SUMMARY

Diverticular disease of the colon is the fifth most important gastrointestinal disease in terms of direct and indirect healthcare costs in western countries. Uncomplicated diverticular disease is defined as the presence of diverticula in the absence of complications such as perforation, fistula, obstruction and/or bleeding. The distribution of diverticula along the colon varies worldwide being almost always left-sided and directly related to age in western countries and right-sided where diet is rich in fibre.

The pathophysiology of diverticular disease is complex and relates to abnormal colonic motility, changes in the colonic wall, chronic mucosal low-grade inflammation, imbalance in colonic microflora and visceral hypersensitivity. Moreover, there can be genetic factors involved in the development of colonic diverticula. The use of non-absorbable antibiotics is the mainstay of therapy in patients with mild to moderate symptoms, and the effect of fibre-supplementation alone does not appear to be significantly different from placebo, although no definite data are available.

More recently, alternative treatments have been reported. Mesalazine acts as a local mucosal immunomodulator and has been shown to improve symptoms and prevent recurrence of diverticulitis. In addition, probiotics have also been shown to be beneficial by re-establishing a normal gut microflora. In this study, the current literature on uncomplicated diverticular disease of the colon is reviewed.

Aliment Pharmacol Ther 23, 1379–1391
INTRODUCTION

Colonic diverticulosis is a common acquired condition characterized by the presence of mucosal and submucosal outpouchings at points of weakness in the muscularis propria where feeding blood vessels (vasa recta) penetrate the muscle layer. These pseudodiverticula frequently occur mostly in the sigmoid colon, usually in parallel rows, vary in number and are generally 5–10 mm in diameter.1, 2 Recently, this condition has been defined in a consensus conference in Rome3 according to the presence of symptoms: diverticulosis when asymptomatic and diverticular disease (DD) when associated with symptoms. Diverticular disease is subdivided into uncomplicated or complicated when perforation, fistula, obstruction and/or bleeding are present.

Diverticular disease represents the fifth most important gastrointestinal (GI) disease in western countries in terms of direct and indirect healthcare costs with an estimated mortality rate of 2.5 per 100 000 per year.4 Although present worldwide, DD is highly prevalent in industrialized countries with the highest rates reported in the United States, Europe and Australia.5–8 The prevalence rises with age and diverticulosis in the UK affects approximately 5% of people in the fifth decade of life increasing to almost 50% by the ninth decade9–11 with the exception of vegetarians in whom the frequency of DD is much lower.12 In contrast to the west, DD is almost unknown in rural Africa and Asia where the prevalence is <0.2%,9, 13 even if in urbanized areas such as Singapore, Japan and Hong Kong, it occurs in about 20% of people.14–17 The distribution of DD also varies between western and eastern countries. In western countries diverticulosis is mostly limited to the left colon6, 18 whereas in Asia isolated right-sided diverticulosis is common.14, 15 The process of urbanization with the introduction of a western-style diet lacking in fibre has been associated with a gradual rise in the prevalence of diverticulosis in developing countries, but the disease remains predominantly right-sided.16, 19–21

PATHOGENESIS

Diverticular disease of the colon is the result of complex interactions between dietary fibre, colonic wall structure and intestinal motility.

Fibre intake

The recommended dietary fibre intake for adults is about 20–35 g/day, but the average intake in the west is only 14–15 g/day.22 Painter and Burkitt7 were the first to report on the importance of dietary fibre in the pathogenesis of DD, coining the term ‘a deficiency disease’ in 1968. Cellulose (a fibre that is not hydrolysed by human digestive enzymes23) has been shown to be particularly protective leading to more bulky and voluminous stools, resulting in a wider-bore colon and thus preventing hypersegmentation and high intraluminal colonic pressures.24, 25 The amount of dietary fibre intake is the principal factor that influences bowel transit times and stool volume, both of which are markedly reduced in the UK subjects compared with Ugandans.26 However, a difference in dietary composition does not entirely explain the pathogenesis of DD as no differences have been demonstrated in transit times and stool volume in patients with and without DD.27

