DIVERTICULAR DISEASE OF THE COLON: ANTIBIOTICS OR PROBIOTICS?

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ABSTRACT: Antibiotics and probiotics share a common rationale in the treatment of diverticular disease of the colon. They can restore the composition of the colonic microflora, which is involved in the mucosal inflammation and indirectly related functional changes of the colon such as visceral hypersensitivity and smooth muscle hypertrophy. However, to date, reliable controlled therapeutic trials and solid scientific evidence about the use of antibiotics and probiotics in diverticular disease of the colon are still lacking. The available data show that both antibiotics and probiotics can improve symptoms and maintain symptom-free remission up to one year in most patients. On the contrary, the use of antibiotics in preventing acute diverticulitis seems to be limited, and probably it should be restricted to patients with previous complications of diverticular disease, such as perforation or bleeding. Unfortunately, data on the usefulness of probiotics in the long-term prevention of diverticulitis are still lacking, so far.

KEY WORDS: Antibiotics, Diverticular disease, Probiotics

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Colonic diverticular disease (DD) is an acquired condition in which areas of mucosa and sub-mucosa herniate through defects in the colonic wall. Its prevalence is difficult to measure, as most patients are asymptomatic. Post-mortem studies estimate that the prevalence of diverticulosis is similar in men and women and increases from 5–10% among adults less than 50 years of age, to 50–66% among those aged 70 years or older (Tursi, 2007; Almy et al, 1980). Approximately 20% of individuals with diverticulosis develops symptomatic DD, including abdominal pain or discomfort, bloating and changes in bowel habits, and only 1-2% and 0.5% of patients will experience a complicated DD, characterised by diverticulitis (i.e., inflammation of one or more diverticula) associated with gross or microscopic perforation requiring hospitalization and surgery, respectively (Stollman et al, 2004; Eastwood et al, 2009).

Unfortunately, to date, factors predicting the onset and development of symptoms and complications in DD remain to be identified. Epidemiological studies identified several factors associated with the development of symptoms and complications. Increased intra-colonic pressure and irritable bowel syndrome (Cortesini et al, 1991; Jung et al, 2010), diet with low intake of fiber and high intake of refined carbohydrates (Aldoori et al, 1998), physical inactivity (Aldoori et al 1995) and psychological factors (Humes et al, 2008) are associated with increased risk of asymptomatic and symptomatic diverticulosis. Young age and brief history of pain (Cortesini et al, 1991; Ambrosetti et al 1994), obesity (Hjern et al, 2012; Dobbins et al, 2012), physical inactivity (Hjern et al, 2012; Strate et al, 2009) smoking habit (Turunen et al, 2010; Papagrigroriadis et al, 1999), NSAIDs, opiate analgesic and corticosteroid use are risk for perforation (Humes et al, 2011; Piekarke et al, 2008). Furthermore, NSAIDs and antiplatelet drugs use, and hypertension are also recognised risk factors for diverticular bleeding (Niikura et al, 2012; Yamada et al, 2008).

Besides these epidemiological evidences, the pathogenetic mechanisms of DD are still unclear, but intestinal inflammation and potentially related impaired bowel function and visceral hypersensitivity are the main factors involved (Bassotti et al, 2012; Simpson et al 2009). Changes in intestinal microflora could be one of the mechanisms responsible for intestinal inflammation. Most patients with DD exhibit bacterial overgrowth (D’Inca et al, 2007; Tursi et al, 2005), which could contribute to chronic low-grade mucosal inflammation leading to the development of visceral hypersensitivity, smooth muscle hypertrophy and ultimately DD complications.

Therefore changes in colonic microbiota may be of crucial importance in the pathogenesis of DD and its manipulation, by using probiotics or antibiotics, may be used in the management of symptoms and in the prevention of complications of DD of the colon.

The medical treatment of DD is primarily aimed at relieving symptoms and/or preventing major complications (i.e., perforation and bleeding) and should be recommended mainly for symptomatic patients with recurrent uncomplicated DD of the colon.
The standard therapeutic approach of symptomatic colonic DD still remains to be defined. A high-dose fiber diet or treatment with non-absorbable antibiotics, mesalazine, and probiotics, either alone or in combination have been used (Maconi et al, 2011). However, although many reviews and practice guidelines on the management of DD have been published, the treatment for DD still relies mainly on data from uncontrolled studies, most of which of suboptimal methodological quality.

