New strategies for the management of diverticular disease: insights for the clinician

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Abstract: Diverticulosis is one of the most common gastrointestinal conditions affecting the general population in the Western world. It is estimated that over 2.5 million people are affected by diverticular disease in the United States. The spectrum of clinical manifestations of diverticulosis ranges from asymptomatic diverticulosis to complicated diverticulitis. Treatment for symptomatic diverticular disease is largely based on symptoms. Traditional therapy includes fiber, bowel rest, antibiotics, pain control and surgery for selected cases. This review discusses recent advances in the medical treatment of diverticular disease such as the use of mesalamine, rifaximin and probiotics as our understanding of the disease evolves.

Keywords: diverticulitis, diverticular disease, diverticulosis

Introduction

Since its first description in the 1800s, colonic diverticulosis has been recognized as an increasingly common clinical condition in industrialized countries. Diverticulosis is a term used to describe the presence of colonic diverticula, small sac-like outpouching of mucosal and submucosal layers of the colonic wall. Diverticular disease is a term used to include diverticulosis and diverticulitis. It may include clinically significant and symptomatic or asymptomatic diverticulosis [Strate *et al.* 2012]. Symptoms of diverticular disease range from uncomplicated or complicated diverticulitis to chronic abdominal pain, bloating and irregular bowel habits.

Even though the pathogenesis and management of diverticulosis and diverticular disease remain uncertain, new hypotheses and observations are changing how we treat diverticular disease to improve symptoms and prevent serious complications. This review focuses on the emerging evidence in the pathophysiology and management strategy of diverticular disease.

Epidemiology

Diverticular disease is a common gastrointestinal condition in the Western world with the highest rates in the United States and Europe. It can affect patients of all age groups but the prevalence increases with age. Cases in young individuals are more likely to be complicated. By age 80, about 70% of individuals in the United States have diverticulosis [Shaheen *et al.* 2006]. Diverticular disease was noted to be the fifth most important gastrointestinal disease in terms of direct and indirect cost. The burden of diverticular disease has been estimated at $2.66 billion per year [Sandler *et al.* 2002]. Even though diverticular disease can manifest significant symptoms and complications, about 80–85% of the people with this condition are asymptomatic. Of the 15–20% symptomatic patients, 75% of them will have painful diverticular disease without inflammation, 1–2% will require hospitalization and 0.5% will require surgery [Stollman and Raskin, 2004; Sopena and Lanas, 2011].

Pathophysiology

It has been postulated that a low fiber diet plays an important role in the development of diverticulosis [Burkitt, 1973; Gear *et al.* 1979]. Age-related changes in the connective tissue of the colon include an increase in collagen crosslinking and increased elastin content that may lead to increased colonic rigidity [Stollman and Raskin,

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2004; Van Patten and West, 2011]. Low fiber diets can reduce stool volume and predispose individuals to develop constipation that in turn leads to increased intraluminal pressure and colonic wall tension. Painter and colleagues [Painter *et al.* 1968] noted that contractions separated the colon into distinct compartments of high intraluminal pressures termed segmentation. Intracolonic pressures have been recorded in patients with diverticulosis. Segmentation of the colon can generate excessively high pressures favoring herniation. The hypothesis is that diverticula develop due to high intracolonic pressure at points of weakness in the muscular wall where the vasa recta insert [West and Losada, 2004].

While most people with colonic diverticulosis remain asymptomatic, about 20% will experience complications [Stollman and Raskin, 2004]. The two most common and well-recognized complications are acute episodes of bleeding and diverticulitis. Patients may also experience chronic and vague gastrointestinal symptoms including abdominal pain, bloating, constipation and diarrhea.

Acute diverticulitis is characterized by inflammation, microperforation and abscess formation; 25–33% of these patients may have recurrent episodes [Haglund *et al.* 1979; Janes *et al.* 2005]. In patients with gastrointestinal symptoms without overt diverticulitis, low grade inflammation, gut dysbiosis, visceral hypersensitivity and colonic dysmotility have been identified as potential contributing factors to symptoms [Floch, 2006].

