2.1)	2 (0.6)
Sinusitis	34 (1.3)	7 (2.1)	7 (2.3)
Headache	42 (1.6)	4 (1.2)	9 (2.9)
Arthralgia	17 (0.7)	3 (0.9)	8 (2.6)

- **In a phase 3 study of patients with relapsing symptoms of IBS-D, repeat rifaximin treatment was efficacious and well tolerated.**

Gastroenterology. 2016 Dec;151(6):1113-1121

FDA Approves Rifaximin for IBS

- In patients with IBS, the dose is one 550 mg tablet 3 times a day for 14 days, with retreatment for recurrence up to two additional rounds.

Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth

L. Gatta*† & C. Scarpignato*

Background
Small intestinal bacterial overgrowth (SIBO) is a heterogeneous syndrome, characterised by an increased number and/or abnormal type of bacteria in the small bowel. Over the past decades, rifaximin has gained popularity for this indication despite its use is not evidence based.

Aim
To perform a systematic review and meta-analysis to summarise evidence about the efficacy and safety of rifaximin to eradicate SIBO in adult patients.

Methods
MEDLINE, EMBASE, CCRCT, Scopus and Web of Science were searched from inception to March 16, 2015 for RCTs and observational studies. Furthermore, abstract books of major European, American and Asian gastroenterological meetings were also examined.

Results
Thirty-two studies involving 1331 patients were included. The overall eradication rate according to intention-to-treat analysis was 70.8% (95% CI: 61.4–78.2; I^2 = 89.4%) and to per protocol analysis 72.9% (95% CI: 65.5–79.8; I^2 = 87.5%). Meta-regression identified three covariates (drug dose, study design and co-therapy) independently associated with an increased eradication rate. The overall rate of adverse events was 4.6% (95% CI: 2.3–7.5; I^2 = 63.6%). In the subset of studies (n= 10) allowing the analysis, improvement or resolution of symptoms in patients with eradicated SIBO was found to be 67.7% (95% CI: 44.7–86.9; I^2 = 91.3%).

Conclusions
Rifaximin treatment seems to be effective and safe for the treatment of SIBO. However, the quality of the available studies is generally poor. Well-designed RCTs are needed to substantiate these findings and to establish the optimal regimen.

Aliment Pharmacol Ther. 2017 Mar;45(5):604–616

Treatment duration	Stool type		Initial visit	4 weeks	8 weeks	12 weeks	P
4 weeks group	Diarrhea	Likert score	2.4 ± 1.0	4.6 ± 1.1	-	-	< 0.05
		Bristol scale	6.1 ± 0.8	4.3 ± 0.9	-	-	< 0.05
	Mixed	Likert score	2.2 ± 0.8	5.1 ± 0.7	-	-	< 0.05
		Bristol scale	2.3 ± 0.8	4.1 ± 0.8	-	-	< 0.05
8 weeks group	Diarrhea	Likert score	2.2 ± 1.2	4.3 ± 1.1	5.1 ± 0.8	-	< 0.05
		Bristol scale	6.3 ± 0.7	4.1 ± 1.3	3.9 ± 1.0	-	< 0.05
	Mixed	Likert score	2.0 ± 0.9	4.3 ± 1.2	5.2 ± 1.0	-	< 0.05
		Bristol scale	2.0 ± 1.1	3.7 ± 0.9	4.3 ± 0.7	-	< 0.05
12 weeks group	Diarrhea	Likert score	1.9 ± 1.1	4.2 ± 1.3	4.8 ± 1.2	5.3 ± 1.5	< 0.05
		Bristol scale	6.4 ± 1.2	4.9 ± 1.1	4.5 ± 1.5	4.2 ± 1.1	< 0.05
	Mixed	Likert score	1.8 ± 0.9	3.9 ± 0.9	4.5 ± 1.3	[illegible]	< 0.05
		Bristol scale	2.8 ± 0.9	3.2 ± 1.1	3.4 ± 1.3	4.9 ± 0.9	< 0.05

*There were statistically significant between initial and last scores.

□ Baseline value
■ 90 min value
■ LBT sum*

cording to treatment dura-
at for 12 weeks, statistically
t 90 min ($P < 0.05$) and its
different among all groups.
data during 90 min.