A recent systematic review identified 31 prospective studies of the treatment of DD of the colon, including 6 placebo controlled trials, only one of which long-term, double-blind and placebo controlled. The studies showed wide heterogeneity of the study design, patients’ characteristics, regimens and combination of treatment, and outcome reporting, thus precluding the pooling of results. Ten of these studies investigated non-absorbable antibiotics, such as Rifaximin, and 5 studies probiotics, alone or combined with mesalazine or fibres. One study examined the combination of Rifaximin and probiotics; Giaccari et al. 1993.

The rationale of using probiotics in DD relies in that they are live microorganisms that can alter the intestinal microbial flora when ingested, and confer beneficial health effects to the host. Apart from the secondary prophylaxis of complicated DD, their usefulness has been assessed in various gastrointestinal conditions, including inflammatory bowel disease, irritable bowel syndrome and antibiotic-associated diarrhoea. Rifaximin is a non-absorbable antibiotic, currently used for patients with bacterial bowel infections, traveller's diarrhoea, for pre- and post-operative prophylaxis in gastrointestinal surgery and for patients with irritable bowel syndrome or small-bowel bacterial overgrowth, where it can reduce bloating, abdominal pain,

### TABLE 1. Summary of trials on probiotics in the treatment of symptomatic (previously-symptomatic) uncomplicated diverticular disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Maintenance treatments compared (daily dose)</th>
<th>Treatment period</th>
<th>N. Patients</th>
<th>Outcome Measures</th>
<th>No symptom at the end of follow-up N (%)</th>
<th>Results</th>
<th>Side effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giaccari 1993</td>
<td>Open</td>
<td>Rifaximin 400 mg b.i.d. 7 days/mth followed by Lactobacillus cps 7 days/mth</td>
<td>12 months</td>
<td>79</td>
<td>Intensity of symptoms (pain, tension, meteorism, number of evacuation and characteristic of the faeces) quantified with scale from 0 (absent) to 4 (severe)</td>
<td>88%</td>
<td>Rifaximin together with Lactobacillus treatment is proved to be effective well tolerated and safe</td>
<td>0</td>
</tr>
<tr>
<td>Fric 2003</td>
<td>Open</td>
<td>Dichlorchinolinol 250 mg t.i.d + Active coal tablet 320 mg t.i.d.</td>
<td>1 wk</td>
<td>15</td>
<td>Average of the period remission obtained with antimicrobials plus absorbent vs. the same regimen followed by probiotics therapy Score for abdominal symptoms were assessed every 2 months</td>
<td>N.A.</td>
<td>The average length of remission was longer following probiotic therapy than with antimicrobials plus absorbent only All symptoms decreased significantly following probiotic therapy</td>
<td>0</td>
</tr>
<tr>
<td>Dughera 2004</td>
<td>Open RT</td>
<td>Polybacterial lyase suspension (Escherichia coli, Proteus vulgaris) bid for 2 wk/mth No treatment</td>
<td>3 months</td>
<td>43</td>
<td>The intensity of symptoms (recurrent abdominal pain, intermittent diarrhoea, bloating and fever) weekly quantified on a quantitative scale from 0 (absent) to 4 (severe)</td>
<td>N.A.</td>
<td>The sum of scores of symptoms was significantly better in patients treated with polybacterial lyase both at 1 and 3 mo</td>
<td>0</td>
</tr>
<tr>
<td>Annibale 2011</td>
<td>Open RT</td>
<td>High fiber only L. paracasei sub. paracasei F19 (1 sachet bid for 2 wks/mth) plus fiber</td>
<td>6 months</td>
<td>18</td>
<td>Symptoms assessed according to Rome II criteria. Presence and intensity of short and prolonged abdominal pain, bloating and dyspeptic symptoms assessed by a visual analogic scale.</td>
<td>N.A.</td>
<td>Lactobacillus paracasei F19, in association with a high-fibre diet, is effective in reducing abdominal bloating and prolonged abdominal pain in symptomatic uncomplicated diverticular disease</td>
<td>0</td>
</tr>
</tbody>
</table>
Diverticular disease of the colon

In DD, probiotics and antibiotics can restore commensal flora and confer health benefits by a variety of mechanisms: a) changing peri-diverticular bacterial flora by reducing colonic transit and stasis of faecal material into diverticula, which then predisposes to bacterial overgrowth; b) Improving mucosal barrier function, by reducing inflammatory cytokine release and localized peri-diverticular low-grade microscopic colitis, that can progress to microperforation and diverticulitis or produce functional changes such as visceral hypersensitivity and smooth muscle hypertrophy (Tursi, 2007b).

