

Leaky Gut Syndrome & Small Intestinal Bacterial Overgrowth

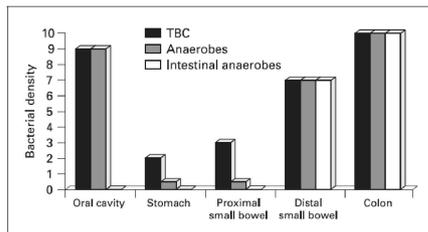
아주의대 가정의학교실
김규남



Overview of Gut

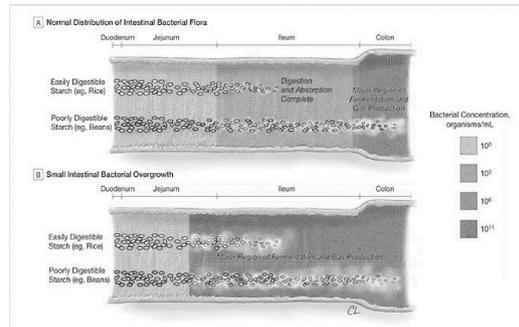
- The gut: 25–30 feet long
- 100 square yards of surface area
- Gut lumen is “not inside” the body
- Dynamic physiologic organ
- Primary functions:
 - Digestion and absorption of nutrients
 - Barrier to differentiate friend from foe
 - Metabolism and detoxification

정상 균수



Einar Husebye, Chemotherapy 2005;51(suppl 1):1-22

Intestinal bacteria distribution in SIBO



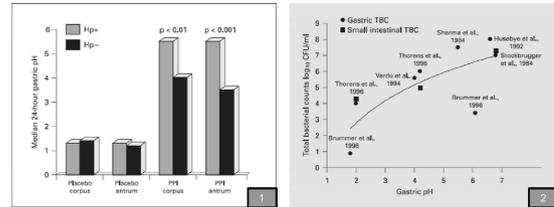
Lim HC JAMA;18:852-858



The Pathogenesis

- 1. Failure of the Gastric Acid Barrier
- 2. Failure of Intestinal Clearance

Failure of the Gastric Acid Barrier



1. Verdu EF, et al: Gut 1995;36:539-543
 2. Einar Husebye, Chemotherapy 2005;51(suppl 1):1-22

Effects of long-term PPI treatment on producing bowel symptoms and SIBO

Debora Compare, Loredana Pica, Alba Rocco, Francesco De Giorgi, Rosario Cuomo, Giovanni Sarnelli, Marco Romano and Gerardo Nardone

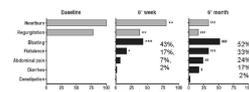


Figure 2. Percentage of patients with mean symptom total score ≥ 4 baseline, at 6-week and 6-month checkpoints. Fisher's exact test; *Statistically significant versus baseline; **P < 0.05; ***P < 0.001; ****P < 0.0001; %6-month checkpoint versus baseline; %P < 0.05; ***P < 0.001; ****P < 0.0001.

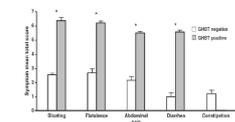


Figure 3. Mean total score of symptoms in patients subdivided according to GHB results. NERD: non-erosive reflux disease; GHB: glucose hydrogen breath test; Mann-Whitney test; *P < 0.05.

- Patients (42) with NERD not complaining of bowel symptoms
- esomeprazole 20 mg bid for 6 months
- Prolonged PPI treatment may produce bowel symptoms and SIBO
- The strategy of step-down or on-demand PPI therapy should be encouraged in GERD.

Eur J Clin Invest. 2010 Dec 3.