ORIGINAL ARTICLE
JKMS
http://dx.doi.org/10.3346/jkms.2015.30.6.1 • J Korean Med Sci 2015; 30: 1-6

Determination of Rifaximin Treatment Period According to Lactulose Breath Test Values in Nonconstipated Irritable Bowel Syndrome Subjects

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Received: 20 October 2014
Accepted: 28 January 2015

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Small intestinal bacterial overgrowth (SIBO) can partly explain irritable bowel syndrome (IBS), and rifaximin has been observed to improve abdominal symptoms in nonconstipated IBS patients. However, there are few reports on the association of the rifaximin treatment periods with the results of a lactulose breath test (LBT). Therefore, we performed a retrospective review of patient charts to investigate the relation between the rifaximin treatment periods with LBT results in nonconstipated IBS patients. We also evaluated the time to achieve a symptomatic improvement in the IBS patients as compared to the changes in the LBT. We reviewed the charts for patients who showed IBS-symptoms with documented positive results for LBT during their initial visit and who had a follow-up LBT after treatment with rifaximin. The LBT values were compared to the subjects' symptom scores. A total of 102 subjects had a follow-up LBT to assess LBT normalization. The subjects were divided into groups according to treatment periods of 4 weeks (n = 36), 8 weeks (n = 43), and 12 weeks (n = 23). The groups with a longer treatment exhibited an increase in the hydrogen gas value at 90 min and its sum during 90 min at the initial LBT. There were significant differences in hydrogen gas value at 90 min and in its sum during 90 min at the initial LBT between the groups treated for 4 weeks and 12 weeks. The most significant treatment response was observed during the first 4 weeks for all treatment groups. A symptomatic improvement occurred earlier than LBT normalization in the treatment period over 4 weeks. The results indicate that different rifaximin treatment periods are needed in accordance with LBT levels to effectively eradicate SIBO.

Keywords: Irritable Bowel Syndrome; Small Intestinal Bacterial Overgrowth; Lactulose Breath Test; Rifaximin

- Conclusion
  → When rifaximin treatment is administered in response to IBS symptoms, a premature termination of the treatment can happen while SIBO still exists.
  → The adjustment of the treatment period more efficient management of SIBO symptoms.

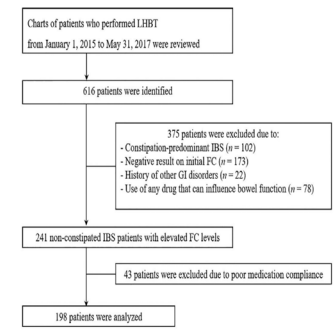
CLINICAL INVESTIGATION

Changes in Fecal Calprotectin After Rifaximin Treatment in Patients With Nonconstipated Irritable Bowel Syndrome

Seok-Hoon Lee, MD, Cho-Rong Kim, MD and Kyu-Nam Kim, MD, PhD

Department of Family Practice and Community Health, Ajou University School of Medicine, Suwon, Gyeonggi-do, Republic of Korea

Am J Med Sci. 2019 Jan;357(1):23-28.



Am J Med Sci. 2019 Jan;357(1):23-28.

Treatment duration		Initial visit	4 weeks	8 weeks	12 weeks	*P*-value*
4 weeks group (*n* = 115)	Fecal calprotectin	84.5 ± 131.8	< 11.5 mg/kg	-	-	
	Likert scale	4.4 ± 0.8	2.1 ± 0.7	-	-	<0.05
8 weeks group (*n* = 39)	Fecal calprotectin	136.4 ± 216.7	91.7 ± 144.1	< 11.5 mg/kg	-	
	Likert scale	4.5 ± 0.7	2.9 ± 0.9	2.2 ± 0.8	-	<0.05
12 weeks group (*n* = 8)	Fecal calprotectin	95.4 ± 91.5	125.5 ± 209.1	123.5 ± 280.8	< 11.5 mg/kg	
	Likert scale	4.7 ± 1.0	3.1 ± 0.8	2.3 ± 0.9	1.9 ± 0.9	<0.05
P value**		0.137				

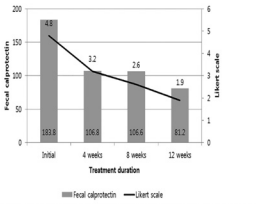
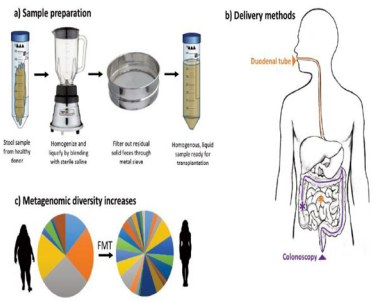


FIGURE 2. Mean values of the initial and follow-up fecal calprotectin and Likert scale in patients with persistent elevated fecal calprotectin levels after a 12-week treatment (*n* = 39).

These findings suggest that fecal calprotectin might be a useful biomarker for measuring the effect of rifaximin therapy in nonconstipated irritable bowel syndrome patients with elevated fecal calprotectin values.

Am J Med Sci. 2019 Jan;357(1):23-28.

Fecal Microbiota Transplantation schematic



A) Donor fecal matter is blended with saline solution and pushed through a metal sieve to achieve a homogenous liquid solution. **B)** Processed fecal microbiota is either delivered via a duodenal tube or colonoscopy. **C)** Representative data showing metagenomic diversity increases following FMT from lean donor to obese recipient.

Yale J Biol Med. 2016 Sep 30;89(3):383-388

Fig. 2. Fecal microbiota transplantation procedures. (A) Donor stool and normal saline (1:3) ground in a blender. (B) Fecal suspension in 50-mL syringes. (C) Infusion using colonoscopy.