While there is no rationale for using any medical treatment, including probiotics or antibiotics, in asymptomatic diverticulosis, in colonic DD probiotics and/or antibiotics, alone or in combination with fiber or mesalazine, could be useful to reduce frequency and intensity of symptoms, to maintain patient symptom free and to prevent acute diverticulitis and complications.

Improvement of symptoms and prevention of recurrences

As far as the efficacy of therapies in reducing symptoms is concerned, a recent meta-analysis showed that the treatment with fiber plus rifaximin provides a significant improvement in symptoms and greater prevalence of symptom-free patients at 1-year compared to fiber alone, with a pooled rate difference (RD) for symptom relief of 29.0% and a number needed to treat (NNT) patients = 3 (Figure 1) (Bianchi M. et al, 2011). In particular, data form the unique long-term double-blind placebo-controlled study showed that 68.9% of patients treated with fiber (Glucomannan 2 g/day) plus rifaximin 400 mg b.i.d for 1 week/month, were symptom-free compared with 39.5% of patients treated with fiber plus placebo at the end of 1-year follow-up (Papi C. et al, 1995). However, it should be taken into account that in this study the difference between treatments was statistically significant starting from 6 months of therapy and that among the 6 considered symptoms, a statistically significant difference emerged only for bloating (at 6 months), lower abdominal pain (at 9 months), and abdominal tenderness (at 12 months), whilst no significant improvement was observed for diarrhoea, upper abdominal pain and tenesmus. Moreover, at 12-month follow-up, symptoms-free patients and those with mild symptoms were arbitrarily grouped together for statistical comparison between the two therapeutic arms. Therefore, it remains unclear how many patients really became asymptomatic following therapy, and whether a difference between asymptomatic (score 0) and symptomatic (score 1) distribution between the two treatment groups did occur. Also the treatment with probiotics, in particular when combined with mesalazine has been proved to be effective in reducing symptoms and maintaining symptom-free remission in colonic DD.

The efficacy of probiotics in colonic DD has been assessed in 8 studies, including only 3 randomised comparative studies, evaluating also the combination of probiotics and anti-inflammatory drugs.

Four studies assessed the efficacy of probiotics in inducing symptom remission and symptomatic DD (Table 1). In the first study, Giaccari et al. followed 79 patients with post-diverticulitis colonic stenosis who received rifaximin 400 mg twice daily for 7 days then two lactobacillus capsules daily for 7 days each month for 12 months (Giaccari S. et al, 1993). At the end of follow-up, 88% remained symptom-free and no patients developed acute diverticulitis or other complications. Another observational study showed that the administration of probiotics \textit{E. coli} strain Nissle (Mutaflor) following an antimicrobials treatment provided a longer length of remission than antimicrobials plus absorbent only (Fric P. et al, 2003). Another uncontrolled study, performed in patients with a recent attack of acute diverticulitis, showed the sum of score of intensity of symptoms, weekly quantified on a quantitative scale, was significantly better in patients treated with polybacterial lysate (\textit{E. coli} and \textit{Proteus vulgaris}) compared with no treatment both after 1 and 3 months (Dughera L. et al, 2004). More recently, a pilot study showed the effectiveness of Lactobacillus paracasei sub. paracasei F19 coupled with fibre in comparison with fibre alone in reducing abdominal symptoms, in particular abdominal pain and bloating, in patients with symptomatic uncomplicated colonic DD, during a follow up of 6 months (Annibale et al, 2011).
Probiotics have been proved also to be effective in preventing symptomatic recurrence of DD (Table 2). An open-label study including 46 patients with previously symptomatic DD, showed that a synbiotic mixture (SCM-III) containing *Lactobacillus acidophilus* and *Bifidobacterium* spp. was effective in preventing recurrence in 68% of patients after 6 months of treatment (Lamiki P. et al 2010). Three other randomised studies showed that probiotics are effective in preventing symptoms recurrence. On this regard, two open randomised studies showed that intermittent treatment with *Lactobacillus casei* (2 cps x 10-14 days / month) or mesalazine 800 mg b.i.d. were equally effective in preventing recurrence in symptomatic uncomplicated DD up to 24 months of follow-up, but also showed that their association was significantly more effective (Tursi A. et al, 2006; Tursi A. et al, 2008). Another comparative study showed that intermittent treatment with high-potency probiotic mixture (VSL#3) for 15 days/month seems to be more effective in preventing symptomatic relapse after an attack of acute uncomplicated diverticulitis of the colon if combined with a pulsed treatment with balsalazide (Tursi et al, 2007c).