Changes in the colonic wall

A decrease in tensile strength of both the collagen and muscle fibres of the colonic wall, which occur as a result of ageing, may also be an important factor.28 The reason for this change seems to be related to an increase in cross-linking of abnormal collagen fibrils29–31 and to the continuous deposition of elastin throughout life in all layers of the colonic wall.24 The extracellular matrix (ECM) is important in maintaining the strength and integrity of the colonic wall.32 It has been postulated that both damage and breakdown of mature collagen, and the synthesis of immature collagen may lead to a weakened colonic wall23 and to more distensible muscle fibres.33, 34 Colonic compliance in the sigmoid and descending colon has also been demonstrated to be lower than that in the transverse and ascending colon, explaining at least in part the left-sided predominance of diverticulosis in western countries.23 Thompson et al.30 reported that collagen fibrils in the left colon were smaller and more tightly packed than those in the right colon with increasing age, and that this difference was accentuated in DD. However, abnormalities of both the circular and longitudinal muscle layers (taeniae coli) of the colon in DD exceed the effect ascribed to ageing alone.35 Structural changes in the colonic wall may

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also be responsible for the appearance of diverticula at an early age in connective tissue disorders such as Marfan’s and Ehlers-Danlos syndrome and polycystic kidney disease.36, 37

Matrix metalloproteinases (MMP) are a group of zinc-dependent endopeptidases that are involved in ECM degradation and remodelling.38, 39 They are secreted as inactive precursors by a variety of cells including mesenchymal cells, macrophages, monocytes, T cells, neutrophils, myofibroblasts and tumour cells.40 Conversion into the active enzyme usually occurs in the pericellular or extracellular space. MMPs are structurally related but can be divided into sub-classes: collagenases (MMP-1, -8, 013 and 018), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -7, -10 and -11), elastase (MMP-12), membrane types (MMP-14, -15, -16, -17, -24 and -25) and others (MMP-19, -20, -23, -26, -27 and -28).40 Activation of an MMP usually results in an enzymatic cascade resulting in degradation of all classes of ECM, including collagens, non-collagenous glycoproteins and proteoglycans. Tissue inhibitors of metalloproteinases (TIMPs) are also present, which block the effects of endogenous MMP, and are produced by the same cells that produce MMPs. Under normal conditions, MMPs are present at low levels, usually in the inactive form, and are responsible for normal physiological tissue turnover.40 Tissue expression of MMP is regulated by several mechanisms;41 TIMPs control the local activity of MMPs in tissues. However, if the production of MMPs exceeds that which can be regulated by TIMPs, breakdown of ECM occurs. MMPs have been shown to have an important role in both tissue injury and healing in the gut.30 Recent studies have shown an increase in MMPs in the inflamed gut and in fistulae associated with inflammatory bowel disease.42, 43 In stenotic Crohn’s disease, isolated tissue myofibroblasts have been shown to express high levels of TIMP-1, which inhibits MMP-mediated ECM degradation.44 An increase in collagen synthesis and TIMP-1 has also been demonstrated in collagenous colitis45 and DD.38 Mimura et al. demonstrated an increase in collagen deposition in the mucosa, submucosal layer and muscularis propria together with increased expression of TIMP-1 and TIMP-2 in both complicated and uncomplicated DD.38 Stumpf et al. also demonstrated changes in tissue expression of MMPs in DD, reporting a decrease in the expression of MMP-1 in association with decreased levels of mature collagen type 1, in patients with diverticulitis.46 These studies suggest that changes in MMP and TIMP expression may contribute to the structural changes in the colonic wall seen in patients with DD.