Clin Endosc. 2016 May;49(3):257-65

Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial

Peter Holger Johnsen, Frank Hilpüsch, Jorunn Pauline Cavanagh, Ingrid Sande Leikanger, Caroline Kolstad, Per Christian Valle, Rasmus Goll

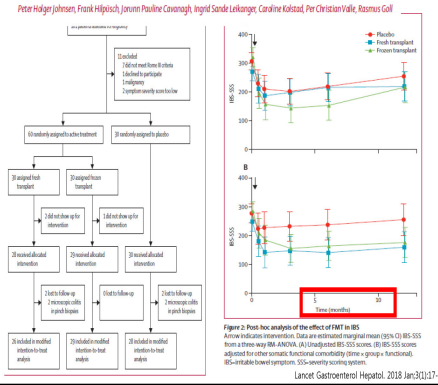


Figure 2: Post-hoc analysis of the effect of FMT in IBS
Arrow indicates intervention. Data are estimated marginal mean (95% CI) IBS-SSS from a three-way RM-ANOVA. (A) Unadjusted IBS-SSS scores. (B) IBS-SSS scores adjusted for other somatic functional comorbidity (time × group × functional). IBS=irritable bowel symptom. SSS=severity scoring system.

Lancet Gastroenterol Hepatol. 2018 Jan;3(1):17-24

Study Protocol Systematic Review

Medicine

OPEN

Fecal microbiota transplantation for patients with irritable bowel syndrome

A meta-analysis protocol

Wenting Wen, MD, Haibo Zhang, MD, Junlong Shen, PhD*, Luxia Wei, PhD, Shunong Shen, PhD*

Abstract

Irritable bowel syndrome (IBS) is a common functional bowel disease characterized by chronic or recurrent abdominal pain, bloating, constipation, and diarrhea. Many patients with IBS have a poor quality of life due to abdominal discomfort, diarrhea, constipation, and the presence of other diseases. At present, intestinal motility inhibitors, adsorbents, astringents, intestinal mucosal protective agents, and antidepressants have been combined to treat IBS, but the treatment process is long, which results in a large economic burden to patients. Fecal microbiota transplantation (FMT) is a treatment involving the transplantation of functional bacteria from healthy human feces into the gastrointestinal tract of patients; thus, replacing the intestinal flora and modulating intestinal and extra-intestinal diseases. In recent years, the efficacy and economic benefits of FMT in the treatment of IBS have received increasing attention from researchers.

A search for randomized controlled trials (RCTs) on treating IBS with FMT will be performed using 9 databases, including PubMed, the Cochrane Library, Embase, ClinicalTrails, China National Knowledge Infrastructure, Sino Med, ScienceDirect, VIP, and Wanfang Data. Two reviewers will independently screen data extraction studies and assess study quality and risk of bias. The risk of bias for each RCT will be assessed against the Cochrane Handbook standards to assess methodological quality. RevMan V. 5.3 software will be used to calculate data synthesis when meta-analysis is allowed.

This study will provide a high-quality synthesis of existing evidence on the effectiveness and safety of FMT in the treatment of IBS. This study will determine if FMT is an effective and safe intervention for IBS.

PROSPERO registration number is PROSPERO CRD42018108080.

Abbreviations: CIs = confidence intervals, FMT = fecal microbiota transplantation, IBS = irritable bowel syndrome, RCTs = randomized controlled trials.

Keywords: fecal microbiota transplantation, irritable bowel syndrome, meta-analysis, protocol

Replace

- **Agents for digestive support**
  - → **Consider a short course of pancreatic enzymes and in some cases Betaine HCL if low acidity.**
- **This step may not be necessary.**

Reinoculate

- Reinoculate refers to the reintroduction of desirable GI microflora (probiotics) to obtain a more desirable balance of microflora, as well as support for these probiotics with prebiotic fibers.

- Clinical approaches may include:
  - Bifidobacteria
  - Lactobacillus
  - Inulin or fructooligosaccharides (FOS), soy fiber
  - Soluble rice fibers
  - Arabinogalactans

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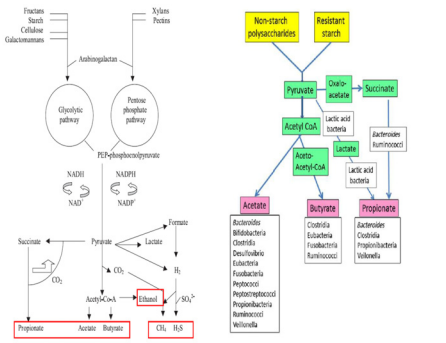
Fermentable oligosaccharides, disaccharides, monosaccharides and Polyols (FODMAPs)



Hijova E, et al. Short chain fatty acids and colonic health. Bratisl Lek Listy. 200 7;108(8):354-8. Review

Ramakrishna BS. Role of the gut microbiota in human nutrition and metabolism. J Gastroenterol Hepatol. 2013 Dec;28 Suppl 4:9-17.