Several case series have demonstrated that chronic inflammation is present in the colon in patients with diverticulosis without overt diverticulitis. Random biopsies from 16 out of 17 patients with diverticulosis showed abnormal pathology including mild chronic inflammation and microscopic colitis with lymphocytic and collagenous deposition [Floch, 2006]. A much larger series of 930 patients [Horgan *et al.* 2001] noted that about 75% of surgical specimens from patients with symptomatic uncomplicated diverticular disease had chronic inflammation in and around diverticula even though the degree and extent of inflammation did not correlate with symptoms. It has been proposed that the chronic inflammation in diverticular disease is similar to that in inflammatory bowel disease (IBD) [Di Mario *et al.* 2006]. For this reason, 5-aminosalicylic acid (5-ASA) drugs that are commonly used in IBD have been studied in the management of symptomatic uncomplicated diverticular disease and recurrent diverticulitis. Humes and colleagues demonstrated that the presence of ongoing low-grade inflammation and upregulation of tachykinins in symptomatic diverticulosis patients may explain their visceral hypersensitivity [Humes *et al.* 2012]. In the study, symptomatic patients had a much lower threshold to moderate discomfort than asymptomatic patients during barostat study. There was a significant correlation between barostat visual analogue *scale* (VAS) pain scores and neurokinin-1 (NK-1) expression. They were also noted to have increased expression of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-?).

The role of bacterial flora has been investigated in the pathogenesis of diverticular disease. Alteration of bacterial flora occurs as a result of slow colonic transit and stagnation of fecal material in the diverticula seen in colonic diverticulosis, which in turn triggers intestinal inflammation by impairing mucosal barrier function and upregulating inflammatory cytokine release [Tursi *et al.* 2007]. Low fiber diet is also associated with changes in colonic flora with significant increase in anaerobic counts. Since diverticulosis is associated with low fiber diet, dysbiosis is probably common in patients with diverticular disease. Probiotics may restore the balance of gut flora by decreasing pathogenic gram negative bacteria [Bengmark, 1998] and have been proposed to be used in diverticular disease to prevent inflammation.

Patients with symptomatic diverticulosis were noted to have higher motility indices than asymptomatic patients or healthy controls [Arfwidsson *et al.* 1964]. Later these findings were confirmed by Painter and colleagues in two studies [Painter, 1964; Painter *et al*, 1968]. Another study noted that there was significant increased and overall greater motor activity in the diverticulosis affected segments of the colon compared to the unaffected colon [Singh and Rao, 2011]. Whether this increased colonic motor activity is the primary event leading to formation of diverticula is unknown.

Clinical features
Although diverticulosis remains asymptomatic in the majority of patients, when patients start to have symptoms related to this condition, it becomes symptomatic diverticular disease.

Table 1. Stages of diverticular disease [Sheth *et al.* 2008].

Stage 0	Development of diverticular disease
Stage I	Asymptomatic disease
Stage II	Symptomatic disease
	a. Single episode
	b. Recurrent
	c. Chronic (pain, diarrhea, segmental colitis associated with diverticula)
Stage III	Complicated
	Abscess
	Phlegmon
	Obstruction
	Fistulization
	Bleeding
	Sepsis
	Stricture

Classification of diverticular disease is largely based on symptoms. Stages of the disease begin with the development of diverticulosis, to asymptomatic disease, to symptomatic uncomplicated diverticular disease (SUDD) and finally to complicated disease when patients develop abscesses, phlegmon, bleeding, fistula and sepsis (Table 1). Symptoms can be acute or chronic. Clinicians may see patients with SUDD for nonspecific gastrointestinal symptoms that are similar to those of irritable bowel syndrome including vague abdominal pain, bloating, constipation and diarrhea.

Management
Once patients develop symptoms of diverticular disease, medical therapy is employed. The goal of management is to treat infection, improve symptoms, and prevent recurrence of symptoms or development of serious complications. As our understanding of diverticular disease continues to improve, we now know that diverticular disease can not only manifest as acute diverticulitis or bleeding episodes but also as a chronic medical illness. Patients may have chronic abdominal pain, tenderness, bloating and changes in bowel habits. There is evolving evidence that inflammation, dysbiosis, visceral hypersensitivity and colonic dysmotility may all play a potential role in the etiology of diverticular disease. Multiple clinical trials are ongoing to evaluate a few agents that act on these factors. The rest of this article focuses on these agents.

Acute diverticulitis
In most patients the diagnosis of acute diverticulitis is clinical based on history, physical examination and laboratory test, but computed tomography (CT) has become a sensitive, widely used diagnostic tool.

Guidelines from various societies on management of acute diverticulitis have been published without recent updates. The American Society of Colon and Rectal Surgeons published practice parameters for sigmoid diverticulitis [Rafferty *et al.* 2006]. It recommended dietary modification and use of antibiotics targeting common gut bacteria, which is successful in 70–100% of acute uncomplicated diverticulitis [West and Losada, 2004; Di Mario *et al.* 2006; Tursi *et al.* 2007; Rafferty *et al.* 2006]. Large diverticular abscesses (>3 cm) should undergo percutaneous drainage under radiological guidance. The American College of Gastroenterology had published similar guidelines for acute diverticulitis management [Stollman and Raskin, 1999]. However, surgical management is reserved for patients with signs of bowel obstruction, perforation, peritonitis or hemodynamic instability, or those who fail medical management. Recently the role of antibiotics in acute uncomplicated diverticulitis has been challenged. A multicenter randomized trial by Chabok and colleagues showed that antibiotic treatment did not accelerate recovery or prevent complications/recurrence [Chabok *et al.* 2012]. Further studies are needed to determine the need for antibiotic treatment in acute uncomplicated diverticulitis.