Proton Pump Inhibitor Therapy Use Does Not Predispose to Small Intestinal Bacterial Overgrowth

Shiva K. Rahaqali, MD¹, Taylor C. Ellington¹, Mary-Teresa O'Neill, MD¹, Sarah B. Umar, MD¹, Lucinda A. Harris, MD¹, Amy E. Fox-Orenstein, DO¹, George E. Burdick, MD¹, John K. DiBaise, MD¹, Brian E. Lacy, MD¹ and Michael D. Crowell, PhD, FACF, AGAF¹

Table 2. Comparison of GHB positivity between PPI users and nonusers

Breath test criteria	PPI users (n=566)	PPI nonusers (n=625)	P value
H ₂ > 20, n (%)	71 (13)	87 (14)	0.49
H ₂ > 10, n (%)	146 (26)	149 (24)	0.44
CH ₄ > 15, n (%)	77 (14)	72 (12)	0.28
Either H ₂ > 20 or CH ₄ > 15, n (%)	126 (22)	131 (21)	0.59

CH₄, methane; GHB, glucose hydrogen breath testing; H₂, hydrogen; PPI, proton pump inhibitor.

- 이유 :
- 1. Breakthrough surges of acid production occur regularly.
- 2. Even a few hours of pH below 4.0 → inhibit bacterial overgrowth.
- 3. The type of bacteria that are found in hypochlorhydric state → oropharyngeal microbes different from gram (-) seen in intestinal dysmotility
- 4. Pancreatobiliary secretion → antibacterial activity → inhibit SIBO.

Am J Gastroenterol. 2012 Feb 14 [Epub ahead of print]

Extensive Atrophic Gastritis Increases Intraduodenal Hydrogen Gas

Yoshihisa Urita,¹ Toshiyasu Watanabe,² Tadashi Maeda,¹ Tomohiro Arita,¹ Yosuke Sasaki,¹ Takamasa Ishii,¹ Tatsuhiko Yamamoto,¹ Akira Kugahara,¹ Asuka Nakayama,¹ Makie Nanami,¹ Kaoru Doman,² Susumu Ishihara,² Hirohito Kato,¹ Kazuo Hike,⁴ Norikok Hara,⁴ Shuji Watanabe,⁴ Kazushige Nakanishi,¹ Motonobu Sugimoto,¹ and Kazumasa Miki³

TABLE 2. Intra-gastric and intraduodenal hydrogen levels in relation to the grade of atrophic gastritis.

	Closed type	O-1	O-2	O-3
Number of patients	200	66	101	289
Age (mean ± SD)	55.1 ± 13.9	58.1 ± 13.6	59.1 ± 12.5	66.1 ± 9.8
Male/female	60/140	22/44	39/62	90/199
Stomach (ppm)	10.5 ± 17.3*	7.4 ± 10.2	8.0 ± 12.0	7.5 ± 17.0
P values vs.*	-	.085	.105	.031
Duodenum (ppm)	7.1 ± 12.7	4.4 ± 8.2	8.1 ± 18.5	21.5 ± 88.1**
P values vs.**	.009	.055	.061	***

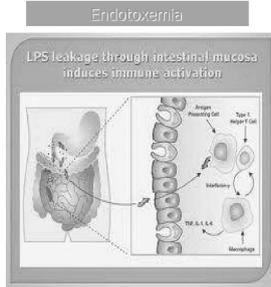
- The intraduodenal hydrogen levels were increased with the progression of atrophic gastritis.
- The influence of hypochlorhydria on bacterial overgrowth in the proximal small intestine is more pronounced, compared to that in the stomach.

Gastroenterol Res Pract. 2008;2008:564929.