Colonic motility

Abnormal colonic motility is thought to be an important factor in the pathogenesis of DD.1, 34, 37 Patients with diverticulosis demonstrate abnormal motility and excessive colonic contractility, particularly in segments bearing diverticula.42–50 Studies in patients with DD have shown either a normal51 or increased intraluminal pressure52, 53 with a significant increase in intraluminal pressure, or colonic activity, after a meal or prostigmine provocation.51–53 Myoelectrical recordings from implanted catheters in patients with DD demonstrate an alteration in ‘slow waves’,54 corresponding to colonic pacemaker activity, and excessive segmental activity55 or ‘spikes’, reflecting muscle contractions.56 The term ‘slow waves’ is used to describe the spontaneous rhythmic electrical activity that is present within the circular and longitudinal smooth muscle layer of the gut wall.57 Slow waves are generated by a specialized network of cells of mesenchymal origin, the so-called interstitial cells of Cajal (ICC).58 When excited sufficiently, a slow wave is associated with circular muscle contraction; slow waves determine the frequency and propagation of smooth muscle contractile activity.59 The ICC are crucial to the generation and propagation of pacemaker activity and together with the enteric nervous system57 is responsible for the control of GI motility. ICC are necessary for normal intestinal motility,60 and also mediate neurotransmission from enteric motor neurones61, 62 to the muscle in the gut wall.57, 63 The role of ICC as intestinal pacemakers has been demonstrated in experimental animal models, which have shown that a lack of ICC networks leads to the absence of slow waves, and delayed or absent intestinal motility.64, 65 Furthermore, ICC have also been shown to be reduced or absent in diseases associated with alterations in GI motility, such as hypertrophic pyloric stenosis,66 diabetic gastroparesis,67 intestinal pseudo-obstruction68 slow-transit constipation69, 70 and congenital absence of the enteric nervous system, or Hirschsprung’s disease.66 Morphological abnormalities of ICC have also been demonstrated in patients with ulcerative colitis71 and in animal models of colonic inflammation, and this may explain the colonic dysmotility, which is described in colitics.72
In the human colon, three populations of ICC have been identified:\textsuperscript{73, 74} ICC-SM (submucosal plexus), along the submucosal surface of the circular muscle layer;\textsuperscript{57} ICC-MY (myenteric plexus), within the intermuscular space between circular and longitudinal muscle layers and ICC-M (intramural), within the muscle fibres of the circular and longitudinal muscle layers. In normal healthy tissue, the majority of ICC are found in the myenteric plexus and are equally distributed throughout the entire colon.\textsuperscript{60} Slow wave activity is generated by the ICC-SM and ICC-MY\textsuperscript{75} whereas ICC-IM is involved in neurotransmission from the enteric nervous system to muscle cells.\textsuperscript{76} A recent study by Bassotti \textit{et al.}\textsuperscript{77} demonstrated that patients with diverticulosis have significantly reduced numbers of all subpopulations of colonic ICC and enteric glial cells, but normal numbers of enteric neurones compared with healthy controls. A reduction or loss of ICC function may decrease or eliminate colonic electrical slow wave activity, thereby resulting in delayed transit.\textsuperscript{77} Although the ICC is essential for normal motility in the gut, the enteric nervous system may also play a role. In diverticulosis, loss of smooth muscle choline acetyltransferase activity, upregulation of M3 receptors, and increased \textit{in vitro} sensitivity of the smooth muscle to exogenous acetylcholine have been documented, suggesting that cholinergic denervation hypersensitivity may occur in this condition.\textsuperscript{55, 78} This together with a decrease in ICC may explain the motor abnormalities described in DD. However, what is unclear is whether the abnormal motility precedes\textsuperscript{29} or follows the development of diverticula.\textsuperscript{49}