Chronic disease
Fiber. Fiber is believed to be beneficial in diverticular disease. Since the 1970s, there have been a number of retrospective and epidemiological studies that tried to demonstrate the benefits of fiber on colonic function and its possible effect on preventing diverticular disease and its complications [Smith *et al.* 1981; Payler *et al.* 1975; Kirwan *et al.* 1974; Hyland and Taylor, 1980; Painter, 1974; Leahy *et al.* 1985; Heaton, 1981; Parks, 1973; Aldoori *et al.* 1994, 1995; Aldoori and Ryan-Harshman, 2002; Crowe *et al.* 2011]. Two of these studies [Aldoori *et al.* 1994; Crowe *et al.* 2011] concluded that total dietary fiber intake was inversely associated with the risk of diverticular disease after adjustment for age, energy-adjusted total fat intake, and physical activity.

Based on these studies and the widely accepted concept [Painter *et al.* 1968] of the role of a low fiber diet in the pathogenesis of colonic diverticulosis, fiber supplementation has been a common recommendation of clinicians. The National Diverticulitis Study Group (NDSG) has made a level 1 recommendation for dietary fiber greater than 10 g/d and preferably between 20 and 30 g/d for all patients with diverticular disease except for those suffering from an acute attack [Trivedi and Das, 2008]. Although there are several small randomized controlled trials that studied the use of fiber in SUDD, the results were mixed [Ornstein *et al.* 1981; Taylor and Duthrie, 1976; Hodgson, 1977; Brodribb, 1977]. Orstein and colleagues [Orstein *et al.* 1981] did not find a significant benefit of fiber supplementation on either lower bowel symptoms score (pain, sensation of incomplete emptying, straining, stool consistency, flatus and aperients taken) or total symptom score (belching, nausea, vomiting, dyspepsia and abdominal distension). In addition, the causal relationship between low fiber diet and diverticulosis has been challenged recently [Peery *et al.* 2012; Strate, 2012]. The effectiveness of fiber for managing chronic diverticular disease symptoms still needs to be confirmed with high quality randomized clinical trials.

Anticholinergic/antispasmotic agents. The rationale for using anticholinergic and antispasmotic agents is based on the observed hypermotility of the sigmoid colon in many patients with symptomatic disease [Bassotti *et al.* 2004]. Patients with diverticulosis were found to have higher resting, postprandial and neostigmine-stimulated pressures in the colon compared with controls [Huizinga *et al.* 1999]. Altered motility is thought to contribute to symptoms of chronic diverticular disease although the definite correlation is yet to be established.

The use of anticholinergic and antispasmodic agents may be useful for some patients [Morris *et al.* 2003]. A small double-blind study by Srivastava and colleagues showed that a 4-week course of fiber plus alverine citrate (smooth muscle relaxant) *versus* the fiber sterculia alone had some advantage in relieving the passage of stool, flatus and abdominal distension [Srivastava *et al.* 1976]. Chronic symptoms of diverticular disease of abdominal pain, bloating and altered bowel habit can overlap with IBS. It is difficult to tell whether symptoms are caused by IBS or diverticular disease. Antispasmodic agents can help with abdominal pain due to IBS, so sometimes it is reasonable to try these agents if diagnosis cannot be confirmed.

Nonabsorbable antibiotic: rifaximin. In colonic diverticulosis, luminal content stasis can lead to bacterial overgrowth [Ventrucci *et al.* 1994]. The luminal stasis and bacterial overgrowth in colonic diverticula may give rise to chronic low grade mucosal inflammation [Colecchia *et al.* 2003]. The chronic mucosal inflammation sensitizes intrinsic primary afferent neurons in the submucosal and myenteric plexus [Barbara *et al.* 2002]. The sensitization induces visceral hypersensitivity and changes in colonic motor function [Sanovic *et al.* 1999; Premysl *et al.* 2003].

Rifaximin is a poorly absorbed antibiotic used for hepatic encephalopathy and traveller's diarrhea in the United States. It is effective against Gram-positive and Gram-negative bacteria and has high bioavailability in the gastrointestinal tract. It has been shown that rifaximin could be useful in irritable bowel syndrome and small bowel bacterial overgrowth by reducing bloating, abdominal pain, flatulence and loose stools [Sharara *et al.* 2006; Pimentel *et al.* 2011].

