

Prevention and Conservative Therapy of Diverticular Disease

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Keywords

Diverticulitis · Diverticular disease · Antibiotics · Mesalamine · Mesalazine · Dietary fiber

Summary

Background: Diverticular disease is a common problem. Prevention and treatment of complications depend on the stage of the disease. Lifestyle modifications are suitable preventive measures, aiming to reduce obesity and to balance the diet with a high amount of fiber and a low amount of meat. However, evidence to guide the pharmacological treatment of diverticular disease and diverticulitis is limited. **Methods:** Literature review. **Results:** Antibiotics are not proven to be effective in patients with uncomplicated diverticulitis and without further risk factors; neither do they improve treatment nor prevent complications. Mesalazine might have an effect on pain relief in diverticular disease even though it has no significant effect on the outcome of diverticulitis. In complicated diverticulitis, inpatient treatment including antibiotics is mandatory. **Conclusion:** Evidence for the treatment of diverticular disease is limited. Further research is needed.

Introduction

Diverticulosis and diverticular disease is a common issue in daily clinical practice. Diverticulosis is age-related and mainly affects a population above 60 years of age. One third of all persons with asymptomatic diverticulosis will at one point develop diverticular disease with symptoms such as pain in the lower left abdomen. 5% will also develop complications like abscess or perforation. Despite the high frequency, evidence-based pharmacotherapy

is limited. Various classifications [1, 2] of diverticular disease are in use, resulting in studies which are difficult to compare. We prefer the new classification of diverticular disease proposed by the German guideline on diverticular disease [3, 4].

Current Evidence

Antibiotics

Presuming that diverticulitis is a bacterial infection due to the obstruction of a diverticular collum [5], different guidelines have been advising the use of antibiotics so far, even in uncomplicated diverticulitis [6, 7]. However, new studies question such recommendations [8].

Data from Sweden demonstrated a good outcome in mild diverticulitis treated non-pharmacologically. This retrospective study compared antibiotic therapy (intravenous cephalosporin and metronidazole) with intravenous fluid therapy alone (n = 118 vs. n = 193) [9]. The decision to add antibiotics was based on clinical symptoms such as fever as well as blood tests and computed tomography (CT) scan. Patients treated with antibiotics had significantly higher levels of C-reactive protein (CRP) or white blood cell (WBC) count. Furthermore, in this group, fever was more common and a higher proportion of patients were classified as severe assessed by CT scan. The outcome of both groups was comparable. 3% of the patients treated with antibiotics underwent surgery compared to none in the group following fluid-only regimen. 7 patients (4%) in the fluid-only group became in need of rescue therapy with antibiotics due to aggravating symptoms. Patients treated with antibiotics had a longer hospital stay (5 vs. 3 days). Further occurrence of diverticulitis was not avoided by antibiotic therapy: During an average follow-up of 30 months, 29% of the patients in the antibiotic group developed diverticulitis or complications resulting in surgery compared to 28% in the fluid-only group.

The same study group conducted a large prospective randomized controlled multicenter trial comprising 623 subjects. Only patients with left-sided mild diverticulitis confirmed by CT scan

were included. Patients with fever, peritonitis, sepsis, immunosuppressive therapy, and/or signs of complications on the CT scan (abscess, fistula, or free air) were excluded. 314 patients were randomized for an antibiotic treatment, and 309 patients were treated with fluid only. The two groups differed in the rate of previous incidents of diverticulitis (44.8% in the antibiotic group vs. 35.6% in the fluid-only group; $p = 0.02$). This study proved that antibiotic therapy is not superior to fluid-only therapy in preventing complications. There were no significant differences in the duration of hospital stay, the risk of perforation, or the need of hospital readmission in the two groups. Compared to 1 patient treated with antibiotics ($p = 0.8$), 3 patients treated by fluids only developed an abscess. Within 1 year, 16% had a recurrence of diverticulitis in both groups irrespective of the therapy [10].

A case-control study in patients with mild diverticulitis from the Netherlands compared 191 patients treated without antibiotics with 81 patients treated by antibiotics. The results were comparable in both groups [11].

Rifaximin

Rifaximin is a nonabsorbed antibiotic agent. Even in affected colonic mucosa only 1% will be absorbed. Rifaximin is approved for the treatment of traveler's diarrhea and hepatic encephalopathy by the German authorities. It is effective against gram-positive and gram-negative bacteria.

