A META- ANALYSIS AND SYSTEMIC REVIEW

SIBO (SMALL INTESTINAL BACTERIAL OVERGROWTH)

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INTRODUCTION

There is a lack of awareness about (small intestinal bacterial overgrowth) SIBO in medical communities, in about every country. I believe, the reasons for that are that the clinicians face numerous obstacles for recognition and proper diagnosis of SIBO. Among these obstacles, unrealibilty/invasive nature of the available diagnostic testing which often needs specialized laboratories and expense, comes first. In addition, there are so much uncertainty and controversies surrounding SIBO diagnosis.

These controversies stem from SIBO's wide-ranging and nonspecific signs and symptoms (see Table 3), that often overlaps with other heterogeneous gastrointestinal disorders such as, irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), intestinal pseudo-obstruction, and other functional gastrointestinal disorders (1-3).

My interest in SIBO comes from my sister's diagnosis of SIBO, many years ago, following her gastric surgery (Billroth II, vagotomy), and cholecystectomy. Since then, she continues to struggle with recurrent bouts of SIBO, which always require my involvement.

To better help my sister, I have been closely following medical literature, and reading everything I can about SIBO. I believe this family challenge, over the years, made me an expert in SIBO. Seeing a lack of knowledge, on this subject, among practicing physicians, I have decided to share my humble opinion, know how, and experience on SIBO with my colleagues.

SIBO is an acronym; it stands for "Small Intestinal Bacterial Overgrowth". It is more a syndrome than a disease (4). Many factors and pre-existing gastrointestinal disorders predispose patients to develop SIBO (Table 1).

Tablo 1. Pre-disposing factors for SIBO

CATEGORIES	FACTORS
Demography	Female
	Old age
Existing diseases/conditions	Diabetes and neuropathy
	AF, CAD
	Parkinson's disease
	Hypothyroidism
	Crohn's disease (IBD)
	Systemic sclerosis
	Chronic pancreatitis
	Intestinal dysmotility
	Small intestinal diverticulum
	Intestinal pseudoobstruction
Abdominal surgeries	Gastric surgeries (Billroth, vagotomy)
	Cholecystectomy
Long lasting medication usage	Opioids
	Proton pump inhibitors

Since SIBO is a small intestinal bacterial overgrowth disorder, to understand its pathogenesis better, we should look at the human's gut microbiome population and their metabolic activities (Table 2), more closely, without getting lost in the immense scientific data on the enteric bacterial eco system (2,5,6).

Even though gut microbiome is necessary for our well- being, under certain circumstances overgrowth of bacteria in the gastrointestinal tract, called dysbiosis, could occur and become a major health liability for the human host.

The lesson we learned from a gastric acid resistant enteric pathogen **Helicobacter pylori's** role in the pathogenesis of peptic ulcers, chronic gastritis, gastric polyps, gastric cancer, have warned medical researchers about the potential risk other bacteria, commensal or pathogenic, could play a pathogenetic roles in many other gastro-intestinal diseases. Human microflora should be thoroughly investigated.

We know that human gut microbiome, especially the colon, is home to the vast kingdom **(10^{14})** of mostly beneficial, symbiotically living commensal bacteria. This number is ten times more than the

Tablo 2. Metabolic activities of intestinal microbiota

- Degradation of undigestible polysaccharides of plant origin
- Production of folate, B vitamins, vitamin K, and short chain fatty acids
- Production regulatory signals for neuro-anatomical development of the gut and mucosal immune system
- Biotransformation of bile acid
- Conversion of prodrugs to active metabolites
- Regulation of fat deposit
- Breakdown of dietary oxalate
- Protection of the host from the invasion of pathogenic microorganisms

number of cells in human body. This diverse microbiome population is composed of 500 to 1,000 different bacterial species, viruses, and fungi.

Much of the studies of human microflora have been done on colonic microbiota population by stool studies, which give us valuable information on colonic luminal microbiome. However, it gives us little to no information about colonic epithelial bacteria, which are adhered to the epithelial cells, and are not readily excreted in the stool, nor about the small intestinal microbiome population.

One cannot help but wonder, why are there so many and so diverse microorganism with their own DNA, living symbiotically but independently in our guts?

Unlike colon, the small intestine is mostly devoid of luminal bacteria, except distal small intestine which contain **10^8** commensal bacteria/ml. There are several endogenous defense mechanisms, as seen in (Table 3) that prevent bacterial overgrowth in the small intestine (2,6-8).

When these endogenous defense mechanisms are compromised with diseases or conditions (see Table 1), an overgrowth of different bacterial populations in the small intestine, easily occur. This is the root cause of SIBO.