There are five randomized trials and comparative studies comparing rifaximin with placebo or fiber supplementation [Papi *et al.* 1992, 1995; Latella *et al.* 2003; Colecchia *et al.* 2007; D'Inca *et al.* 2007]. These studies suggested that cyclic administration of rifaximin was effective in reducing symptoms (abdominal pain, bloating), complication frequency and severity of diverticular disease [Rocco *et al.* 2009]. Latella and colleagues pointed out that rifaximin reduced the metabolic activity of the intestinal bacterial flora, in particular the degradation of dietary fiber and the production of methane [Latella *et al.* 2003]. Papi and colleagues first reported a multicenter open trial with 217 SUDD patients who were treated with glucomannan alone or with glucomannan plus rifaximin [Papi *et al.* 1992]. They were followed for 12 months and their global symptomatic score was assessed at the end of the follow up. The score was significantly lower in patients treated with fiber plus rifaximin than the group treated with fiber alone [Pimental *et al.* 2011]. In a meta-analysis of four of the five trials, Bianchi and colleagues found that at one-year follow up, 64% of patients treated with rifaximin plus standard fiber supplement were symptom free compared with 34.9% of patients treated with fiber alone [Bianchi *et al.*

2011]. The number needed to treat (NNT) was three for rifaximin *versus* placebo to achieve symptom relief. NNT was nine to avoid complications of diverticular disease.

Anti-inflammatory agent: mesalamine.   It is clear that inflammation is the main feature of acute diverticulitis. After resolution of an acute episode of diverticulitis, about 25–33% of patients go on to develop recurrent episode(s) [Haglund *et al.* 1979; Janes *et al.* 2005].

As stated earlier, some patients with colonic diverticulosis have evidence of chronic mucosal inflammation. During elective colonoscopy performed by a single endoscopist on 2566 consecutive outpatients, 21 patients were identified with endoscopic evidence of diverticular inflammation. Only one patient had clinical evidence of acute diverticulitis at the time of colonoscopy [Ghorai *et al.* 2003]. Another study by Tursi and colleagues showed that lymphocytic infiltrate was found in all patients affected by every degree of diverticular disease [Tursi *et al.* 2008]. Lymphocytic infiltrate seems to be increased according to disease severity, ranging from a median value of 6.5 in asymptomatic diverticulosis to a median value of 11 in acute uncomplicated diverticulitis. Lymphocytic infiltrate in diverticular disease was higher than in healthy controls. The overall median inflammatory infiltrate in diverticular disease was 7, compared with 4 in healthy controls. All patients affected by symptomatic diverticular disease showed at least mild lymphocytic infiltrate, whereas all controls showed only a focal presence of lymphocytes. In asymptomatic diverticulosis a higher inflammatory cell density was found compared with controls.

It has been proposed that the inflammation in diverticulitis may be similar to that in IBD and symptoms of diverticular disease might be at least partially attributed to the inflammation. The inflammatory cascade in diverticulitis can lead to an imbalance of cytokines and interleukins similar to that in IBD [Lenza and Das, 2011]. Mesalamine has been investigated in multiple studies as a single agent to achieve and to maintain remission. In a randomized, open-label study by Trepsi and colleagues [Trepsi *et al.* 1999], 166 patients with mild to moderate, symptomatic diverticular disease were treated with Unasyn and rifaximin for 7 days first, then randomized to receive either mesalamine 400 mg twice daily (bid) or no treatment for an additional 8 weeks.

These patients were followed for 4 years after completion of treatment. The mesalamine group patients were found to be less likely to experience symptomatic relapse and microhemorrhage [Trepsi *et al.* 1999]. In another open-label study, patients were randomized to receive either daily dosing or 10 days per month for two years. The continuous treatment group had a higher symptom-free rate than the cyclic treatment group [Tursi *et al.* 2007a]. These findings suggest that mesalamine is not only effective in achieving remission but also in maintaining remission in patients with recurrent symptomatic diverticular disease if given continuously.

Stollman and colleagues have reported the results of the DIVA trial, the first randomized controlled trial of mesalamine after CT documented diverticulitis in the US. In this three-arm, multicenter, randomized, double-blinded, placebo-controlled study, the efficacy of delayed release mesalamine, with and without probiotic supplementation, was compared with placebo. The mesalamine group demonstrated higher complete symptom response compared with placebo [Stollman *et al.* 2010].