Fermentable oligosaccharides, disaccharides, monosaccharides and Polyols (FODMAPs)

Table 1. FODMAP carbohydrates and their richest food sources.

FODMAP	Richest food sources
Fructo-oligosaccharides (fructans)	Wheat, rye, onions, garlic, artichokes
Galacto-oligosaccharides (GOS)	Legumes
Lactose	Milk
Fructose	Honey, apples, pears, watermelon, mango
Sorbitol	Apples, pears, stone fruits, sugar-free mints/gums
Mannitol	Mushrooms, cauliflower, sugar-free mints/gums

Barrett JS et al. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? Therap Adv Gastroenterol. 2012 Jul;5(4):261-8.

The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study

R. H. de Roest,[1,2,3] B. R. Dobbs,[2,4] B. A. Chapman,[2,5] B. Batman,[1,2,3] L. A. O'Brien,[2] J. A. Leeper,[2] C. R. Hebblethwaite,[2] R. B. Gearry[1,2,5]

Int J Clin Pract. 2013 Sep;67(9):895-903

A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome

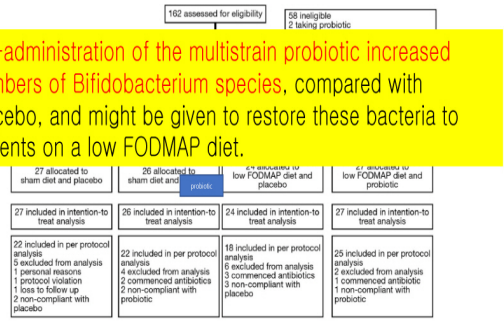
Emma P. Halmos,[1,2] Victoria A. Power,[1] Susan J. Shepherd,[1] Peter R. Gibson,[1,2] and Jane G. Muir[1,2]

Gastroenterology. 2014 Jan;146(1):67-75.e5

5R 프로그램에서 probiotics들은 remove단계 후 복용을 권고하는 것이 좋다.

A Diet Low in FODMAPs Reduces Symptoms in Patients With Irritable Bowel Syndrome and A Probiotic Restores Bifidobacterium Species: A Randomized Controlled Trial

Heidi Maria Staudacher,[1] Miranda C. E. Lomer,[1,2,3] Freda M. Farquharson,[4] Petra Louis,[4] Francesca Fava,[5] Elena Franciosi,[5] Matthias Scholz,[5] Kieran M. Tuohy,[5] James O. Lindsay,[6,7] Peter M. Irving,[1,2] and Kevin Whelan[1]



Co-administration of the multistrain probiotic increased numbers of Bifidobacterium species, compared with placebo, and might be given to restore these bacteria to patients on a low FODMAP diet.

Gastroenterology. 2017 Oct;153(4):936-947

Prebiotics

- Prebiotics :most plant-based foods.
  - → Need at least five grams of them to make an impact
    - ☞ Generally, can not be included within a tiny capsule as a symbiotic.
  - → Eating real (fresh) food is a far better way about getting enough prebiotics

Probiotics for Preventing and Treating Small Intestinal Bacterial Overgrowth

A Meta-Analysis and Systematic Review of Current Evidence

Changqing Zhong, MS, Changmin Qu, MD,* Baoyan Wang, BS,† Shuwen Liang, MS,* and Bolun Zeng, MS**

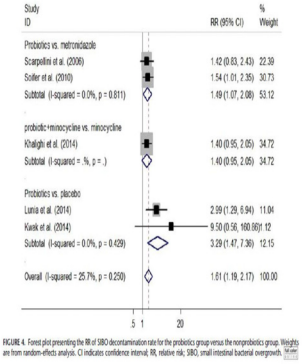


FIGURE 4. Forest plot presenting the RR of SIBO decontamination rate for the probiotics group versus the nonprobiotics group. Weights are from random-effects analysis. CI indicates confidence interval; RR, relative risk; SIBO, small intestinal bacterial overgrowth.

- **Probiotics supplementation could effectively decontaminate SIBO.**

J Clin Gastroenterol. 2017 Apr;51(4):300–311

https://doi.org/10.4082/kjfm.17.0064 • Korean J Fam Med

KJFM
Korean Journal of Family Medicine

■ Original Article

A Randomized Clinical Trial of Synbiotics in Irritable Bowel Syndrome: Dose-Dependent Effects on Gastrointestinal Symptoms and Fatigue

Sang-Hoon Lee[1], Doo-Yeoun Cho[2], Seok-Hoon Lee[1], Kyung-Sun Han[1], Sung-Won Yang[1], Jin-Ho Kim[1], Su-Hyun Lee[1], Soo-Min Kim[1], Kyu-Nam Kim[1,*]