**Visceral sensation**

Symptoms in symptomatic uncomplicated DD may be indistinguishable from those of the irritable bowel syndrome (IBS). Visceral hypersensitivity is the term used to describe an excessive perception or an excessive neural afferent response to physiological stimuli.\textsuperscript{79} Patients with IBS demonstrate an increased visceral perception in response to rectosigmoid distension.\textsuperscript{80–83} Recent study has also suggested that visceral sensation is altered in patients with DD. Clemens \textit{et al.} compared visceral perception of pain in response to rectal and sigmoid colon distension in patients with symptomatic uncomplicated DD, asymptomatic DD and healthy controls.\textsuperscript{84} Patients with symptomatic uncomplicated DD showed an increase in pain perception in the sigmoid colon compared with healthy controls, and also increased pain perception in the rectum compared with asymptomatic diverticular patients and healthy controls. Hence, patients with symptomatic uncomplicated DD show a heightened visceral perception to rectosigmoid distension, which is not found in asymptomatic diverticular patients. This visceral hypersensitivity is not limited to the diverticula-bearing sigmoid colon and is not due to altered compliance of the gut wall. These findings indicate a generalized hyperperception of intestinal stimuli in symptomatic diverticulosis which resembles IBS.\textsuperscript{80, 82}

The cause of the visceral hypersensitivity is not entirely clear but there is increasing evidence of an interaction between the enteric nervous and immune systems.\textsuperscript{85, 86} In experimental models of colitis, local tissue injury results in the release of proinflammatory mediators that can sensitize enteric afferent nerve terminals resulting in a heightened response to noxious stimuli.\textsuperscript{79, 87} These changes may affect the muscle layers as well as the mucosa\textsuperscript{86} and may also occur at non-inflamed sites.\textsuperscript{89, 90} Furthermore, experimental models of colitis also demonstrate that intestinal muscle dysfunction and increased activity of primary afferent enteric neurones may persist after resolution of the acute mucosal inflammation.\textsuperscript{86, 91, 92} Low-grade inflammation has also been demonstrated in the intestinal mucosa of patients with postinfectious IBS, and this may explain in part the heightened visceral sensation in these patients.\textsuperscript{93} Other inflammatory conditions such as inflammatory bowel disease and coeliac disease are also associated with disturbed intestinal motor function and increased sensory perception. Although there is limited data on visceral hypersensitivity in DD, persisting GI symptoms can occur after an episode of diverticulitis, and low-grade inflammation has been reported in patients with symptomatic DD.\textsuperscript{94} In keeping with animal models of intestinal inflammation,\textsuperscript{95} neuronal changes have also been demonstrated in patients with acute diverticulitis with neuronal proliferation evidenced by increased nerve staining within the muscularis propria.\textsuperscript{96}

**Genetic factors**

The association of diverticula with Marfan’s and Ehler’s Danlos syndromes indicates involvement of connective tissue\textsuperscript{97, 98} and a possible genetic predisposition to the development of diverticulosis. Case studies in siblings have been reported\textsuperscript{99} but there have been no definitive studies assessing familial risk in DD. Cross-linking of
collagen is a normal phenomenon which is essential for maintaining the structure of collagen. However, excessive cross-linking is thought to lead to rigidity and loss of tensile strength.\textsuperscript{23} Wess et al.\textsuperscript{100} demonstrated an increase in collagen-linking and the development of diverticulosis in rats fed a fibre-deficient diet for 18 months. The concentration of short chain fatty acids (SCFAs) particularly butyrate, was also lower in the bowel of fibre-deficient rats. SCFAs are the principal end products of microbial carbohydrate fermentation (dietary fibre), and an important source of energy-yielding substrates to the colonic mucosa.\textsuperscript{101} In addition, parental fibre intake may also influence the development of diverticulosis in the offspring,\textsuperscript{102} suggesting an interaction between possible genetic predisposition and environmental factors. Thus, lower fibre diet may cause higher collagen cross-linking possibly through a lower production of SCFAs. Specific alterations in collagen have also been demonstrated in patients with DD. Stumpf et al.\textsuperscript{46} and Bode et al.\textsuperscript{103} demonstrated an increased synthesis of type III collagen, but not type I (mature) collagen, in colonic diverticulosis.