In addition, unlike the colon, the small intestine possess a single layer of absorptive mucosa, with surface area 400^2 m. Even though this single layer absorptive mucosa of the small intestine is well protected by its cellular and immunologic defense mechanism, against invasive organisms. Small

Tablo 3. Endogeneus defense mechanisms to prevent bacterial overgrowth in the small intestine

1. Strong gastric acid secretion that kills all the bacteria that is ingested by food or drinks
2. Intestinal peristalsis and motility
3. Immunoglobulin secretion within the intestinal lumen
4. Bacteriostatic properties of pancreatic and biliary secretions
5. Unidirectional ileo-cecal valve preventing colonic bacteria to enter small intestine

intestinal mucosa easily absorbs nutrients, vitamins, minerals, as well as toxins, bacterial breakdown products and anything else that accumulate in the lumen. These substances could trigger a dysregulated immune reaction, with diffuse inflammatory reaction by the production of pro-inflammatory cytokines and chemokines. Brain fog, and other non-specific signs and symptoms of SIBO (Table 4). Are thought to be due to diffuse inflammation (8-12).

Tablo 4. Signs and symptomps of SIBO

- Diffuse, vague, nonlocalized abdominal pain an distention
- Nausea, and vomiting
- Anorexia, refusal to eat, rapid weight loss
- Foul smelling diarrhea, flatus, or constipation
- Brain fog, mental confusion
- Low grade fever and/or low body temperature
- Malnutrition, lack of nutrient, vitamins and minerals

Colonic epithelium is inhabited by bacteria that differ from luminal bacteria, in a sense that they are metabolically more active, they interact with the host, and exert regulatory effects, and neuro-anatomical and cellular development of the gut.

Scientific studies on the laboratory raised and germ- free, rodents have shown that without regulatory signaling from enteric microflora, their intestine show obvious defects in neuro-anatomical, cellular, and lymphatic developments (2,3,5).

Bacterial signaling molecules are also enable mucosal epithelial cells and dendritic cells, to recognize commensal bacteria from pathogenic bacteria, by their surface pattern recognition receptors, like tall like receptors (TLR) (8-10).

Mucosa is the name given to the external surface of the epithelial cells for its capacity to produce mucus, a viscous solution of polysaccharides in water that cover the mucosal surface. The mucus contains various secretory antibodies (immunoglobulins) and anti-microbial molecules that help to protect the epithelial mucosal cells from the invasion of pathogenic microorganisms, thereby maintaining mucosal homeostasis (2,8,11).

DIAGNOSIS OF SIBO

I personally do not wait for laboratory test results, to treat a patient for SIBO; if my suspicion is high with existence of multiple precipitating factors in patient's history, and the presenting signs and symptoms are compatible with the diagnosis of SIBO, I start the treatment right away, because available diagnostic tests (13,14) are either non-specific, and unreliable or, invasive and expensive. I believe successful empirical treatments are also diagnostic tools.

DIAGNOSTIC TESTS FOR SIBO

1. Breath Testing: It measures the amount of hydrogen or methane after drinking of mixture of glucose. A rapid rise in exhaled hydrogen or methane indicates SIBO (2,13,14).

2. Small intestinal intubation to obtain aspirate and fluid culture: This is gold standard. It is invasive needs gastroscopy with the intubation of small intestine to obtain small intestinal fluid for culture (2).

TREATMENT AND MANAGEMENT OF SIBO (16-18)

I am against using systemic and broad – spectrum antibiotics, if there is no proven sepsis. Treatment of bacterial overgrowth in the small intestine with an oral non-absorbable antibiotic rifaximin is safe and effective. However, patients' general medical condition, nutritional status, electrolytes and vitamin deficiencies, refusal to eat, and other medical conditions have to be taken into consideration. If necessary IV hyperalimentation should be started. In addition, other secondary therapeutic measures, as stated below, should be done.

DIAGNONISIS, THERAPEUTIC MEASURES and MANAGEMENT of SIBO

HIGH SUSPICION

(Multiple risk factors + signs and symptoms)
Start treatment immediately, no test needed.

LOW SUSPICION

(Minimal risk factors + signs and symptoms)
Do breathe testing;
if positive start treatment.
if negative, do jejunal aspirate and culture,
if positive start treatment.