[1]Department of Family Practice and Community Health, Ajou University School of Medicine, Suwon, Korea
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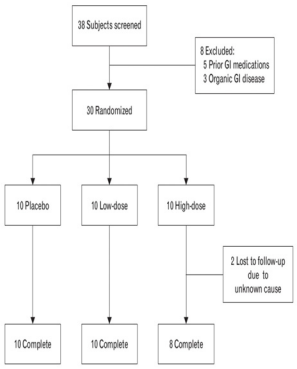


- Ultra-Probiotics-500
- Each capsule contains 10 billion colony-forming units of probiotic bacteria comprising six strains of Lactobacillus (rhamnosus, acidophilus, casei , bulgaricus, plantarum, and salivarius) and two strains of Bifidobacterium (bifidum and longum).
- Each capsule also contains 175 mg of fructooligosaccharides, 150 mg of Ulmus davidiana (Slippery elm bark powder), 10 mg of Geum urbanum (herb bennet) powder, and 100 mg of inulin powder as prebiotics.

Korean J Fam Med. 2018 Oct 26. doi: 10.4082/kjfm.17.0064. [Epub ahead of print]

Table 2. Clinical variables of the study subjects at the last visit, 8 weeks after baseline (n=28)

Variable	Placebo (n=10)	Low-dose (n=10)	High-dose (n=8)	P-value
Abdominal discomfort score	5.4±2.3	3.3±0.9	2.0±1.1	0.002*
Abdominal bloating score	5.4±2.0	4.3±1.8	2.1±1.6	0.006*
Formed stool frequency (per 10 times)	3.4±1.6	5.9±2.7	7.4±2.3	0.007*
Epigastric soreness score	2.9±2.1	2.9±1.9	1.8±2.2	0.379
Nausea score	1.3±1.5	0.9±1.4	0.4±0.5	0.476
Fatigue Severity Scale	42.9±8.3	34.8±10.3	34.0±9.6	0.115
Fatigue Visual Analog Scale	4.9±1.6	3.5±2.2	2.4±1.6	0.028*
Multidimensional Fatigue Inventory	86.0±12.7	74.3±15.2	73.4±13.6	0.041*
White blood cell (×10³/uL)	8.0±1.9	6.4±1.0	6.5±1.0	0.116
Hemoglobin (g/dL)	14.6±1.5	14.2±0.7	13.8±1.2	0.382
Hematocrit (%)	44.5±4.2	43.3±2.3	41.5±3.2	0.299
Platelet (×10³/uL)	232.8±42.2	257.8±40.0	220.0±32.4	0.144
Aspartate aminotransferase (U/L)	30.8±9.4	29.5±11.1	28.1±8.3	0.720
Alanine aminotransferase (U/L)	29.0±19.7	23.3±14.7	18.1±6.7	0.359
γ-Glutamyltranspeptidase (U/L)	28.4±18.0	20.1±8.5	18.4±6.1	0.701
Blood urea nitrogen (mg/dL)	12.0±2.0	13.4±2.4	15.8±5.2	0.186
Creatinine (mg/dL)	0.9±0.2	0.8±0.1	0.9±0.1	0.181

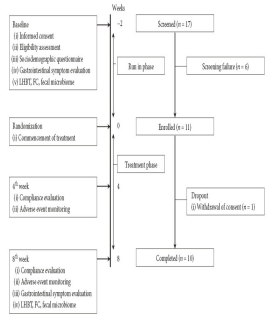
Values are presented as mean±standard deviation. P-values from the Kruskal-Wallis test.
*P<0.05.

Clinical Study

The Therapeutic Effect of a Multistrain Probiotic on Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Study

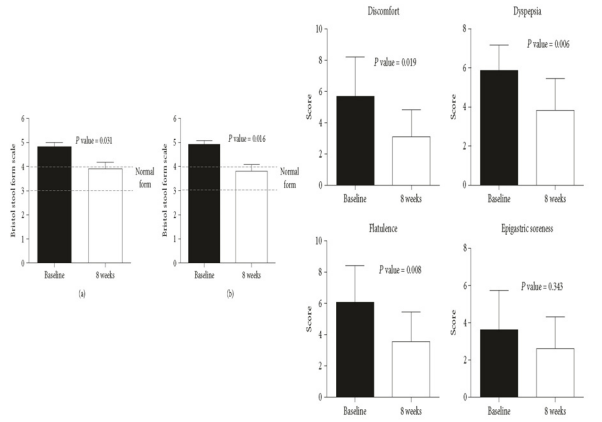
Seok-Hoon Lee, Nam-Seok Joo, Kwang-Min Kim, and Kyu-Nam Kim

Department of Family Practice and Community Health, Ajou University School of Medicine, Suwon, Republic of Korea



- The probiotic agent used in the present study was Ther-Biotic® Complete, a multi-species probiotic combination (Ther-Biotic® Complete; ProThera, Inc., USA) designed and marketed for various digestive problems including IBS.
- Each capsule contains 25 billion active bacteria with 12 different strains: *Lactobacillus rhamnosus* 6.0 billion CFU; *Bifidobacterium bifidum* 5.0 billion CFU; *L. acidophilus* 3.0 billion CFU; *L. casei* 2.5 billion CFU; *L. plantarum* 2.0 billion CFU; *L. salivarius* 2.0 billion CFU; *B. longum* 1.0 billion CFU; *Streptococcus thermophilus* 1.0 billion CFU; *L. bulgaricus* 1.0 billion CFU; *L. paracasei* 0.5 billion CFU; *B. lactis* 0.5 billion CFU; and *B. breve* 0.5 billion CFU.