**CLINICAL ASPECTS**

An estimated 20\% of patients with diverticulosis will develop symptoms throughout their lifespan, 50–70\% of patients treated for the first episode of diverticulitis will recover and have no further clinical problems and only 20\% of these patients will develop recurrent symptoms. Furthermore, 25\% of patients with recurrent uncomplicated DD will develop complications, and about 1–2\% will require hospitalization and 0.5\% surgery.\textsuperscript{104} In addition, 25\% of patients with DD may present with diverticular colitis\textsuperscript{105–107} characterized by oedematous, hyperaemic, granular and occasionally ulcerated mucosal folds with sparing of the diverticular orifices. The pathogenesis of the colitis and its association with the presence of diverticula remains unclear. Histologically, diverticular colitis may be indistinguishable from that of Crohn’s colitis.\textsuperscript{106, 108}

The mechanisms by which symptoms develop are still unclear\textsuperscript{56, 109} and probably relate to the interaction between colonic dysmotility, mucosal inflammation and intestinal microflora. Changes in the intestinal microflora may explain, in part, the development of symptoms in patients with colonic diverticulosis. Stasis of luminal contents occurs in colonic diverticula resulting in bacterial overgrowth.\textsuperscript{110} This in turn may give rise to chronic low-grade mucosal inflammation which sensitizes intrinsic primary afferent neurones in the submucosal and myenteric plexus,\textsuperscript{111, 112} resulting in visceral hypersensitivity and changes in colonic motor function.\textsuperscript{95, 113} Such changes may be mediated by alterations in neurochemical transmitters. Increased levels of substance P, an excitatory neurotransmitter that is important in visceral nociception,\textsuperscript{114} have been reported in patients with DD and abdominal pain, but without inflammation.\textsuperscript{115} Other authors have also described similar increases in the level of substance P in patients with chronic right iliac fossa pain in association with neuroproliferative changes within the appendix, in the absence of inflammation.\textsuperscript{116} Studies have also shown an increase in the inhibitory neurotransmitter vasoactive intestinal polypeptide (VIP) in patients with DD,\textsuperscript{117} which may explain the alterations in colonic motility. Methane, which is produced by gut bacteria, may also have an effect by slowing intestinal transit and reducing post-prandial plasma levels of serotonin.\textsuperscript{118}

The most common symptom of uncomplicated DD is abdominal pain,\textsuperscript{119} which may be exacerbated by eating and eased by defecation or the passage of flatus. Other symptoms such as nausea, episodic diarrhoea, constipation and bloating may also be present. However, a causal relationship of these non-specific symptoms with diverticulosis is sometimes difficult to establish due to the high prevalence of IBS in western countries.\textsuperscript{120} The symptoms of right-sided DD are similar to those of left-sided DD with the exception of symptom localization and age of onset.\textsuperscript{121, 122} However, the frequency of diverticula of the right colon does not increase with age, suggesting that the condition might be self-limiting.\textsuperscript{16} Severe bleeding is also more common in right-sided DD whereas diverticulitis and fistulation are more frequent in left-sided DD.\textsuperscript{123}

Many patients with DD present with symptoms at an age when colorectal cancer is common\textsuperscript{124} and for this reason colonoscopy is often the preferred investigation.\textsuperscript{125} However, the presence, localization and severity of diverticulosis are better assessed with double contrast barium enema.\textsuperscript{126–128} In contrast, barium enema has a poor sensitivity for the detection of small colonic adenomas and may miss up to 50\% of large adenomas (>1.0 cm diameter).\textsuperscript{129} This is more so in patients with severe sigmoid diverticulosis in whom radiological interpretation can be extremely difficult due to the presence of multiple ‘pockets’, luminal narrowing and colonic spasm.\textsuperscript{128, 130} Colonoscopy may also be difficult in such patients due to difficulty in visualization of the
colonic lumen as a result of luminal narrowing from prominent enlarged folds, or fixation from previous inflammation and pericolic fibrosis. The nature and time course of symptoms may also help in deciding on the most appropriate investigations. The indication for an initial ultrasound examination is related to the difficulty in attributing symptoms to the lower GI tract, and its usefulness is related to the experience of the sonographer. In case of suspected complicated DD, ultrasound, computerized tomography (CT) scan or magnetic resonance imaging (MRI) are preferred because of the potential risk of perforation associated with either colonoscopy or double-contrast barium enema. Finally, there is insufficient data to support the routine use of virtual colonography in patients with severe diverticulosis.