The prevention of diverticulitis with rifaximin was investigated in a meta-analysis comprising data from four studies encompassing 1,660 patients. The diagnosis of diverticulosis was made by colon contrast enema or colonoscopy. Controlled studies comparing treatment with fibers only or treatment with fibers and rifaximin 400 mg were included. The dosing regimen was twice daily over a 7-day period every month and a total period of 1 year. The primary outcome was pain in the lower abdomen indicating the development of diverticular disease. After 12 months, 34.9% in the rifaximin group had developed pain, compared to 64.0% in the control group, resulting in a number needed to treat (NNT) of 3 for pain in diverticular disease. Diverticulitis, though, could not be prevented. 20 of 690 patients in the control group developed a diverticulitis compared to 10 of 970 patients in the rifaximin group, resulting in an NNT of 59 for diverticulitis [12]. The authors concluded that rifaximin possibly controls or conceals the symptoms but does not prevent diverticulitis. However, the weakness of this meta-analysis is a result of the low scientific quality of the included studies. Only one study was placebo-controlled. Dosing regimens as well as secondary outcomes were generally variable, resulting in a high heterogeneity of the included studies.

Mesalazine

Aminosalicic acids inhibit multiple signal pathways. Cytokines and second messengers like interleukins (IL-1), tumor necrosis factor (TNF) alpha, necrosis factor $\text{NF-}\kappa\text{B}$, leukotrienes, prostaglandins, and free radicals are suppressed. Functions of both B and T lymphocytes are also influenced. The effects of aminosalicic acid on diverticulitis were examined in different studies.

In a German prospective randomized multicenter study the effect of mesalazine in uncomplicated diverticulitis was studied. 117 patients with pain in the left lower quadrant of the abdomen with at least four diverticula in the colon were randomized. The patients were treated either with mesalazine, 1,000 mg 3 times/day ($n = 56$), or placebo ($n = 61$). The intention-to-treat analysis did not result in any difference; however, mesalazine reduced pain significantly, as shown by per protocol analysis [13].

The American multicenter DIVA study examined the effect of mesalazine alone or mesalazine in combination with probiotics on acute diverticulitis over a period of 12 weeks. The study design was tripartite. 117 patients with acute diverticulitis were randomized into 3 groups: placebo (41 patients), mesalazine 2.4 g/day (40 patients), and mesalazine 2.4 g/day in combination with *Bifidobacterium infantis* 35624 (36 patients). Initially, the patients were treated with antibiotics together with mesalazine or placebo. After terminating the antibiotic therapy, probiotics were added to one half of the patients already treated with mesalazine. After a follow-up of 1 year, there was a better symptom control with mesalazine. The probiotics did not show an additional effect. The recurrence rate was low and similar in all of the three groups [14].

An Italian study compared intermittent treatment with mesalazine and placebo regarding the prevention of recurrent diverticulitis. 92 patients were treated up to 5 years after acute diverticulitis with either 800 mg mesalazine twice a day (45 patients) or placebo (47 patients). The primary endpoint was the recurrence after 6, 12, 18, and 24 months. After 12 months no difference was seen ($5/45 = 11\%$ recurrence rate in the mesalazine group; $6/47 = 13\%$ in the placebo group). After 24 months mesalazine was superior ($6/45 = 13\%$ recurrence rate in the mesalazine group; $13/47 = 28\%$ in the placebo group) [15].

Another Italian study compared the effect of mesalazine and rifaximin on the recurrence of diverticulitis. Of 130 prospectively assessed patients who had recovered from acute uncomplicated diverticulitis, 59 received mesalazine 1.6 g/day and 52 rifaximin 800 mg/day for a 7-day period every month. Follow-up included clinical and endoscopic assessment after 6, 12, and 24 months. The mesalazine group had a lower recurrence rate as well as a better endoscopic and histological outcome compared to the rifaximin group [16].

Two double-blinded and placebo-controlled studies concerning the prevention of recurring diverticular disease (PREVENT I and PREVENT II) showed disappointing preliminary results [17].

Probiotics

In some smaller studies, the effect of probiotics in the prevention of diverticulitis was investigated. A very small open study with 15 participants investigated symptoms and recurrence rates under treatment with *Escherichia coli* Nissle after uncomplicated diverticulitis. Patients treated with *E. coli* Nissle had a longer recurrence-free interval by 2.4 months [18].

The effect of *Lactobacillus casei* in addition to a therapy with mesalazine was investigated in 90 patients with acute uncomplicated diverticulitis. Remission had been obtained with rifaximin 800 mg/day plus mesalazine 2.4 g/day for 10 days in all included

patients. This was followed by either mesalazine 1.6 g/day, or *L. casei*, or both substances for 8 weeks. Follow-up was conducted over 12 weeks, and 85 patients could be analyzed. By this time, 75 patients were free of symptoms (23/27 in the mesalazine group; 23/29 in the *L. casei* group; 29/29 in the group treated with both substances). The authors concluded that both substances may have some effect on symptom relief and prevent a recurrence [19]. However, the small number of patients studied, the lack of placebo control, and the short follow-up are the limits of this study.

