

# Gut Microbiota, Inflammation and Symptomatic Diverticular Disease. New Insights into an Old and Neglected Disorder

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In an era when inflammatory bowel disease (IBD) attracts much attention from researchers and enjoys the fruits of innovative approaches to therapy and irritable bowel syndrome (IBS) undergoes a true renaissance as a subject of active scientific enquiry, colonic diverticula and their complications remain relatively forgotten. This despite the fact that diverticulitis and its sequelae are more common than IBD and that some of its complications, such as perforation, accompanied by a significant mortality [1-3] whereas IBS, despite its impact on quality of life, does not kill people. In England, for example, over half a million hospital admissions (mostly emergencies) for diverticular disease were recorded over a 10-year period up to 2006; the 30-day mortality was 5% and the one-year mortality 15% [4]. More staggering is the estimate that as many as 20% of all who possess diverticula (referred to as diverticulosis) will experience an inflammatory complication of the condition; when one realizes that as many as 60% of 70 year olds in the West harbor diverticula that true prevalence of the condition becomes evident [1, 2]. Furthermore, some recent data from both England and the United States suggest that hospitalization rates for diverticulitis are increasing and, especially, among younger people [4-6].

While it is has been recognised for some time that a sizable proportion of patients who suffer an acute episode of diverticulitis may suffer a recurrence, it has, recently, become evident that others may experience more chronic symptoms in the aftermath of acute diverticulitis. In one series, 25% of a total of 162 patients followed prospectively following a sigmoid colon resection for acute diverticulitis suffered chronic symptoms [7]. A pathological basis for these chronic symptoms was provided by the description of inflammatory changes around diverticula [8] and of a more frank process,

peridiverticular colitis, or segmental colitis associated with diverticulosis (SCAD), in a minority [8-10]. Whether the latter is a true manifestation of diverticular disease or a variant of IBD remains controversial [9].

The other issue is the much debated association between uncomplicated diverticular disease and gastrointestinal symptoms. Initially the term “symptomatic diverticular disease” was assigned to the combination of diverticula and lower gastrointestinal symptoms; others questioned this concept suggesting that it represented no more than the coincident occurrence of IBS in an individual who just happened to have sigmoid diverticula. While longitudinal studies suggest that the outcome for these patients (however defined) is benign [11], there is now some evidence to suggest that painful diverticular disease may, indeed, be a real entity related, at least in part, to ongoing inflammation and its effects on neuromuscular function in the colon [12-15]. Perhaps the most definitive support for this concept comes from a report of symptomatic remission following sigmoid resection among a group of patients described as suffering from “smouldering” diverticular disease [16]. Most were found to have chronic inflammatory changes in the resected specimens and over three-quarters were still in remission one year following surgery. Reports of symptomatic responses to anti-inflammatory agents, such as mesalazine also support this concept [17-23].

Regardless of one’s opinion regarding either the pathogenesis of chronic symptoms in the aftermath of acute diverticulitis or the integrity of the link between uncomplicated diverticulosis and symptoms, a common thread begins to emerge, the possibility that low-grade inflammation may be fundamental to the pathophysiology of symptoms in both scenarios. This suggestion becomes all the more intriguing in the context of the active exploration of the roles of immune activation and/or low-grade inflammatory processes in the pathogenesis of IBS. In the latter, subtle changes in cell populations and cytokine profiles both in the mucosa and the systemic circulation have been identified with some consistency and it has been postulated that the ability of a variety of mediators released by activated mast cells, lymphocytes and other cells involved in the immune

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response to modulate motor and sensory neurons, as well as muscle function, in the gut, could explain the initiation and perpetuation of symptoms in this common disorder [24]. If such subtle changes are being invoked as important in IBS why not accept that the more gross inflammatory changes that seem so well described in diverticular disease could also generate a clinical expression? What initiates and maintains this immune activation/inflammation? In IBD, where the inflammatory response is orders of magnitude more intense and even macroscopically obvious, there is now a large body of evidence to implicate the gut flora (or, more correctly, microbiota) and the host response to it. Microbiota-host interactions are also now invoked as important in IBS, one of the strands of evidence used to support this argument being the beneficial effects of certain strains of probiotics [25-30]. While changes in the colonic microbiota are clearly critical to the pathogenesis of such complications of diverticula as diverticulitis and peri-diverticular abscesses, more subtle changes in the microbiota have also been postulated as important to more chronic manifestations of diverticulosis. Hard data on the latter is, however, not at present available. The intestinal epithelium is exposed to the bacterial antigens of the commensal microflora on a daily basis, an interaction that induces a state of "controlled" inflammation and leads to the induction of systemic immune tolerance and IgA secretion [31]. The enteric flora also helps to sustain the function and integrity of the epithelial barrier and its blood supply, promotes the development of the gut associated lymphoid tissue (GALT) and is essential for the development of gut motility [32]. Alterations in the number, distribution and composition of enteric bacteria may disrupt this balance, as evidenced by the consequences, to the host, of enteric exposure to pathogens or small intestinal bacterial overgrowth [33]; local quantitative or qualitative changes in the colonic bacterial population could, thus, be seen to induce the inflammatory and neuromuscular changes associated with symptomatic diverticular disease.