There are no good predictive factors for the development of symptoms although it has been shown that the involvement of a short segment of colon, a young age (<50 years), and lack of physical activity may be associated with an increased risk. A large prospective study found that a diet low in fibre and high in fat and red meat carries a threefold risk of developing symptomatic DD. The importance of low-grade colitis in chronically symptomatic DD has been highlighted by Horgan et al. In this study mild inflammatory changes of the mucosa were found in 76% of patients undergoing surgery and resolution of symptoms was reported by over 75% of these patients.

TREATMENT

No treatment or follow-up needs to be offered to the majority of patients with diverticulosis, and to those with a single previous episode of symptoms of uncomplicated DD due to the low risk of recurrence. Treatment of recurrent uncomplicated DD is aimed at relief of symptoms and prevention of major complications, but the standard approach is still debated. The principal treatments are a fibre-rich diet and non-absorbable antibiotics, but alternatives include mesalazine and probiotics (Table 1). Anticholinergic and antispasmodics agents may be effective in some cases of uncomplicated DD, but their use remains to be confirmed by controlled studies.

Fibre-supplementation

Dietary fibre consists of the structural and storage polysaccharides and lignin in plants that are not digested in the human stomach and small intestine. These fibres are incompletely or slowly fermented by microbiota in the colon and promote normal laxation. The recommended intake of fruit or vegetables is 20–35 g/day for healthy adults, and age plus 5 g/day for children. Fibre intake may be supplemented as soluble and insoluble fibre. Soluble fibre (psyllium, ispaghula, calcium polycarbophil) dissolves in water, forming a gel, and is fermented in the colon by bacteria to a greater extent than insoluble fibre. Short chain fatty acids and gas are the active metabolites of soluble fibre, both of which shorten the gut transit time alleviating constipation and intracolonic pressure, possibly resulting in a reduction of pain. In contrast, insoluble fibre (corn fibre, wheat bran) undergoes minimal change causing an increase in the faecal mass.

Painter was the first to advocate fibre-supplementation in symptomatic DD and the beneficial effects were first reported in 1977 in two double-blind controlled trials. These studies showed significant improvement in symptoms after a high-fibre regimen over a 3-month period compared with placebo. Two subsequent smaller randomized-controlled trials reported differing results. The first trial found no significant difference between bran (7 g/day fibre), ispaghula husk (9 g/day fibre) and placebo (2 g/day fibre) on symptom relief after 4 months, although both active treatments significantly reduced straining at stool, increased wet stool weight and stool frequency, and significantly softened the stools. The second study comparing methylcellulose (1 g daily) and placebo also reached a similar conclusion over a follow-up period of 3 months. Both studies did not assess complication rates related to DD. Finally, previous observational studies have reported that a high fibre diet prevents the development of symptomatic DD and its complications despite a compliance rate of only 72% for fibre-supplementation. Therefore, there is limited evidence for the effectiveness of fibre in the treatment of uncomplicated DD. From results of a systematic review of fibre treatment in IBS, fibre-supplementation showed a significant improvement of global symptoms and constipation. Soluble and insoluble fibres affected IBS differently: soluble fibre was beneficial for global symptom improvement whereas insoluble fibre resulted in worsening of abdominal pain in some patients when compared with a normal diet. Nowadays, a high-fibre diet is often suggested for the prevention of DD, and insoluble
fibres from fruits and vegetables seem to be more protective than those from cereals. 136, 137, 147