**Prevention of acute diverticulitis**

To date, only one randomised, double-blind placebo-
controlled trial assessed the usefulness of therapy in the prevention of acute diverticulitis. In this 1-year follow-up trial all patients received glucomannan (2 g/d) plus rifaximin (400 mg twice a day for 7 days each month) or placebo. The results of this study showed that both regimens were equally effective in preventing acute diverticulitis, which occurred in 2.4% of patients in both study arms (Papi et al, 1995). A recent meta-analysis grouping the results on this study and those of 3 other open randomized trials (comprising a total of 1492 patients) comparing rifaximin plus glucomannan or fiber supplementation vs. glucomannan or fiber alone, reported that rifaximin led to a slight benefit in preventing acute diverticulitis (Bianchi M. et al 2011). In particular, the cumulative data showed that the rate of acute diverticulitis was significantly less frequent in patients treated with rifaximin plus fiber supplementation than with fiber alone (11/970 (1.1%) vs. 20/690 (2.9%); \( P = 0.012 \)), but with a number needed to be treated to prevent an attack of acute diverticulitis in 1 year with the rifaximin plus fiber supplementation regimen of 57 (Figure 2) (Bianchi et al, 2011).

The usefulness of antibiotics in the prevention of acute diverticulitis has been also assessed in a large retrospective study examining 505 patients admitted to the surgical ward form 1967 to 1991 for complications of DD (occlusion, perforation, fistula, bleeding). Non operated patients have been divided in 2 groups. One group included patients with prescription of fiber or bulking agents and antibiotics (Neomycin associated with Bacitracin, Paromomycin or Rifaximin) at the end of hospital period, and the other patients discharged with fiber or bulking agents alone. The authors found that antibiotic treatment was more effective in reducing the prevalence of hospital re-admission (6.3% vs. 12.3%) and operations (13.6% vs. 52.6%) for complications of DD of the colon, compared to treatment with fiber or bulk agents alone (Porta E. et al, 1994).

As far as the usefulness of probiotics in the prevention of acute diverticulitis is concerned, only 1 study was specifically designed to examine this topic. This open-label comparative study with a follow-up of only 3 months examined the efficacy of a polybacterial lysate (\( E. \) coli and \( P. \) vulgaris) compared with no treatment, in patients with a recent attack of acute diverticulitis (Dughera et al, 2004). The study showed that the prevalence of acute diverticulitis in the follow-up was significantly more frequent in patients without treatment compared with that of patients treated with probiotics \([2/43 (4.6\%) \text{ vs. } 5/40 (12.5\%); \ P < 0.05\])

In conclusion, antibiotics and probiotics share a common rationale in the treatment of DD of the colon, restoring the composition of the colonic microflora involved in diverticular and colonic inflammation and related functional changes. However, to date, reliable controlled therapeutic trials and solid scientific evidence for the use of antibiotics and probiotics, in the treatment in the DD of the colon are still lacking. The available data show that both antibiotics and probiotics can be useful in improving symptoms in most patients. On the contrary, the use of antibiotics in preventing acute diverticulitis seems to be limited, and probably should be restricted to the patients with symptomatic and complicated DD. Data on the usefulness of probiotics in the long term prevention of diverticulitis are still lacking.

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![FIGURE 2. Pooled Rate Difference (95% CI) for complication rate (acute diverticulitis) in at the end of 1-year follow-up in prospective randomised trials using fiber plus rifaximin vs. fiber alone, showing a significant benefit in favour of rifaximin (1.1 vs. 2.9%) but with a number needed to treat patients = 57 (29).](image-url)


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