Failure of Intestinal Clearance

- Abnormal Intestinal Anatomy
- Failure of Intestinal Mechanical Clearance (Intestinal Motility)
 - Neuromuscular Diseases
 - Diseases and Injury of the Gut Wall
 - ↳ Radiation Injury
 - ↳ Inflammation
 - ↳ Connective Tissue Diseases
- Metabolic and Endocrine Disorders
 - Thyroid Disease
 - Diabetes mellitus
- Drug-Induced Dysmotility
- Surgery

SIBO의 임상적 중요성



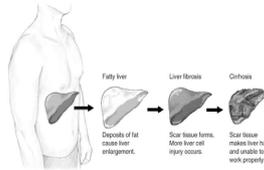
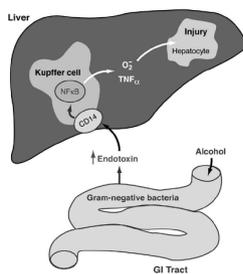
- **LPS**
 - induces the **NK-kB-mediated production of nitric oxide.**
 - ⇒ **NK function is inhibited and opportunistic infections.**
- **Chronic inflammatory condition**
 - **Chronic Fatigue Syndrome**
 - **allergic or auto-immune diseases**
 - ⇒ **RA, asthma, multiple sclerosis, Addison' s disease, lupus...**
 - **Nutritional deficiencies**
 - **Increased absorption of environmental toxins**

Jonathan Cohen Nature 420, 885-891(19 December 2002)

SIBO의 임상적 중요성

- Histologic change; subtotal atrophy and mucosal inflammation
- **Facultative anaerobes;**
 - injure the intestinal surface by direct adherence & production of enterotoxins
- Aerobes;**
 - produce enzymes and metabolic products capable of causing epithelial cell injury
- **Deconjugation of bile salt by bac.**
 - Bile salt injury to the mucosal surface
 - Mal absorption of fat
- **Degradation of intestinal brush-border & pancreatic enzymes by bac. Proteases**
 - Malabsorption of protein
 - CHO malabsorption related to decreased brush-border hydrolase activities
- **AA to Vasoactive amine by bac. Decarboxylase**
 - Dilation & contraction of bowel vessel

SIBO의 임상적 중요성

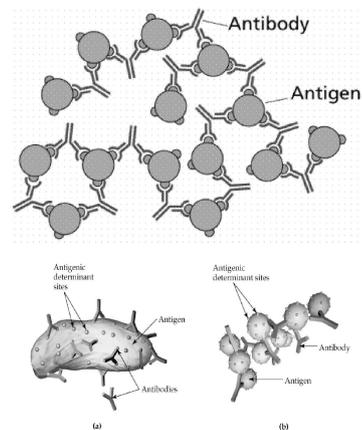


Over time, up to 20 percent of patients with NASH may develop cirrhosis.

Leaky Gut Syndrome (Increased Intestinal Permeability)

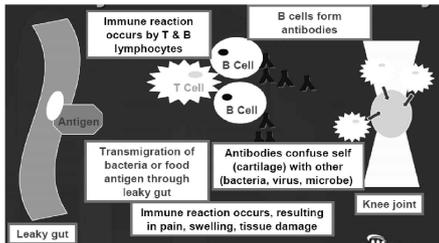
Pathophysiology of LGS

1. Endotoxemia
2. Ag-Ab immune complex
3. Detoxification impairment



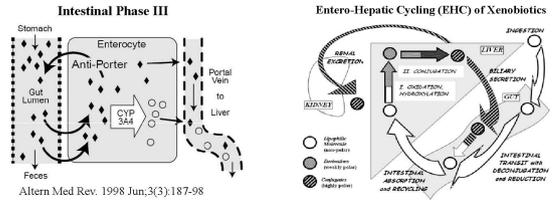


Cross-reactivity Model: 'Leaky Gut' and Autoimmunity



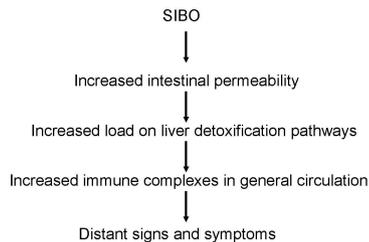
Increased immune response to *Klebsiella* in patients with AS, UC, CD and to *Proteus* in patients with RA

Intestine Detoxification metabolism



By Epithelial Damage, Pathogenic bacteria can produce toxins (endotoxin, enterotoxin, etc) that can enter circulation and increase toxic load