It is from our greater understanding of the commensal flora, as well as from clinical and experimental studies, that the concept of probiotics ("good" bacteria) emerged; the current interest in these organisms stems from their potential to advance our understanding of the bacterial flora and to serve as new therapeutic options in the management of gastrointestinal disease [34]. Given the size and diversity of the colonic flora as well as the fundamental role of the flora in colonic homeostasis, as well as in determining the physical nature and chemical composition of feces, it should come as no surprise that colonic disorders have been a major focus for those engaged in this area. In IBD, IBS and diverticular disease species and strains that exert anti-inflammatory effects have of course, been of special interest.

For all of these reasons, some interest in a potential role for probiotics in diverticular disease has been spurred, not only by the recognition that bacterial "colonization" or entrapment within diverticula is a prerequisite of the development of acute diverticulitis, but also by the potential for probiotics to modify the persistent, yet localized,

inflammatory state that may prevail in some patients in between acute episodes of diverticulitis [36] and that may underpin the development of symptoms among those with uncomplicated diverticular disease. These observations have encouraged the use of anti-inflammatory approaches, including probiotics. Indeed, a small number of controlled and uncontrolled studies generally support a role for probiotics, either alone or in combination with mesalazine in diverticular disease [21, 22, 36]; data to date are insufficient to generate clear recommendations. Lamiki and colleagues in the March issue of this journal now provide further support for probiotics in IBS [37].

These authors studied 46 patients with symptomatic but uncomplicated diverticular disease. In an open study, patients were prescribed a probiotic cocktail containing *L. acidophilus* strain 145, *L. helveticus* ATC 15009 and *Bifidobacterium* spp 420 in a medium enriched with a number of plant extracts which may have exerted prebiotic effects and followed for 6 months. Prior to randomization patients had experienced an average of 1.2 symptom episodes per month; at the end of the study 68% of the patients had remained asymptomatic throughout the entire six-month study period. While one has to remain cautious in the interpretation of such observations in a non-randomized, non-placebo controlled study in a symptom-based disorder, a complete remission rate of this magnitude sustained for such a long period of time is impressive and indicates that this approach, at the very least, deserves further study. One additional feature of this study that deserves comment is the rigorous approach that the authors took to confirming the transit and viability of the ingested strains and to demonstrating their ability to alter the colonic microbiota.

These findings also add further ammunition to the growing body of evidence to suggest, firstly, that "painful diverticular disease" may well be a real entity [38] and, secondly, that alterations in the colonic microbiota, be they very local or more generalized, together with the immune response that they engender may be of fundamental importance to the genesis of the more chronic manifestations of this common disorder be they pain, disturbances in bowel habit or recurrent diverticulitis [39, 40]. It is to be hoped that clinical investigators worldwide will take up the gauntlet that Lamiki and colleagues, as well as other investigators, have thrown down.

## References

1. Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet* 2004;363:631-639.
2. Sheth AA, Longo W, Floch MH. Diverticular disease and diverticulitis. *Am J Gastroenterol* 2008;103:1550-1556.
3. Humes DJ, Solaymani-Dodaran M, Fleming KM, Simpson J, Spiller RC, West J. A population-based study of perforated diverticular disease incidence and associated mortality. *Gastroenterology* 2009;136 1198-1205.
4. Jeyarajah S, Faiz O, Bottle A, Aylin P, Bjarnason I, Tekkis PP, Papagrigroriadis S. Diverticular disease hospital admissions are increasing, with poor outcomes in the elderly and emergency admissions. *Aliment Pharmacol Ther* 2009;30:1171-1182.

