

Small Intestinal Bacterial Overgrowth and Rifaximin: An Update

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ABSTRACT

Excessive bacteria and nutrient malabsorption are the two major events need to clarify small intestinal bacterial overgrowth (SIBO). Clinically, SIBO is defined as a condition with the existence of $> 10^6$ colony-forming units (CFU) bacteria in the human intestine. It is the only generally accepted criteria to diagnose the SIBO in clinical practice. The main problem is that several clinical disorders are happening in patients with SIBO; thus actual discrimination will be relatively difficult. Exploration of the current status of SIBO management and suggesting rifaximin as a main clinical target is our optimal goal. Although the quality of performed randomized clinical trials needs to be re-evaluated, rifaximin seems the only suitable option for treatment of SIBO. Undoubtedly, new treatment should include the correction of ongoing small intestinal microflora with proper antibiotic therapy. Personalized medicine is another option that should be studied thoroughly before entering the area of SIBO treating using proton pump inhibitors. Finally, we have to focus on the available option to have better management of patients with SIBO.

Keywords: Small intestinal bacterial overgrowth, Rifaximin, Rifamycin, Microbiota, Antibiotic, Treatment

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INTRODUCTION

Presence of various microbial communities with large quantity in human intestine raises many questions about their roles and possible biological functions (1). Recent comparative analysis using animal models indicates that specific intestinal flora is essential for maintaining the health status of the human immune system (1-3). Human microbiota contains more than 10^{14} bacterial cells, which are 10 times more than human cells (4,5). Presence of these number of bacteria and probability for rapid

growth in the small intestine is bound to a biological phenomenon termed “bacterial overgrowth” (4,6-10). Small intestinal bacterial overgrowth (SIBO) is a complex syndrome characterized by an excessive number of abnormal bacteria in the human small intestine. In clinical practice, disrupted normal homeostatic mechanisms that alter bacterial populations result in SIBO (11,12). So far, dysmotility in the small intestine and reduced gastric acid secretion are the two major causes impacting on normal homeostatic action/movement by the human small intestine (13-16). In addition, malfunction in gastrointestinal immune response is also another predisposing factor for SIBO. The main problem is that following the SIBO, patients start to complain about many gastroduodenal disorders including malnutrition, iron deficiency syndrome, diverticular diseases, and irritable bowel syndrome (17-19). On the other hand, due to the non-specific symptoms of SIBO and lack of sufficient sensitive diagnostic methods for this clinical problem, it has been estimated that the current prevalence of SIBO reported worldwide is underestimated (8,20-23). As described

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already, SIBO is a clinical dilemma and challenging situation, which needs to be managed properly (24). The accurate detection of SIBO is more difficult when gastrointestinal abnormalities and gastroduodenal post-surgical complaints are incorporated (25-28). Indeed, discrepancy between those signs and SIBO will be very difficult and limit our approaches to have better management of this syndrome. Another side of the problem is that clinicians first need to discover the main cause of SIBO in each patient (29). For example, misuse of antibiotics or proton pumps inhibitors (PPIs). In this case, stopping the regimen can be useful in the treatment of SIBO. Abnormal gastrointestinal motility is also a cause of SIBO. Indeed, patients with disorders in small intestine motility are highly predisposed to suffer from the SIBO. Aging and metabolic disorders are the remaining factors involved in the development of SIBO in subjects. With regard to the etiology of SIBO, an ideal treatment can be expectable. Therefore, antibiotic-dependent SIBO can be easily treated with discontinuing the prescribed antibiotics. Notably, the change in antibiotic therapy should not target the elimination of whole bacterial content of the small intestine. To be fair, antibiotic-associated complaints of SIBO is much higher than other non-antibiotic induced SIBO (22,30-33). In our opinion, an empiric therapy containing a wide-spread antibiotic to cover both aerobic and anaerobic microorganisms is an ideal solution. In the last decade, many antibiotics were used to treat the SIBO, but still, no definite antibiotic achieved acceptable effects exist to be generalized in clinical practice (27,30,34-36). Unfortunately, there is no clear recommendation on how to manage the patients with SIBO. There are some evident facts in choosing antibiotics to treat the SIBO; I) it should be an effective antibiotic on both aerobic and anaerobic microorganisms because of its mix condition in the small intestine, II) it should have relatively low side-effects. In fact, providing those criteria in selecting this effective antibiotic highly restricts clinicians' options. Given the above mentioned considerations, there is no long list of antibiotics to use in treating SIBO, but recently, rifaximin was introduced and it may get more attention in near future to change the current scenario in the treatment of SIBO.

Rifaximin: Potentially effective and promising antibiotic

Rifaximin is a semisynthetic derivative of rifamycin with broad-spectrum activity against both gram-negative and gram-positive bacteria. Due to the low absorption in the blood and urine (less than 0.5%), it is highly recommended to treat infections in the gastrointestinal tract (37-39). Rifaximin is poorly absorbed rifamycin derivative, which binds to the β subunit of the bacteria DNA dependent RNA polymerase (40,41). This binding can irreversibly inhibit the protein synthesis in target cells. Interestingly, the presence of extra pyridoimidazole ring in rifaximin made it a non-absorbable rifamycin derivative. The main preference of rifaximin in comparison with other antibiotics is its almost zero absorption rate in the gastrointestinal lumen. This factor can be considered as the main determining preference to use rifaximin in treating the patients with SIBO. Rifaximin showed a neglectable severe effect on the normal flora of human intestine (39,40). Taking together, preliminary investigations have shown the potential effectiveness of rifaximin in treating the SIBO (7,23,35,36).

Treatment of SIBO with rifaximin: Clinical considerations and limitations

It can be concluded that application of rifaximin made a great change in treating the SIBO. However, there are some limitations that need further studies and detailed research. One of the major considerations is for patients to be treated. Indeed, all patients suspected as having SIBO should not be the target of therapy. As we mentioned earlier, only patients who receive antibiotics that change their microflora (in the wrong direction) should have correct antibiotic therapy. Thus, choosing the right patients is not less important than rifaximin application in the management of such patients. In next paragraph, we discuss using PPIs and their effects in those patients. Indeed, we should consider patients who receive PPI and aim to start rifaximin therapy even for short time.

Proton pump inhibitors and SIBO

Regardless of the beneficial impacts of application of PPIs in treating many gastroduodenal diseases in human, they mostly cause a great change (modification) in the human intestinal bacterial

populations (42). From the biological point of view, PPIs induce acid suppression in gastric microniche, so it will modify the bacterial composition in the rest of gut lumen. Induction of dysbiosis is the main observed change following prescribing PPIs for those patients (43-45). Using new technologies and administration of probiotics, clinicians will be able to control the human microflora; a good idea to control the dysbiosis. It seems that the relationship between the application of PPIs and occurrence of SIBO is something like two-edge sword! Clinicians should continue to use it while they should not forget its side-effects in some occasional situations. Personalized medicine is another option that should be studied thoroughly before entering the area of SIBO treating using PPIs.

Conclusive remarks

The projects focused on human intestinal microbiome are quickly increasing worldwide and new dimensions are being shaped. Clinicians need to optimize sampling and analyse methods for aspirated specimens. That analysis in controlled populations, after treating patients and also long-term follow-ups can reveal many facts about this complex new syndrome in the current century. Taking together, the quality of performed randomized clinical trials needs to be re-evaluated. Rifaximin seems the only suitable option for treatment of SIBO. Finally, we have to focus on available options to for better treatment of patients with SIBO.

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CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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