Recently, there have been a small number of large-scale randomized, double blind, placebo-controlled prospective studies by Shire Pharmaceutical Development evaluating mesalamine in the prevention of recurrent diverticulitis. The PREVENT 1 and PREVENT 2 trials by Shire [ClinicalTrials.gov identifiers NCT00545740 and NCT00545103] studied the use of Multi Matrix System (MMX®) mesalamine in the prevention of recurrent diverticulitis. In each study, 584 patients with resolved diverticulitis were given 1.2, 2.4 or 4.8 grams of MMX mesalamine daily for 2 years and followed for recurrent acute diverticulitis. The preliminary results of these studies have been disappointing. They showed that mesalamine did not prevent recurrent attacks. But the study group was limited to only subjects who had attacks months earlier. Since the studies did not attain their primary endpoints, the manufacturer Shire has subsequently decided not to pursue a regulatory filing to add diverticular disease as an indication for MMX mesalamine. We are still awaiting the full results of these large-scale studies with the hope that some of the secondary endpoints may shed some light on this issue.

Mesalamine has also been studied in combination with the use of rifaximin. Tursi and colleagues showed that in 218 patients with recurrent

diverticulitis, at 1 year follow up the group with combination therapy of 7 days/month rifaximin 400 mg bid and mesalamine 800 mg bid did better than the monotherapy group with rifaximin alone in terms of symptom management, normalizing bowel habits and preventing recurrence [Tursi *et al.* 2002].

In a prospective, randomized open trial, Di Mario and colleagues compared the efficacy of cyclic use of rifaximin to mesalazine (mesalamine) in achieving symptom relief in patients with symptomatic uncomplicated colonic diverticular disease [Di Mario *et al.* 2005]. They found mesalazine was as effective as rifaximin for diminishing symptoms but better than rifaximin for improving the global score in those patients.

Probiotics. Probiotics are live organisms formulated from gut microorganisms. They have been used in the management of various colonic conditions including constipation, diarrhea, bloating, *Clostridium difficile* colitis, irritable bowel syndrome, inflammatory bowel disease and diverticulitis. The rationale for the use of probiotics is based on the theory that endogenous intestinal microflora play a crucial role in the pathogenesis of these disorders [Quigley, 2007]. The use of probiotics will restore the normal intestinal flora that may have been altered in diverticular disease due to stasis and reduced colonic transit time. There are few data available about the use of probiotics in diverticular disease. Most studies were small and uncontrolled. In one prospective open trial by Fric and Zarovral, *Escherichia coli* strain Nissle 1917 was administered to 15 patients with uncomplicated diverticular disease [Fric and Zarovral, 2003]. These patients had longer periods of remission and improved abdominal symptoms after receiving probiotic compared to before treatment.

Probiotics have also been studied with the use of other agents such as anti-inflammatory agents (aminosalicylate). Tursi and colleagues conducted a multicenter prospective randomized controlled study where 90 patients with symptomatic diverticular disease were randomized to three groups to take mesalazine alone, *Lactobacillus casei* alone or both [Tursi *et al.* 2006]. The combination group was 100% symptom free at 12-month follow up compared with 76.7% of the mesalazine group or *Lactobacillus* group. Mesalazine and *L. casei* together were superior to either treatment alone in preventing symptom recurrence. Subsequently, the same group conducted a similar study with a

longer follow-up period with similar results [Tursi *et al.* 2008]. Another aminosalicylate balsalazide was combined with VSL#3 in an open-label trial [Tursi, 2007b]. The combination also provided higher rates of remission after 12 months. However, the DIVA study included a mesalamine plus probiotic arm in which the probiotic had shown no additive benefit [Stollman *et al.* 2010].

Conclusion

Our understanding of the pathogenesis and management of diverticular disease continues to improve. The use of fiber, probiotics, mesalamine, rifaximin and their combinations may be useful in the treatment of symptomatic uncomplicated diverticular disease, improving quality of life and preventing disease recurrence. High quality randomized, double-blind, placebo-controlled studies are needed to assess the efficacy of these agents to justify their use.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Aldoori, W., Giovannucci, E., Rimm, E., Wing, A., Trichopoulos, D., Willett, W. *et al.* (1994) A prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr* 60: 757–764.

Aldoori, W., Giovannucci, E., Rimm, E., Wing, A., Trichopoulos, D. and Willett, W. (1995) A prospective study of alcohol, smoking, caffeine, and the risk of symptomatic diverticular disease in men. *Ann Epidemiol* 5: 221–228.

Aldoori, W. and Ryan-Harshman, M. (2002) Preventing diverticular disease: review of recent evidence on high-fibre diets. *Can Fam Physician* 48: 1632–1637.

Arfwidsson, S., Knocking, N., Lehmann, L. and Winberg, T. (1964) Pathogenesis of multiple diverticula of the sigmoid colon in diverticular disease. *Acta Chir Scand* 342(Suppl.): 1–68.