Progress of Problem



Symptoms associated with LGS

- | | |
|---------------------|------------------------------|
| Abdominal pain | Gas |
| Aggressive behavior | Indigestion |
| Anxiety | Mood swings |
| Asthma | Nervousness |
| Bed wetting | Poor exercise tolerance |
| Bloating | Poor immunity |
| Chronic joint pain | Poor memory |
| Chronic muscle pain | Primary biliary cirrhosis |
| Confusion | Recurrent bladder infections |
| Constipation | Recurrent vaginal infections |
| Diarrhea | Shortness of breath |
| Fatigue and malaise | Skin rashes |
| FUO | Toxic feelings |
| Fuzzy thinking | |

Solving the Digestive Puzzle, 1995

Common Clinical Conditions Associated with Increased Intestinal Permeability

- | | | |
|--|--|--|
| <ul style="list-style-type: none"> ▪ Acne ▪ Aging ▪ AIDS ▪ Alcoholism ▪ Allergic disorders ▪ Ankylosing spondylitis ▪ Arthritis /Inflammatory joint dis. ▪ Asthma ▪ Autism ▪ Celiac disease ▪ Chemotherapy ▪ Childhood hyperactivity | <ul style="list-style-type: none"> • Chronic fatigue syndrome • Crohn's disease • Cystic fibrosis • Eczema • Endotoxemia • Environmental illness • Food allergies or sensitivities • Giardiasis • HIV positive • Hives • Inflammatory bowel dis. • Intestinal infections | <ul style="list-style-type: none"> • IBS • Liver dysfunctions • Malabsorption • Malnutrition • Multiple chemical sensitivities • NSAID enteropathy • Pancreatic insuff. • Psoriasis • Reiter's syndrome • RA • Schizophrenia • SLE • Thermal injury • Trauma • Ulcerative colitis |
|--|--|--|

Am J. Nephrol. 16: 500-05, 1996

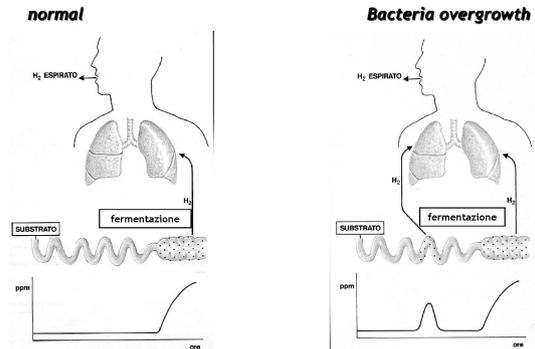
Evaluation

SIBO
Intestinal Permeability

SIBO 진단법

- 배양법
- 호기 검사법
 - 락툴로오스
 - 포도당, Sucrose

Lactulose H₂ BREATH TEST



Lactulose Hydrogen Breath Test

- lactulose ingestion (10 g lactulose in 20 mL water solution)
- taken every 20 minutes for 3 hours
- Positive indication of bac. overgrowth
 - baseline value of H₂ or CH₄ >20 ppm
 - a >20 ppm increase in H₂ or CH₄ above the baseline value within 3 hours

Glucose Challenge Test

- Normally absorbed before it reaches the large intestine
- Metabolize by bac. in small bowel before absorption of glucose
 1. Fasting breath sampling
 2. Ingestion of 75g glucose solution
 3. Collect breath samples every 15mins for 2 hrs

Glucose Challenge Test

- Typical normal fasting breath sample
 - < 10 ppm of breath hydrogen or methane
- Positive indication of bac. overgrowth
 - Rise of 12 ppm in breath hydrogen within 1 hr
 - high fasting breath hydrogen or methane level > 20 ppm

Non-invasive assessment of barrier integrity and function for Intestinal Permeability

- ASSESSMENT OF THE EPITHELIAL BARRIER INTEGRITY
- FUNCTIONAL ASSESSMENT OF INTESTINAL BARRIER LOSS



Treatment

The 5R Program