TREATMENT

Rifaximin 1650 mg/day, PO for two weeks, in divided doses.
Probiotics
Prokinetic agents
Laxatives, enemas if constipated
IV hyperalimentation (if needed)
Low FODMAP diet

Some additional and precautionary words about probiotics, diet, preventative measures about SIBO. Probiotics are two-edged sword in the treatment of SIBO. In a study (16-18) where patients were patients were given rifaximin (18) and a probiotic "Lactobacillus casei,"have had greater improvement in their symptoms. Other studies have shown patients symptoms got worse with probiotics.

When it comes to diet, we should bear in mind that gut bacteria ferment carbohydrates such as glucose, lactose, fructose and oligosaccharides resulting in excess gas formation and bloating. Therefore, FODMAB diet the best diet for SIBO patients to follow.

It should also be remembered that human body needs at least 1600 to 2000 calories a day, just to maintain basic metabolic and organ's function.

Maintenance dose of antibiotic usage for prevention of SIBO, in my search, has not been addressed in medical literature. I personally keep my SIBO patients on 400 mg of rifaximin daily, along with "Lactobacillus casei" containing probiotic, and FODMAB diet to prevent recurrence of SIBO.

One more precautionary note is that when a SIBO patient is on anti–coagulant therapy and maintenance dose of antibiotics, vitamin K dependent coagulopathy and excessive bleeding could occur (19). This is what happened to my patient.

REFERENCES

1. Rao SSC, Bhagatwala J. Small intestinal bacterial overgrowth: Clinical features and therapeutic management. Clin Transl Gastroenterol 2019;10:e00078.
2. O 'Mahony S, Shanahan F. Enteric microbiota and small intestinal bacterial overgrowth. Sleisenger and Fordran's Gastrointestinal and Liver Diseases. Saunders, Philadelphia,2010.
3. Achufusi TGO, Sharma A, Zamora EA, at al. Small intestinal bacterial overgrowth: Comprehensive review of diagnosis, prevention, and treatment methods. Cureus 2020;12:e8860.
4. Bres J, Cyrany J, Kohouta D, et al. Small intestinal bacterial overgrowth. World J Gastroenterol 2010;16:2978-90.
5. Quigley EMM, Murray JA, Pimentel M. AGA Clinical Practice Update on Small Intestinal Bacterial Overgrowth. Expert Review. Gastroenterology 2020;159:1526-32.
6. Stearn TJ, Lynch MD, Senadheera A, at al. Bacterial biography of the human digestive tract. Sci Rep 2011;1:170.
7. Drasar BS, Shiner M, McLean GM. Studies on the bacterial flora, the bacterial flora of the gastrointestinal tract in healthy and achlorhydric persons. Gastroenterology 1969;56:71-9.
8. Tak WM, Mary ES. The Immune Response. Basic and Clinical Principles. Elsevier 2006, Boston.
9. Rakooff NS ,Paglino J, Eslami E, et al. Recognition microflora by tall like receptors is required for intestinal homeostasis. Cell 2004;118:220-41.
10. Artis D. Epithelial-cell recognition of commensal bacteria in the gut. Nat Rev Immunol 2008;8:411-20.
11. Yuan Q, Walker WA. Innate immunity of the gut. Mucosal defense in health and disease. J Ped Gastroenterol Nutri 2004;38:463-73.
12. Uchimura Y, Fuhrer T, Li H, et al. Antibodies set boundaries limiting bacterial metabolites penetration and resultant mammalian host response. Immunity 2018;49:545-59.

13. Rezaie, A, Buresi M, Lembo A, et al. Hydrogen and methane based testing in gastrointestinal disorders. North American Consensus: A J Gastroenterol 2017;112:775-84.

14. Erdogan A, Lee YY, Bedger C, et al. What is the optimal threshold for an increase in hydrogen and methane level with glucose breath test (GBT) for detection of SIBO? Gastroenterology 2014;146:500-32.a

15. Rao SSC, Rehman A, Yu S, et al. Brain fogginess, gas, bloating: A link between SIBO, probiotics and metabolic acidosis. Clin Transl Gastroenterol 2018;9:162.

16. Shah SC, Day LW, Sumosuk M, et al. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2013;11:925-54.

17. Gatto L, Scarpignato C. Systemic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestinal bacterial overgrowth. Alim Pharmacol Ther 2007;45:614-16.

18. Zhong C, QU c, Wang B, et al. Probiotics for prevention and treating small intestinal bacterial overgrowth: A meta-analysis and current evidence. B J Clin Gastroenterol 2017;51:300-11.

19. Oliveira RB, Martinelli ALC, Troncon LEA, Elias J Jr. Small intestinal bacterial overgrowth (SIBO) and vitamin K-responsive coagulopathy: a previously unrecorded association. BMJ Case Rep 2018;2018:bcr2017223531.