Diverticular disease of the colon: New perspectives in symptom development and treatment

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Abstract
Diverticular disease of the colon is a common disease worldwide. Although the disease is asymptomatic in about 70-80% of patients, it represents, at least in Western countries, one of the most important gastrointestinal diseases in terms of direct and indirect health costs. Pathogenesis of the disease is still unknown. However, it is the result of complex interactions between colonic structure, intestinal motility, diet and genetic factors. Whilst efficacious preventive strategies remain to be identified, fibre supplementation in the diet is recommended. Why symptoms develop is still unclear. Results of recent experimental studies on irritable bowel syndrome speculated that low grade inflammation of colonic mucosa, induced by changes in bacterial microflora, could affect the enteric nervous system, which is crucial for normal gut function, thus favouring symptom development. This hypothesis could be extrapolated also for diverticular disease, since bacterial overgrowth is present, at least in a subgroup of patients. These perspectives on symptom development are reviewed and new therapeutic approaches are hypothesized.


INTRODUCTION
Diverticular disease (DD) of the colon is very common especially in the elderly[1]. Although DD is present worldwide, a higher incidence has been reported in developed countries, compared to underdeveloped countries[2]. DD has important socioeconomic implications on the health system, due not only to its worldwide distribution, but also to the lack of knowledge concerning its natural history and the risk factors involved in development of symptoms. As a consequence, it is difficult to define efficacious preventive strategies.

According to a recent report by the American Gastroenterological Association on the burden of digestive diseases in the United States[3], DD represents, in terms of direct and indirect costs, the 5th most important gastrointestinal disease, with a mortality-rate of 2.5 per 100,000 per year.

DD is a manifestation of an acquired deformity of the colon wall and is characterized by the development of pseudo-diverticula, i.e., protrusions of the mucosa and submucosa through the muscular wall. These protrusions occur in weak areas of the wall where blood vessels penetrate due to the high pressure inside the colon[4].

No uniform definition of DD exists as yet. However, according to a recent Consensus Development Conference[5], colonic DD can be defined as a condition involving primarily the sigmoid region of the colon. This condition may be either asymptomatic, and is referred to as “diverticulosis”, or associated with symptoms, and termed “diverticular disease”, which may, in turn, be either complicated or non-complicated. The term diverticulitis is used to indicate inflammation of the bowel wall.

A brief review is made herein of the epidemiology, pathogenesis and treatment of DD, and in accordance with recent experimental results, some hypotheses on pathogenesis of symptom development are advanced, which may be usefully taken into consideration in defining more effective preventive strategies.

EPIDEMIOLOGY
Epidemiological studies have demonstrated that the prevalence rates differ considerably from one country to another. Indeed, the disease is very common in Western developed countries, with a much higher frequency (30-40%) than that in Eastern and developing countries (1-4%)[2, 6-8].

Furthermore, in Western countries, about 90% of the patients have diverticula in the sigmoid segment, while in Asian populations the caecum and the right colon are most frequently involved[9-12].

Recent studies, however, indicate an increase in the prevalence rate of DD also in Eastern populations, possibly due to increasing globalization and the fact that lifestyle has become increasingly similar in various parts of the world[11, 13].

No definitive data have emerged, so far, on the prevalence rate of DD, mainly because the majority of patients are asymptomatic, and are hence difficult to identify. The most important risk factor appears to be aging, the prevalence rate increases with age and varies from <10% in subjects <40 years old to an estimated 50-66% in patients >85 years old[11, 14, 19].

Some studies have reported a slightly higher frequency in females, however, no sex-related predominance has been demonstrated[6, 17].

PATHOGENESIS
The pathogenetic mechanisms of DD are still poorly understood, however it is generally recognized that these are probably related to complex interactions between colon structure, intestinal motility, diet as well as genetic features[18].

DD has been correlated with “a low residue diet”[22], and furthermore, the prevalence of diverticulosis is higher with a reduced dietary intake of raw fibres[19] and lower in vegetarians[20]. These data are supported by studies both in
animal[21, 22] and humans[23-28]. However, although the fibre deficiency hypothesis has been widely quoted, conflicting evidence and much controversy still exist[29, 30]. The exact mechanism involved remains to be defined, even if prolonged colonic transit time and decreased stool volume in subjects on a low residue diet, seem to induce an increase in intraluminal pressure, which in turn, predisposes to diverticular herniation[31, 32]. Furthermore, the lower faecal bile acid output in patients with DD suggests a pathogenetic role of these compounds which stimulate colonic motor activity and as a result reduce colonic transit time[33]. Albeit, these hypotheses have not been confirmed by controlled clinical studies comparing healthy subjects with DD patients[34].

As far as colonic structure is concerned, early surgical and autopsy studies demonstrated an association between muscular hypertrophy of the colon and presence of DD[34, 35], thus suggesting that increased muscle bulk plays a role in enhancing intraluminal pressure.