Barbara, G., De Giorgio, R., Stanghellini, V., Cremon, C. and Corinaldesi, R. (2002) A role for

inflammation in irritable bowel syndrome? *Gut* 51(Suppl. 1): 41–44.

Bassotti, G., Sietchiping-Nzepa, F., De Roberto, G., Chistolini, F. and Morelli, A. (2004) Colonic regular contractile frequency patterns in irritable bowel syndrome: the 'spastic colon' revisited. *Eur J Gastroenterol Hepatol* 16: 613–617.

Bengmark, S. (1998) Ecological control of the gastrointestinal tract: the role of probiotic flora. *Gut* 42: 2–7.

Bianchi, M., Festa, V., Moretti, A., Ciaco, A., Mangone, M., Tornatore, V. *et al.* (2011) Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. *Aliment Pharmacol Ther* 33: 902–910.

Brodribb, A. (1977) Treatment of symptomatic diverticular disease with a high fibre diet. *Lancet* 1: 664–666.

Burkitt, D. (1973) Diverticular disease of the colon epidemiological evidence relating it to fibre-depleted diets. *Trans Med Soc Lond* 89: 81–84.

Chabok, A., Påhlman, L., Hjern, F., Haapaniemi, S. and Smedh, K.; AVOD Study Group (2012) Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. *Br J Surg* 99: 532–539.

Colecchia, A., Sandri, L., Capodicasa, S., Vestito, A., Mazzella, G., Staniscia, T. *et al.* (2003) Diverticular disease of the colon: new perspectives in symptom development and treatment. *World J Gastroenterol* 9: 1385–1389.

Colecchia, A., Vestito, A, Pasqui, F., Mazzella, G., Roda, E., Pistoia, F. *et al.* (2007) Efficacy of long-term cyclic administration of the poorly absorbed antibiotic rifaximin in symptomatic, uncomplicated colonic diverticular disease. *World J Gastroenterol* 13: 264–269.

Crowe, F., Appleby, P., Allen, N. and Key, T. (2011) Diet and risk of diverticular disease in Oxford Cohort of European Prospective Investigation into Cancer and Nutrition (Epic): prospective study of British vegetarians and non-vegetarians. *BMJ* 343: d4131.

Di Mario, F., Aragona, G., Leandro, G., Comparato, G., Fanigliulo, L., Cavallaro, L. *et al.* (2005) Efficacy of mesalazine in the treatment of symptomatic diverticular disease. *Dig Dis Sci* 50: 581–586.

Di Mario, F., Comparato, G., Fanigliulo, L., Aragona, G., Cavallaro, L., Cavestro, G. *et al.* (2006) Use of mesalazine in diverticular disease. *J Clin Gastroenterol* 40: S155–S159.

D'Inca, R., Pomerri, F., Vettorato, M., Dal Pont, E., Di Leo, V., Ferronato, A. *et al.* (2007) Interaction between rifaximin and dietary fibre in patients with diverticular disease. *Aliment Pharmacol Ther* 25: 771–779.

Floch, M. (2006) A hypothesis: is diverticulitis a type of inflammatory bowel disease? *J Clin Gastroenterol* 40(Suppl. 3): S121–S125.

Fric, P. and Zavoral, M. (2003) The effect of non-pathogenic Escherichia coli in symptomatic uncomplicated diverticular disease of the colon. *Eur J Gastroenterol Hepatol* 15: 313–315.

Gear, J., Ware, A., Fursdon, P., Mann, J., Nolan, D., Brodribb, A. *et al.* (1979) Symptomless diverticular disease and intake of dietary fibre. *Lancet* 1(8115): 511–514.

Ghorai, S., Ulbright, T. and Rex, D. (2003) Endoscopic findings of diverticular inflammation in colonoscopy patients without clinical acute diverticulitis: prevalence and endoscopic spectrum. *Am J Gastroenterol* 98: 802–806.

Haglund, U., Hellberg, R., Johnsen, C. and Hulten, L. (1979) Complicated diverticular disease of the sigmoid colon. An analysis of short and long term outcome in 392 patients. *Ann Chir Gynaecol* 68: 41–46.

Heaton, K. (1981) Is bran useful in diverticular disease? *BMJ (Clin Res Ed)* 283: 1523–1524.

Hodgson, W. (1977) The placebo effect. Is it important in diverticular disease? *Am J Gastroenterol* 67: 157–162.

Horgan, A., McConnell, E., Wolff, B., The, S. and Paterson, C. (2001) Atypical diverticular diseases: surgical results. *Dis Colon Rectum* 44: 1315–1318.