Prevention through Dietary Fibers and Diet

The observation that diverticular disease is very common in the western world and almost unknown in Africa led to the hypothesis that a low-fiber diet facilitates diverticular disease. It was supposed that low fiber intake causes obstipation, consequently leading to high-pressure zones in the bowel in which diverticula develop [20]. A recent cross-sectional study with 2,014 patients questions the hypothesis of any effect that fibers might have on the prevention of diverticulosis. 878 patients with diverticulosis were compared to 1,226 patients without. The intake of fibers was retrospectively evaluated in the last year before the colonoscopy was performed. In this study, a high-fiber diet did not reduce the prevalence of diverticulosis [21].

Numerous other studies, however, accounted for a significant effect of fibers to prevent diverticulosis. A study from Great Britain showed a reduced risk for vegetarians to be admitted to a hospital or to die related to diverticulitis. This epidemiological study included 47,033 men and women. 14,459 (33%) declared to be vegetarian. The risk for hospital admission due to diverticulosis was 4.4% for non-vegetarians compared with 3.0% for vegetarians. People with a fiber intake of 25.5 g/day had a 41% lower risk compared to people with a fiber intake of less than 14 g/day [22].

A prospective study from Sweden showed that obesity is associated with a higher risk of complicated diverticular disease. 7,494 men from Gothenburg were included in the study. They were followed for up to 28 years. 112 (1.5%) men were admitted to hospital with diverticulitis. The lowest risk was found in men with a low body mass index (BMI) between 20 and 22.5 kg/m², while the risk increased consequently with the BMI. Men with a BMI above 30 kg/m² were exposed to a hazard ratio of 4.4 [23].

In another Swedish study 36,592 women were included. A questionnaire evaluated BMI, physical activity, smoking, and other lifestyle-associated risk factors. During a follow-up of 12 years, 626 women underwent their first-time hospital admission for diverticulitis. 2 women with diverticulitis were listed in the register of death. A multivariate analysis showed a 29% increased risk for women with a BMI of 25–29.9 kg/m². For women with a BMI of 30 kg/m² the risk was 1.33 higher than in women with a BMI between 20 and 24.99 kg/m². Low physical activity below 30 min/day showed a 41% increased risk compared to women with a daily activity of more than 30 min/day [24].

Recommendations for Conservative Therapy

In *stage 0* (asymptomatic diverticulosis), a high-fiber and vegetarian diet is recommended for the prevention of diverticulitis. Physical activity and normal body weight is regarded as beneficial. A fiber-rich diet also prevents cardiovascular disease, diabetes, and cancer and is therefore widely recommended [25].

In *stage 1a* (uncomplicated diverticulitis), administration of fluids without specific therapy might be sufficient when no individual risk factors such as immunosuppression, hypertension, chronic kidney diseases, and allergic predisposition are present.

Pain should be treated with spasmolytic agents and analgesic medication. Mesalazine may also be helpful for pain reduction as well as fasting. Nonsteroidal antirheumatic drugs should be avoided due to the risk of recurrence [11] or perforation [26]. In patients not treated with antibiotics close clinical control is mandatory. In the case of risk factors the patient should be admitted to a hospital.

In *stage 1b* (diverticulitis with phlegmonous peridiverticulitis) or *stage 2a* (concealed perforation, small abscess ≤ 1 cm), antibiotic treatment is regarded as indicated. Antibiotic therapy should also be considered in the presence of highly elevated inflammatory markers like CRP, WBC count, or fever above 38.5 °C. Usually, microbiological isolates contain anaerobes such as *Bacteroides*, *Peptostreptococcus*, *Clostridium*, and *Fusobacterium* species followed by gram-negative aerobes, especially *E. coli*. Less common are gram-positive bacteria such as *Streptococcus* [5]. The antibiotic therapy should be targeted at these bacteria. Therefore, a therapy with quinolone in combination with metronidazole, alternatively amoxicillin with beta-lactamase inhibitor, or a cephalosporin of the third generation is recommended. Severely ill patients should be treated with intravenous antibiotics, especially if oral intake is not possible. All other patients can be treated with oral agents. In this case, agents with good bioavailability like quinolone or metronidazole should be given. In case of complication, additional intervention (drainage, operation) in *stage 2b* (macro-abscess) or surgery in *stage 2c* (peritonitis) is paramount.

Conservative treatment in *stage 3* is difficult. Therapy of SUDD (symptomatic uncomplicated diverticular disease *stage 3a*) should be differentiated from the secondary prevention of relapsing diverticulitis without complications (*stage 3b*) or with complications (*stage 3c*). Data in this field are insufficient. Therefore, an evidence-based recommendation is not possible for the long-term prevention and treatment of chronic diverticulitis. An irritable bowel syndrome as a result of an acute diverticulitis should be excluded.

Disclosure Statement

The authors have no conflict of interest regarding the covered subject.