Gastroenterology Research and Practice, Volume 2018



Gastroenterology Research and Practice, Volume 2018

Table 2: Fecal microbiome analysis before and after probiotic ingestion.

	Group	Mean ± SD		P value	95% CI
		Baseline	8 weeks		
Observed OTUs (ChaO1)	FAS	251.1 ± 60.7	198.7 ± 63.0	0.017	−93.8, −11.2
	PPS	245.8 ± 61.2	188.1 ± 55.1	0.017	−102, −13.3
Beneficial bacteria	FAS	42.9 ± 16.9	54.3 ± 14.6	0.020	2.3, 20.6
	PPS	41.2 ± 16.8	53.7 ± 15.3	0.018	2.7, 22.5
Deleterious bacteria	FAS	12.5 ± 13.3	4.9 ± 3.8	0.010	−19.5, −0.7
	PPS	13.0 ± 13.9	4.7 ± 4.0	0.010	−19.2, −0.8
Lactic acid bacteria	FAS	0.89 ± 1.0	4.2 ± 5.1	0.010	0.3, 8.9
	PPS	1.03 ± 1.0	4.56 ± 5.16	0.010	0.553, 8.9

(a) Lactulose hydrogen breath test

Positive subjects at baseline (%)	Positive subjects at 8th week (%)
6 (54.5)	4 (40)

(b) Fecal calprotectin

	Mean value at baseline (mg/kg)	Mean value at 8th week (mg/kg)	P value
FAS group	323.4 ± 684.9	180.4 ± 327.1	0.375
PPS group	364.4 ± 729.1	200.9 ± 347.6	0.375

Probiotics: Questions to answer

- Which species is best?
- Are combination agents better?
- What is the appropriate dose?
- What is the appropriate duration of treatment?
- What outcome measures are appropriate?
- What is the appropriate follow-up?
- What is the appropriate patient population?

"Repair"

- Repair refers to providing nutritional support for healing and growth of the GI mucosa.
- Clinical approaches may include:
  - Nutrients important for GI repair: Glutamine, arginine, vitamin A, vitamin D, Vitamin C, zinc
  - Mucosal lining support (e.g., phosphatidylcholine)
  - Mucosal secretion protectants such as phosphatidylcholine, plantain, polysaccharides
  - Support for GALT function (e.g., lactoferrin, lactoperoxidase, whey immunoglobulins)
  - Antioxidants known to function in the GI (e.g. catechins)
  - Micronutrients shown to support healing (e.g., pantothenic acid, vitamin E, carotenoids,)
  - Nutritional anti-inflammatories (e.g., curcumin, EPA and DHA)

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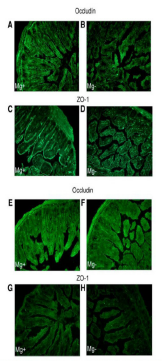
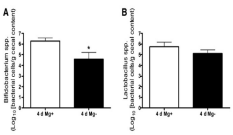
Changes in Intestinal Bifidobacteria Levels Are Associated with the Inflammatory Response in Magnesium-Deficient Mice[1–3]

Barbara D. Pachikian,[4] Audrey M. Neyrinck,[4] Louise Deldicque,[4] Fabienne C. De Backer,[4] Emilie Catry,[4] Evelyne M. Dewulf,[4] Florence M. Sohet,[4] Laure B. Bindels,[4] Amandine Everard,[4] Marc Francaux,[4] Yves Guiot,[5] Patrice D. Cani,[4] and Nathalie M. Delzenne[4]*





- These findings can suggest that decreased bifidobacteria content as a result of short-term Mg deficiency may participate in increased intestinal permeability, resulting in colonic and systemic inflammation.

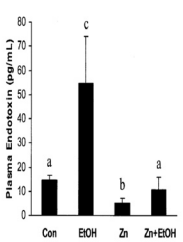
FIGURE 2 Immunofluorescence staining of the ileum epithelial tight junction proteins in mice fed a Mg+ or Mg− diet for 4 d (Occ: A,B; ZO-1: C,D or 21 d (Occ: E,F; ZO-1: G,H.