Furthermore, electron microscopy evidence of a two-fold increase in elastin content in the taenia coli[36] suggests a further pathogenetic mechanism. The elastin content in the taenia results in contraction and bunching of the circular muscle, giving the appearance of a hypertrophic muscle with narrowing of the bowel lumen.

The increased prevalence of DD with aging could be due to a progressive, age-related accumulation of elastin in the taenia coli[37, 38]. In fact, in the elderly, the bowel wall is invariably increased in thickness with reduced elasticity[39] and thus, intraluminal pressure increases and, according to Laplace’s law, formation of diverticula is more likely.

The tendency to elastin accumulation in the taenia coli could be resulted from a low residue diet that extends the bowel intermittently and incompletely, thus favouring prolin (an elastin precursor) uptake[40].

Whilst several pathogenetic hypotheses have been advanced to explain the development of colon diverticula, the fact remains that the pathologic aspects of the disease are resulted from lifelong exposure to a low residue diet and a complex interaction between colonic structure, intestinal motility and genetic factors[41].

However, the hallmark of painful DD is abdominal pain in the absence of any indications of inflammation. Pain is usually colicky, but may also be steady. It is exacerbated by eating, and is typically relieved by flatus or bowel movements. Associated symptoms vary considerably: diarrhea, constipation, flatulence, heartburn, nausea and vomiting, palpable abdominal mass, abdominal distension[42, 5, 38].

**Natural history**

The natural history of DD remains to be elucidated and the few prospective studies carried out so far[43-46] indicate that 80-85 % of patients with DD remain asymptomatic. Of the 15-20 % of patients presenting abdominal pain, approximately 75 % have a painful DD whilst the remainder have diverticulitis, as well as complications of diverticulitis and haemorrhage[47]. Furthermore, about 1-2 % will require hospitalisation and 0.5 % will require surgery[41, 45, 46]. Unfortunately, due to the lack of prospective studies, factors predicting the development of symptoms remain to be identified. However, it has been suggested[47] that evaluation of the colonic motility index (pressure amplitude exceeding 120 mmHg), together with a brief history of left lower quadrant pain, a short segment of involved colon and a relatively younger age (about 50 years), may be useful in recognizing a group of patients at risk of developing symptoms.

Moreover, investigations[48, 49] have suggested that lack of physical activity is independently associated with an increased risk of symptomatic DD, while smoking, caffeine and alcohol intake are not associated with a substantially increased risk of asymptomatic disease. Furthermore, a significant inverse association has been found between insoluble dietary fibre intake (especially fruit and vegetables, e.g. cellulose fibre) and the risk of subsequently developing symptomatic DD[50]. In contrast, a study on the efficacy of fibre supplementation in symptomatic patients with DD did not lead to an improvement in symptoms[51].

Since few data exist on risk factors, preventive measures for the development of diverticula are only speculative, and can be aimed only at preventing development of symptoms. Despite controversial data, fibre supplementation is recommended[42, 38].

**Symptom development**

The causes of symptom development, in some patients, are still unclear. Since it has been observed that DD patients who have a history of diverticulitis have more episodes of recurrent abdominal pain and impaired bowel function[46, 51, 52], a possible role of previous episodes of intestinal inflammation may be hypothesised. This finding is not unlike that which has been recently demonstrated in other gastrointestinal diseases such as infectious enteritis and inflammatory bowel disease[53, 54] and, as also speculated[55] in irritable bowel syndrome (IBS).

In these patients, the presence of a chronic, low-grade intestinal inflammation would induce a sensory-motor dysfunction, leading to symptom development and/or persistence[53, 56].

Changes in intestinal microflora could be one of the putative mechanisms responsible for low grade inflammation, at least in IBS[55]. In patients with DD, bacterial overgrowth may be present[57]. This bacterial overgrowth aided by the faecal stasis inside the diverticula, could contribute to chronic low-grade inflammation which sensitises both intrinsic primary efferent and extrinsic primary afferent neurons. These alterations could lead to smooth muscle hypertrophy, and increased sensitivity to abdominal distension[56, 58], and, finally, to symptom development. This hypothesis is based mainly on experimental studies, investigation in man, being limited at present. However, an increased level of the neuropeptide substance P, which may be related to impaired visceral sensation, has been
demonstrated in patients with DD with abdominal pain but without inflammation. This finding is not unlike that observed by Di Sebastiano et al. who documented a role of neuroproliferation within the appendix, associated with an increased concentration of substance P and vasoactive intestinal polypeptide, in the pathophysiology of right iliac fossa pain in the absence of inflammation. Moreover, in patients with diverticulitis, abnormal nerves with axonal sprouting have been observed, suggesting previous injury. These findings would appear to be compatible with post-inflammatory neural and muscle dysfunction, probably induced also by intestinal bacterial overgrowth, which would contribute to symptom development.