Non-absorbable antibiotics

Over the last decade, there has been much study on the role of non-absorbable antibiotics in the management of uncomplicated DD. Rifaximin is a broad spectrum poorly absorbable antibiotic which has been evaluated in patients with DD. Rifaximin acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. Pharmacokinetic studies have demonstrated that 80–90% of orally administered rifaximin is concentrated in the gut with <0.2% in the liver and kidneys. The mode of action of rifaximin in reducing the frequency of symptoms in patients with DD is unknown, but rifaximin has been shown to influence the metabolic activity of the gut flora, degradation of dietary fibres and the production of gas, as confirmed in patients with IBS. 148 Furthermore, the cyclic administration of rifaximin may have an indirect effect on mucosal inflammation by modulating the gut flora responsible for low-grade, chronic mucosal inflammation. 112 Currently, rifaximin is indicated in patients with acute and chronic Gram-positive and Gram-negative bacterial bowel infections, travellers’ diarrhoea, preoperative and post-operative prophylaxis in GI surgery, but not for symptomatic DD although data on the literature show that rifaximin is more effective than fibre-supplementation alone. Two randomized-controlled trials found that rifaximin plus dietary fibre-supplementation improved symptoms compared with fibre-supplementation alone after 12 months of

<table>
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<tr>
<th>Fibre-supplementation</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Symptom reduction</th>
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<td>Open 62</td>
<td>Bran 12–14 g</td>
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<tr>
<td></td>
<td>9</td>
<td>Bran 6.7 g</td>
<td>&lt;0.02†*</td>
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<td>Brodribb140</td>
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<td>Placebo 0.6 g</td>
<td>12 weeks</td>
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<td>16</td>
<td>Methylcellulose 1 g</td>
<td>&lt;0.01†</td>
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<td>Hodgson142</td>
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<td>12 weeks</td>
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<td>Bran 7 g</td>
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<td>Leahy et al.145</td>
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<td>Papi et al.160</td>
<td>Open 107</td>
<td>Rifaximin 800 mg + glucomannan 2 g</td>
<td>1 week/month</td>
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<td>110</td>
<td>Glucomannan 2 g</td>
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<td>RCT 84</td>
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<td>Latella et al.150</td>
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<td></td>
<td>373</td>
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<tr>
<td>Brandimarte and Tursi152</td>
<td>Open 90</td>
<td>Mesalazine 1.6 g (after rifaximin 800 mg)</td>
<td>8 weeks</td>
<td>96%</td>
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<td>Open 15</td>
<td>Escherichia coli Nissle 5.0 × 10^10</td>
<td>5 weeks</td>
<td>14 months‡*</td>
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<td>(after dichlorchinolinol</td>
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<td></td>
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<td>Dichlorchinolinol 750 mg + active</td>
<td>1 week</td>
<td>2.4 months‡</td>
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<td>coal 960 mg</td>
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* P < 0.05.
† Mean symptom score variation from baseline to the end of treatment.
‡ Remission length.
treatment. The first study randomized 168 patients with uncomplicated DD to fibre-supplementation (glucomannan 2 g/day) plus rifaximin (400 mg b.d.) or fibre-supplementation plus placebo for 1 week out of every month over a period of 1 year. Fibre-supplementation plus rifaximin was associated with a significant increase in the proportion of patients with no or only mild symptoms (69% with rifaximin vs. 39% with placebo), but did not result in a significant improvement in the severity of diarrhoea, tenesmus, or abdominal pain. The second multicentre study enrolled a larger population (968 patients) and compared fibre-supplementation (glucomannan 4 g/day) plus rifaximin (400 mg b.d.) with glucomannan alone. Dietary fibre-supplementation plus rifaximin was shown to significantly improve global symptom score compared with fibre-supplementation alone. Approximately 30% therapeutic gain compared with fibre-supplementation alone may be expected after 1 year of intermittent treatment with rifaximin, and considering its safety and tolerability, rifaximin may be useful in patients with symptomatic uncomplicated DD. Finally, a recent study showed that patients with DD treated with rifaximin over a period of 10 years experienced a 5% relapse rate of symptoms and a 1% rate of complications.