J Nutr.2010 Mar;140(3):509–14

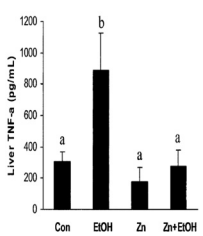
Role of zinc

American Journal of Pathology, Vol. 164, No. 6, June 2004

Preservation of Intestinal Structural Integrity by Zinc Is Independent of Metallothionein in Alcohol-Intoxicated Mice



Plasma endotoxin levels in MT–KO mice 1.5 hours after gastric administration of ethanol



Intrahepatic tumor necrosis factor (*TNF–a*) *levels in mice 6 hours* after gastric administration of ethanol

These results suggest that zinc brought these changes, at least in part, by preventing ethanol-induced transfer of endotoxin from intestine to circulation which could be ascribed to preservation of intestinal morphology and permeability.

Am J Physiol Gastrointest Liver Physiol 294: G208–G216, 2008.
First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.

Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

Juan Kong,[1] Zhongyi Zhang,[1] Mark W. Musch,[1] Gang Ning,[2] Jun Sun,[1] John Hart,[4] Marc Bissonnette,[1] and Yan Chun Li[1]

Departments of [1]Medicine and [2]Pathology, The University of Chicago, Chicago, Illinois; [3]The Huck Institutes for Life Sciences, The Pennsylvania State University, University Park, Pennsylvania; and [4]Gastroenterology and Hepatology Division, Department of Medicine, University of Rochester Medical Center, Rochester, New York

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Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol* 294: G208–G216, 2008. First published October 25, 2007; doi:10.1152/ajpgi.00398.2007.—Emerging evidence supports a pathological link between vitamin D deficiency and the risk of inflammatory bowel disease (IBD). To explore the mechanism we used the dextran sulfate sodium (DSS)-induced colitis model to investigate the role of the vitamin D receptor (VDR) in mucosal barrier homeostasis. While VDR$^{+/+}$ mice were mostly resistant to 2.5% DSS, VDR$^{-/-}$ mice developed severe diarrhea, rectal bleeding and marked body weight loss, leading to death in 2 wk. Histological examination revealed extensive ulceration and impaired wound healing in the colonic epithelium of DSS-treated VDR$^{-/-}$ mice. Severe ulceration in VDR$^{-/-}$ mice was preceded by a greater loss of intestinal transepithelial electric resistance (TER) compared with VDR$^{+/+}$ mice. Confocal and electron microscopy (EM) revealed severe disruption in epithelial junctions in VDR$^{-/-}$ mice after 3-day DSS treatment. Therefore, VDR$^{-/-}$ mice were much more susceptible to DSS-induced mucosal injury than VDR$^{+/+}$ mice. In cell cultures, 1,25-dihydroxy-vitamin D_3 [1,25(OH)$_2$D$_3$] markedly enhanced tight junctions formed by Caco-2 monolayers by increasing junction protein expression and TER and preserved the structural integrity of tight junctions in the presence of DSS. VDR knockdown with small interfering (si)RNA reduced the junction proteins and TER in Caco-2 monolayers. 1,25(OH)$_2$D$_3$ can also stimulate epithelial cell migration in vitro. These observations suggest that VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium. Therefore, vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

tight junction; inflammatory bowel disease; dextran sulfate sodium

The integrity of the intestinal mucosal barrier is preserved by the enormous regenerating capacity of the mucosal epithelium. The intestinal stem cells, located at the base of the crypt, are responsible for replenishing the epithelium through cell division and differentiation. After extensive destruction, rapid resealing of the surface epithelium is accomplished by epithelial cell restitution, proliferation, and differentiation (6). Another important component of the mucosal barrier is the apical and subapical intercellular junctions between the epithelial cells, namely tight junctions and adherens junctions (18). These junction structures seal the paracellular space and regulate the permeability of the mucosal barrier.

IBD, including Crohn's disease and ulcerative colitis, is a major chronic disorder affecting the gastrointestinal tract in humans. Although the etiopathogenesis of IBD has not been clearly elucidated, it is thought to involve a complex interplay among genetic, environmental, microbial, and immune factors (33). One potential pathogenic factor is impaired mucosal barrier function, and intestinal hyperpermeability is common in IBD patients (11). A relatively high number of first degree relatives of patients with Crohn's disease have increased intestinal permeability in the absence of clinical symptoms (32, 42), suggesting barrier dysfunction precedes, or is at least a very early defect, in the disease process that might require genetic predisposition and environmental triggers. Indeed, previous studies have demonstrated decreased expression and differential localization of junction complex proteins in the mucosa of patients with IBD (10, 16, 29). Therefore, dysregulation of junction proteins is an important pathogenic mechanism underlying the increased permeability seen in the intestinal epithelium of IBD patients.

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Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier

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Mechanisms of disease: vitamin D and inflammatory bowel disease.

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Abstract

Until recently, 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3))-the active form of vitamin D-was thought to function primarily as a regulator of calcium and phosphate metabolism. More diverse functionality was indicated by the discovery of the vitamin D receptor in tissues that are not involved in calcium and phosphate homeostasis. Detection of the vitamin D receptor in monocytes and activated T cells has sparked interest in the immunomodulatory properties of vitamin D. Here, we review the role of vitamin D in regulation of the immune system, and evidence for its involvement in the pathogenesis of inflammatory bowel disease.