Huizinga, J., Waterfall, W. and Stern, H. (1999) Abnormal response to cholinergic stimulation in the circular muscle layer of the human colon in diverticular disease. *Scand J Gastroenterol* 34: 683–688.

Humes, D., Simpson, J., Smith, J., Sutton, P., Zaitoun, A., Bush, D. *et al.* (2012) Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. *Neurogastroenterol Motil* 24: 318–e163.

Hyland, J. and Taylor, I. (1980) Does a high fibre diet prevent the complications of diverticular disease? *Br J Surg* 67: 77–79.

Janes, S., Meagher, A. and Frizelle, F. (2005) Elective surgery after acute diverticulitis. *Br J Surg* 92: 133–142.

Kirwan, W., Smith, A., McConnell, A., Mitchell, W. and Eastwood, M. (1974) Action of different bran preparations on colonic function. *BMJ* 4: 187–189.

Latella, G., Pimpo, M., Sottili, S., Zippi, M., Viscido, A., Chiaramonte, M. *et al.* (2003) Rifaximin improves

symptoms of acquired uncomplicated diverticular disease of the colon. *Int J Colorectal Dis* 18: 55–62.

Leahy, A., Ellis, R., Quill, D. and Peel, A. (1985) High fibre diet in symptomatic diverticular disease of the colon. *Ann R Coll Surg Engl* 67: 173–174.

Lenza, C. and Das, K. (2011) Mesalamine in the treatment of diverticular disease. *J Clin Gastroenterol* 45(Suppl.1): S53–S61.

Morris, C., Harvey, I., Stebbings, W., Speakman, C., Kennedy, H. and Hart, A. (2003) Do calcium channel blockers and antimuscarinics protect against perforated colonic diverticular disease? A case control study. *Gut* 52: 1734–1737.

Ornstein, M., Littlewood, E., Baird, I., Fowler, J. and Cox, A. (1981) Are fibre supplements really necessary in diverticular disease of the colon? *BMJ (Clin Res Ed)* 282: 1629–1630.

Painter, N. (1964) The aetiology of diverticulosis of the colon with special reference to the action of certain drugs on the behaviour of the colon. *Ann R Coll Surg Engl* 34: 98–119.

Painter, N. (1974) The high fibre diet in the treatment of diverticular disease of the colon. *Postgrad Med J* 50: 629–635.

Painter, N., Truelove, S., Ardran, G. and Tuckey, M. (1968) Segmentation and the localization of intraluminal pressure in the human colon, with special reference to the pathogenesis of colonic diverticula. *Gastroenterology* 54(Suppl): 778–780.

Papi, C., Ciaco, A., Koch, M. and Capurso, L. (1992) Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon. A pilot multicentre open trial. Diverticular Disease Study Group. *Ital J Gastroenterol* 24: 452–456.

Papi, C., Ciaco, A., Koch, M. and Capurso, L. (1995) Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 9: 33–39.

Parks, T. (1973) The role of dietary fibre in the prevention and treatment of diseases of the colon. *Proc R Soc Med* 66: 681–683.

Payler, D., Pomare, E., Heaton, K. and Harvey, R. (1975) The effect of wheat bran on intestinal transit. *Gut* 16: 209–213.

Peery, A., Barrett, P., Park, D., Rogers, A., Galanko, J., Martin, C. *et al.* (2012) A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology* 142: 266–272.

Pimentel, M., Lembo, A., Chey, W., Zakko, S., Ringel, Y., Yu, J. *et al.* (2011) Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 364: 22–32.

Premysl, F., Miroslav, Z.(2003) The effect of non-pathogeneic Escherichia coli in symptomatic uncomplicated diverticular disease of the colon. *Eur J Gastroenterol Hepatol* 15: 313–315.

Quigley, E. (2007) Probiotics in the management of colonic disorders. *Curr Gastroenterol Rep* 9: 434–440.

Rafferty, J., Shellito, P., Hyman, N. and Buie, W. (2006) Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 49: 939–944.

Rocco, A., Compare, D., Caruso, F. and Nardone, G. (2009) Treatment options for uncomplicated diverticular disease of the colon. *J Clin Gastroenterol* 43: 803–808.

Sandler, R., Everhart, J., Donowitz, M., Adams, E., Cronin, K., Goodman, C. *et al.* (2002) The burden of selected digestive diseases in the United States. *Gastroenterology* 122: 1500–1511.

Sanovic, S., Lamb, D. and Blennerhassett, M. (1999) Damage to the enteric nervous system in experimental colitis. *Am J Pathol* 155: 1051–1057.

Shaheen, N., Hansen, R., Morgan, D., Gangarosa, L., Ringel, Y., Thiny, M. *et al.* (2006) The burden of gastrointestinal and liver disease. *Am J Gastroenterol* 101: 2128–2138.