Mesalazine

Mesalazine, an anti-inflammatory drug that is typically used in patients with inflammatory bowel disease, has recently been reported to be a possible alternative treatment option in patients with uncomplicated DD. Mesalazine was discovered to be therapeutically active in ulcerative colitis through a mechanism of action that appears to be topical rather than systemic, reducing inflammation by blocking cyclo-oxygenase and inhibiting prostaglandin (PG) production in the colon. According to the hypothesis that the symptoms of DD might be secondary to chronic mucosal inflammation, Brandimarte and Tursi treated 90 patients with rifaximin (400 mg b.d.) plus mesalazine (800 mg t.d.s.) for 10 days followed by mesalazine (800 mg b.d.) for a further 8 weeks. At the end of the treatment period, 81% of patients were asymptomatic suggesting that mesalazine might be beneficial in maintaining clinical remission. Although the results of this study are encouraging, further studies are needed with longer follow-up before mesalazine can be considered a valid alternative for the prevention of recurrent symptoms in patients with DD.

Probiotics and prebiotics

Probiotics are a preparation of, or a product containing viable defined microorganisms in sufficient numbers, which alter the host microflora by implantation or colonization in a compartment of the host, exerting beneficial health effects. The strains with beneficial properties most frequently belong to the genera Bifidobacterium and Lactobacillus, but other bacterial strains have been used including certain strains of Escherichia coli and non-bacterial organisms such as Saccharomyces boulardii. The rationale for the use of probiotics is to re-establish the normal bacterial flora, which in the presence of DD may be altered by the reduced colonic transit time and stasis of faecal material within the diverticula. There is little data on the treatment of uncomplicated DD with probiotics. The first report on the use of probiotics in DD comes from a prospective observational trial on the prevention of complications after acute diverticulitis. All patients with a postdiverticular stenosis of the colon were treated sequentially with rifaximin and lactobacilli for a period of 12 months. This treatment proved to be effective in preventing symptom recurrence and complications. The efficacy of probiotic treatment as a single therapy for uncomplicated DD has been assessed in only one study comprising a very small group of patients. A non-pathogenic E. coli strain was given for a mean period of 5 weeks after a course of treatment with an intestinal antimicrobial and absorbent, resulting in a significantly prolonged remission period and significant improvement of all abdominal symptoms. In DD, probiotics may not only relieve functional symptoms but also alleviate intestinal inflammation, normalize gut mucosal dysfunction and downregulate hypersensitivity reactions.

Prebiotics are dietary substances, usually indigestible complex carbohydrates, which stimulate the growth and metabolic activity of beneficial enteric bacteria, especially Lactobacillus and Bifidobacterium species. Bacterial fermentation of poorly absorbed carbohydrates results in a decrease in luminal pH, which suppresses growth of harmful bacteria and production of butyrate (SCFAs), which is a key substrate for colonic cell and mucosal barrier function. Inulin, fructose oligosaccharides, lactulose, germinated barley extracts and psyllium fibre have been shown to promote the growth of luminal Lactobacillus and Bifidobacterium species and butyrate production. Thus, the optimal treatment of uncomplicated DD might be an initial
course of antibiotics to normalize the gut flora followed by a combination of a probiotic to prevent relapse, and prebiotic to maintain growth of protective bacteria.

In conclusion, western diets should be modified by increasing fibre intake and decreasing fat and red meat. This ‘easternization’ of the diet should be the first-line preventative measure for DD as well colorectal cancer. The therapeutic management of uncomplicated DD should include non-absorbable antibiotics such as rifaximin and probiotics, which may also be beneficial in reducing the complications from DD. Treatment of diverticular-associated colitis should include a short course of antibiotics and/or a trial of mesalazine. Future studies should assess not only symptom improvement, but also long-term remission rates, cost of treatment and impact on quality of life.

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