VDR$^{-/-}$ mice. Confocal and electron microscopy (EM) revealed severe disruption in epithelial junctions in VDR$^{-/-}$ mice after 3-day DSS treatment. Therefore, VDR$^{-/-}$ mice were much more susceptible to DSS-induced mucosal injury than VDR$^{+/+}$ mice. In cell cultures, 1,25-dihydroxy-vitamin D_3 [1,25$(OH)_2D_3$] markedly enhanced tight junctions formed by Caco-2 monolayers by increasing junction protein expression and TER and preserved the structural integrity of tight junctions in the presence of DSS. VDR knockdown with small interfering (si)RNA reduced the junction proteins and TER in Caco-2 monolayers. 1,25$(OH)_2D_3$ can also stimulate epithelial cell migration in vitro. These observations suggest that VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium. Therefore, vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

tight junction; inflammatory bowel disease; dextran sulfate sodium

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Original Communications

The following article is one of two articles offered for continuing education credit in this issue. Please see page 304 for details.

The Effect of Supplemental Enteral Glutamine on Plasma Levels, Gut Function, and Outcome in Severe Burns: A Randomized, Double-Blind, Controlled Clinical Trial

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TABLE II
Plasma glutamine concentration, μm/L

	Control group (n = 20)	Gln group (n = 20)	p value
PBD +1	381.1 ± 36.4	357.5 ± 55.4	.18
PBD +12	399.7 ± 40.6	591.0 ± 74.5	.048

TABLE IV
Endotoxin concentration, EU/mL

	Control group (n = 20)	Gln group (n = 20)	p value
PBD +1	0.089 ± 0.023	0.103 ± 0.037	.27
PBD +3	0.107 ± 0.038	0.061 ± 0.017	.021
PBD +6	0.166 ± 0.013	0.145 ± 0.016	.18
PBD +12	0.155 ± 0.035	0.162 ± 0.032	.35

postburn day (PBD)

TABLE III
L/M ratio

	Control group (n = 20)	Gln group (n = 20)	p value
PBD +1	0.221 ± 0.169	0.268 ± 0.202	.538
PBD +3	0.049 ± 0.016	0.025 ± 0.008	.001
PBD +6	0.051 ± 0.013	0.018 ± 0.003	.034
PBD +12	0.036 ± 0.021	0.018 ± 0.013	.23

- Enteral glutamine supplementation improved gut permeability, and initially decreased plasma endotoxin levels in severely thermally injured patients.

Original Communication

aspen

The Role of L-Arginine and Inducible Nitric Oxide Synthase in Intestinal Permeability and Bacterial Translocation

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Abstract

Background: Arginine has been shown to have several immunological and trophic properties in stressful diseases. Its metabolites, nitric oxide (NO) and polyamines, are related to arginine's effects. Thus, the aim of this study was to determine the effects of the NO donor L-arginine and the role of inducible NO synthase (iNOS) on intestinal permeability and bacterial translocation in a model of intestinal obstruction (IO) induced by a simple knot in the terminal ileum. *Material and Methods:* Male C57BL6/J wild-type (WT) and iNOS knockout (iNOS−/−) mice were randomized into 6 groups: Sham and Sham−/− (standard chow), IO and IO−/− (standard chow +IO), and Arg and Arg−/− (standard chow supplemented with arginine + IO). After 7 days of treatment with standard or supplemented chows, IO was induced and intestinal permeability and bacterial translocation were evaluated. The small intestine and its contents were harvested for histopathological and morphometric analysis and the determination of polyamine concentration. *Results:* Pretreatment with arginine maintained intestinal permeability ($P > .05$; Arg and Arg−/− groups vs Sham and Sham−/− groups), increased polyamine concentration in intestinal content ($P < .05$; Arg vs IO group), and decreased bacterial translocation in WT animals (Arg group vs IO and IO−/− groups). Absence of iNOS also presented a protective effect on permeability but not on bacterial translocation. *Conclusion:* Arginine supplementation and synthesis of NO by iNOS are important factors in decreasing bacterial translocation. However, when intestinal permeability was considered, NO had a detrimental role. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Rebalance

- Pay attention to lifestyle choices – sleep, exercise and stress can all affect the GI tract

→ Regular aerobic exercise
- ☞ regular GI motility
- ☞ reduces the stress-induced enzymes that can disrupt the GI barrier.

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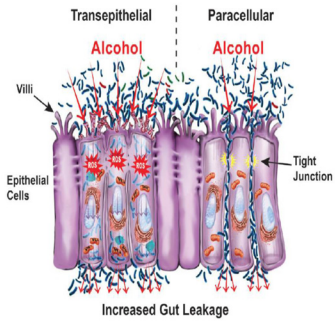
ALCOHOL RESEARCH: *Current Reviews*

Alcohol and Gut-Derived Inflammation



Bishehsari F, et al. Alcohol Res. 2017;38(2):163–171.