Sharara, A., Aoun, E., Abdul-Baki, H., Mounzer, R., Sidani, S. and Elhajj, I. (2006) A randomized double-blind placebo-controlled trial of rifaximin in patients with abdominal bloating and flatulence. *Am J Gastroenterol* 101: 326–333.

Sheth, A., Longo, W. and Floch, M. (2008) Diverticular disease and diverticulitis. *Am J Gastroenterol* 103: 1550–1556.

Singh, S. and Rao, S. (2011) Colonic motility in the pathogenesis of diverticular disease. *J Clin Gastroenterol* 45: S15–S19.

Smith, A., Drummond, E. and Eastwood, M. (1981) The effect of coarse and fine Canadian red spring wheat and French soft wheat bran on colonic motility in patients with diverticular disease. *Am J Clin Nutr* 34: 2460–2463.

Sopena, F. and Lanas, A. (2011) Management of colonic diverticular disease with poorly absorbed antibiotics and other therapies. *Therap Adv Gastroenterol* 4: 365–374.

Srivastava, G., Smith, A. and Painter, N. (1976) Sterculia bulk-forming agent with smooth-muscle relaxant *versus* bran in diverticular disease. *BMJ* 1: 315–318.

Strate, L. (2012) Diverticulosis and dietary fiber: rethinking the relationship. *Gastroenterology* 142: 205–207.

Strate, L., Modi, R., Cohen, E. and Spiegel, B. (2012) Diverticular disease as a chronic illness:

evolving epidemiologic and clinical insights. *Am J Gastroenterol* 107: 1486–1493.

Stollman, N., Magowan, S., Shanahan, F. and Quigley, E. (2010) Efficacy of delayed-release mesalamine in the prevention of GI symptoms following acute diverticulitis: results of the DIVA trial. *Am J Gastroenterol* 105: S139.

Stollman, N. and Raskin, J. (1999) Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 94: 3110–3121.

Stollman, N. and Raskin, J. (2004) Diverticular disease of the colon. *Lancet* 363: 631–639.

Taylor, I and Duthie, H. (1976) Bran tablets and diverticular disease. *BMJ* 1: 988–990.

Trepsi, E., Colla, C., Panizza, P., Polino, M., Venturini, A., Bottani, G. *et al.* (1999) Therapeutic and prophylactic role of mesalazine (5-Asa) in symptomatic diverticular disease of the large intestine. 4 year follow-up results. *Minerva Gastroenterol Dietol* 45: 245–252.

Trivedi, C. and Das, K. (2008) Emerging therapies for diverticular disease of the colon. *J Clin Gastroenterol* 42: 1145–1151.

Tursi, A., Brandimarte, G. and Daffina, R. (2002) Long-term treatment with mesalazine and rifaximin *versus* rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 34: 510–515.

Tursi, A., Brandimarte, G., Giorgetti, G. and Elisei, W. (2006) 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* 40: 312–316.

Tursi, A. (2007) New physiopathological and therapeutic approaches to diverticular disease of the colon. *Expert Opin Pharmacother* 8: 299–307.

Tursi, A., Brandimarte, G., Elisei, W., Giorgetti, G., Inchingolo, C., Danese, S. *et al.* (2008) Assessment and grading of mucosal inflammation in colonic diverticular disease. *J Clin Gastroenterol* 42: 699–703.

Tursi, A., Brandimarte, G., Giorgetti, G. and Elisei, W. (2007a) Continuous *versus* cyclic mesalazine therapy for patients affected by recurrent symptomatic uncomplicated diverticular disease of the colon. *Dig Dis Sci* 52: 671–674.

Tursi, A., Brandimarte, G., Giorgetti, G. and Elisei, W. (2008) Mesalazine and/or *Lactobacillus casei* in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. *Hepato-Gastroenterology* 55: 916–920.

Tursi, A., Brandimarte, G., Giorgetti, G., Elisei, W. and Aiello, F. (2007b) Balsalazide and/or high-potency probiotic mixture (Vsl#3) in maintaining remission after attack of acute, uncomplicated diverticulitis of the colon. *Int J Colorectal Dis* 22: 1103–1108.

Van Patten, K. and West, A. (2011) The pathology of diverticular disease practical considerations and controversies. *J Clin Gastroenterol* 45: S20–S26.

Ventrucci, M., Ferrieri, A., Bergami, R. and Roda, E. (1994) Evaluation of the effect of rifaximin in colon diverticular disease by means of lactulose hydrogen breath test. *Curr Med Res Opin* 13: 202–206.

West, A. and Losada, M. (2004) the pathology of diverticulosis coli. *J Clin Gastroenterol* 38: S11–S16.

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