Further studies, both experimental and in man, are obviously needed to confirm the pathogenetic role (which is summarized in Figure 1) of intestinal infection and low grade inflammation, in the development of symptoms in patients with DD.

Figure 1 Diverticular disease: putative role of intestinal bacterial overgrowth in symptom development. Altered intestinal microflora could contribute to chronic low-grade inflammation (supported by both immunocytes and mast cells) which abnormally sensitised both intrinsic primary efferent and extrinsic primary afferent neurons. This condition could lead to neural and muscle dysfunction (i.e. altered intestinal motility and visceral sensitivity) and, finally, to symptom development.

Non-surgical treatment
There is a general consensus that conservative treatment is indicated in cases with newly onset uncomplicated diverticulitis. The rationale for this strategy is that about 50-70% of patients treated for a first episode of acute diverticulitis will recover and have no further clinical problems. Furthermore, only about 20% of these patients will develop symptoms whilst those with recurrent symptoms have a 60% risk of developing disease complications.

In patients with uncomplicated diverticulosis, a diet with abundant fruit and vegetables is recommended since it seems that this protective effect reduces symptom development and prevents major complications as demonstrated in uncontrolled studies. Nevertheless, recent guidelines advise the use of a high fibre diet, which should be prescribed also for the well-known potential health benefits.

Anticholinergic and antispasmodic agents may be effective in some cases of uncomplicated DD. However, their use remains to be confirmed by controlled studies.

Although the role of antibiotics in uncomplicated DD is still debated, recent clinical studies have demonstrated that cyclic administration of rifaximin (Normix, Alfa Wassermann S.p.A., Alanno Scalo, Chieti, Italy) (a broad-spectrum poorly absorbable antibiotic) is more effective in reducing symptoms than fibre supplementation alone (Table 2).

Latella et al. performed a large, multicentre, prospective, randomized study, enrolling 968 outpatients with symptomatic diverticulosis. Among them, 595 patients received fibre supplement (glucomannan 4 g/day) plus rifaximin 400 mg bid for 7 days, per month, and 373 patients received glucomannan alone. After 12 months, a significant reduction in the occurrence rate of symptoms was documented in the group treated with rifaximin and fibre. 56.5% of the patients were asymptomatic as compared to 29.2% of the fibre group. Moreover, the incidence of major complications was lower in the rifaximin plus fibre group vs the group treated with fibre alone. The mechanism of rifaximin in reducing the frequency of symptoms and the rate of complications of DD is only speculative. It has been suggested that rifaximin reduces the metabolic activity of intestinal bacterial flora, the degradation of dietary fibres, and the production of gas. The latter effect is important since an increased production of intestinal gas and of gas-related symptoms such as pain and bloating have recently been documented, in patients with IBS. Furthermore, treatment with non-absorbable antibiotics was shown to reduce symptoms frequency and intensity in these patients. Similar results were obtained by others who documented an association between small intestinal overgrowth and functional intestinal disorders. Moreover, eradication of bacterial overgrowth seems to be related to a reduction in intestinal symptoms.

In conclusion, if low grade mucosal inflammation is confirmed in DD patients, and if such inflammation is provoked and maintained by changes in bacterial microflora as in IBD, then these impairments likely play a role in the pathogenesis and symptom development of both diseases, and thus, new preventive approaches could be identified. According to this hypothesis, cyclic administrations of antibiotics, and in particular of non-absorbable antibiotics such as rifaximin, could reverse the process, i.e., intestinal bacterial overgrowth which is held to trigger the cascade of events which starts from intestinal low grade inflammation to reach symptom generation. In fact, rifaximin, which is highly

**Table 2** Effects of rifaximin (R) administration on symptoms in patients with diverticular disease

<table>
<thead>
<tr>
<th>First author (year, ref)</th>
<th>Pts (n)</th>
<th>Treatment (type)</th>
<th>Duration (months)</th>
<th>Reduction in symptoms (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papi (1992, 64)</td>
<td>217</td>
<td>R (400 mg daily) + glucomannan (2 g daily) vs glucomannan</td>
<td>12</td>
<td>63.9 vs 47.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Papi (1995, 65)</td>
<td>168</td>
<td>R (400 mg daily) + glucomannan (2 g daily) vs placebo + glucomannan</td>
<td>12</td>
<td>68.9 vs 38.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Latella (2003, 66)</td>
<td>968</td>
<td>R (400 mg daily) + glucomannan (4 g daily) vs glucomannan</td>
<td>12</td>
<td>56.5 vs 29.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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effective against anaerobic bacteria\textsuperscript{[69]} is effective also in intestinal bacterial overgrowth\textsuperscript{[50,71]}. It is important, at this stage, to identify and characterize those DD patients with intestinal bacterial overgrowth and, then, to perform controlled clinical trials to evaluate the effects of antibiotic administration on symptom and complication frequency, i.e., on the natural history of this disease.

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