5. Etzioni DA, Mack TM, Beart RW Jr, Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. *Ann Surg* 2009;249:210-217.
6. Etzioni DA, Cannom RR, Ault GT, Beart RW Jr, Kaiser AM. Diverticulitis in California from 1995 to 2006: increased rates of treatment for younger patients. *Am Surg* 2009;75:981-985.
7. Egger B, Peter MK, Candinas D. Persistent symptoms after elective sigmoid resection for diverticulitis. *Dis Colon Rectum* 2008;51:1044-1048.
8. West AB, Losada M. The pathology of diverticulosis coli. *J Clin Gastroenterol* 2004;38(5 Suppl 1):S11-16.
9. Ierardi E, Hassan C, Zullo A, et al. Segmental colitis associated with diverticula: a rare clinical entity and a new challenge for the gastroenterologist. *Dig Liver Dis* 2009;41:794-797.
10. Tursi A. Segmental Colitis Associated with Diverticulosis: Complication of diverticular disease or autonomous entity? *Dig Dis Sci* 2010 Apr 22. [Epub ahead of print]
11. Salem TA, Molloy RG, O'Dwyer PJ. Prospective, five-year follow-up study of patients with symptomatic uncomplicated diverticular disease. *Dis Colon Rectum* 2007;50:1460-1464.
12. Simpson J, Neal KR, Scholefield JH, Spiller RC. Patterns of pain in diverticular disease and the influence of acute diverticulitis. *Eur J Gastroenterol Hepatol* 2003;15:1005-1010.
13. Simpson J, Scholefield JH, Spiller RC. Origin of symptoms in diverticular disease. *Br J Surg* 2003;90:899-908.
14. Spiller R. How inflammation changes neuromuscular function and its relevance to symptoms in diverticular disease. *J Clin Gastroenterol* 2006;40 Suppl 3:S117-120.
15. Simpson J, Sundler F, Humes DJ, Jenkins D, Scholefield JH, Spiller RC. Post inflammatory damage to the enteric nervous system in diverticular disease and its relationship to symptoms. *Neurogastroenterol Motil* 2009;21:847-858.
16. Horgan AF, McConnell EJ, Wolff BG, The S, Paterson C. Atypical diverticular disease: surgical results. *Dis Colon Rectum* 2001;44:1315-1318.
17. Tursi A, Brandimarte G, Daffinà R. Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 2002;34:510-515.
18. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit* 2004;10:PI70-173.
19. Di Mario F, Aragona G, Leandro G, et al. Efficacy of mesalazine in the treatment of symptomatic diverticular disease. *Dig Dis Sci* 2005;50:581-586.
20. Di Mario F, Comparato G, Fanigliulo L, et al. Use of mesalazine in diverticular disease. *J Clin Gastroenterol* 2006;40 Suppl 3:S155-159.
21. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Mesalazine and/or *Lactobacillus casei* in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol* 2006;40:312-316.
22. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Mesalazine and/or *Lactobacillus casei* in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. *Hepatogastroenterology* 2008;55:916-920.
23. Gatta L, Vakil N, Vaira D, et al. Efficacy of 5-ASA in the treatment of colonic diverticular disease. *J Clin Gastroenterol* 2010;44:113-119.
24. Clarke G, Quigley EM, Cryan JF, Dinan TG. Irritable bowel syndrome: towards biomarker identification. *Trends Mol Med* 2009;15:478-489.
25. Quigley EMM, Flourie B. Probiotics in irritable bowel syndrome: a rationale for their use and an assessment of the evidence to date. *Neurogastroenterol Motil* 2007;19:166-172.
26. Brenner DM, Moeller MJ, Chey WD, Schoenfeld PS. The utility of probiotics in the treatment of irritable bowel syndrome: A systematic review. *Am J Gastroenterol* 2009;104:1033-1049.
27. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the therapy of irritable bowel syndrome: a systematic review. *Gut* 2010;59:325-332.
28. O'Mahony L, McCarthy J, Kelly P et al. A Randomized, placebo-controlled, double-blind comparison of the probiotic bacteria *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome (IBS): symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005; 128: 541-551.
29. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol* 2006;101:326-333.
30. Agrawal A, Houghton LA, Morris J, et al. Clinical trial: the effects of a fermented milk product containing *Bifidobacterium lactis* DN-173-010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2008 Sep 17. (epublication ahead of print).
31. Falk PG, Hooper LV, Mittvedt T, Gordon JI. Creating and maintaining the gastrointestinal ecosystem: what we know and need to know from gnotobiology. *Microbiol Mol Biol Rev* 1998;62:1157-1170.
32. Shanahan F. The host-microbe interface within the gut. *Best Pract Research Clin Gastroenterol* 2002; 16: 915 - 931.
33. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003; 361: 512 - 519.
34. O'Hara AM, Shanahan F. Gut microbiota: mining for therapeutic potential. *Clin Gastroenterol Hepatol* 2007;5:274-284.
35. Floch MH. A hypothesis: is diverticulitis a type of inflammatory bowel disease? *J Clin Gastroenterol* 2006;40(7 Suppl 3):S121-125.
36. Fric P, Zavoral M. The effect of non-pathogenic *Escherichia coli* in symptomatic uncomplicated diverticular disease of the colon. *Eur J Gastroenterol Hepatol* 2003;15:313-315.
37. Lamiki P, Tsuchiya J, Pathak S, et al. Probiotics in diverticular disease of the colon: an open label study. *J Gastrointest Liver Dis* 2010;19:31-36.
38. Comparato G, Fanigliulo L, Aragona G, et al. Quality of life in uncomplicated symptomatic diverticular disease: is it another good reason for treatment? *Dig Dis* 2007;25:252-259.
39. Janes S, Meagher A, Frizelle FA. Elective surgery after acute diverticulitis. *Br J Surg* 2005;92:133-142.
40. Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. *Br Med J* 1969;4:639-642.