Outcome and treatment of acute diverticulitis
Ünlü, Çağdaş

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Systematic review of medical therapy to prevent recurrent diverticulitis.

Ünlü Ç, Daniels L, Vrouenraets BC, Boermeester MA.

ABSTRACT

Aim and background
One of today’s controversies remains the prevention of recurrent diverticulitis. Current guidelines advise a conservative approach, based on studies showing low recurrence rates and a high operative morbidity and mortality. Conservative measures in prevention recurrence are dietary advises and medical therapies, including probiotics and 5-aminosalicylic acid.

Objectives
The aim of this systematic review is to assess whether medical or dietary therapies can prevent recurrent diverticulitis after a primary episode of acute diverticulitis. Method and search strategy We searched different databases for papers published between January 1966 and January 2011. Study selection Clinical studies were eligible for inclusion if they assessed the prevention of recurrent diverticulitis with a medical or dietary therapy. Exclusion criteria were studies without a control group.

Results
Three randomized controlled trials (RCT), all with a Jadad quality score of 2 out of 5, were included in this systematic review. Mesalazine results in significantly less disease recurrence and fewer symptoms after an acute episode. The use of probiotics decreases symptoms but does not reduce recurrence. No difference in effect is seen when Balsalazide is added to probiotics compared to probiotics only. No relevant studies on dietary therapy/advices or antibiotics for prevention of recurrent diverticulitis were found.

Conclusion
The evidence that supports medical therapy to prevent recurrent diverticulitis is of poor quality. Treatment with 5-aminosalicylic acid seems promising. Based on current data, no recommendation of any non-operative relapse prevention therapy for diverticular disease can be made.
INTRODUCTION

One of today’s controversies remains the management of recurrent diverticulitis. Until recently the guideline was based on the assumption that recurrent episodes (2 or more) of diverticulitis will lead to complicated diverticulitis and higher mortality [1]. The data used to support this assumption were based on only a few small older studies that reported recurrence rates of more than 40 % after one episode of diverticulitis with complications occurring in 30–60 % of patients [2, 3]. Nowadays, due to advances in accuracy of diagnostic modalities and modified surgical techniques, both management and outcome of diverticulitis have changed. Current guidelines advise a more conservative approach [4], based on several more recent studies, showing lower recurrence rates [5, 6]. Moreover, multiple episodes of diverticulitis do not seem to be associated with increased mortality or an increased risk of complicated diverticulitis. The overall mortality rate for patients with a prior history of diverticulitis was 2.5 %, comparing favourably with a mortality rate of 10 % for patients with a first presentation of complicated diverticulitis [5]. In addition, 78% of patients with perforated diverticulitis had no prior history of diverticulitis [7]. Elective sigmoid resection for diverticulitis is associated with risks of mortality and colostomy as high as 2.3 % and 14.2 %, respectively [8–10]. Furthermore, the risk of recurrent diverticulitis is not eliminated after sigmoid resection with recurrence rates between 2.6 % and 10.4 % [10]. For all these reasons, conservative treatment has become the preferred choice after an episode of diverticulitis. Conservative measures in prevention of diverticulitis recurrence are dietary advises and medical therapies, including the use of probiotics and 5-aminosalicylic acid. However, the value of these conservative measures is unclear. A systematic review of these dietary and medical management to prevent recurrent diverticulitis is given.

METHODS

Systematic review
Literature search

Two authors (CU, LD) performed a literature search to identify studies investigating the effectiveness of a medical therapy in human subjects to prevent recurrence of diverticulitis. We searched MEDLINE databases for papers published between January 1966 and January 2011, using the following keywords: “Diverticulitis, Colonic” [Mesh] and “Recurrence” [Mesh] and “Therapeutics” [Mesh]. EMBASE database was searched with the following terms: diverticulitis and recurrence and therapeutics. CINAHL database was also checked for relevant studies with the following keywords: (“Diverticulitis“
and “Recurrence” and “Therapy”). The Cochrane database of Systematic Reviews was searched with the following words: Diverticular disease and recurrence.

**Validity assessment**

After identifying relevant titles, all abstracts were read and eligible articles were retrieved. A manual cross-reference search of the bibliographies of relevant articles was performed to identify other studies not found in the search. Only clinical studies published in English were included. No unpublished data were included. A full search strategy is available at request. Two authors independently assessed the methodological quality of the articles using the Jadad score and the checklist of the Cochrane collaboration. The Jadad score is a well-known instrument assigning a numerical score between 0 and 5 to each study, reflecting its quality (0 indicating poor quality and 5 high quality) [11].

**Definition**

In order to be able to reliably compare the data, uncomplicated diverticular disease was defined as symptomatic disease associated with colonic diverticula. This is associated with mild symptoms, usually abdominal pain and/or change in bowel habit, but without clinical features of inflammation. Diverticulosis is asymptomatic colonic diverticula. Diverticulitis is complicated diverticular disease with clinical symptoms and evidence of inflammation. Recurrent disease is characterized by the reappearance of these symptoms. Complicated diverticulitis is perforation, abscess, fistula, bleeding or stricture/obstruction, usually needing surgical or percutaneous intervention. Medical treatment is defined as any non-operative relapse prevention therapy. The following were found, dietary fibre therapy, antibiotics, probiotics and 5-aminosalicylic acid. Inclusion and exclusion criteria

**Types of studies**

Clinical studies were eligible for inclusion if they assessed the medical prevention of recurrent diverticulitis. The following exclusion criteria were used for study selection: non-English literature, studies without comparison with a control group and studies that (also) included patients who were operated because of an episode of complicated diverticulitis.

**Types of participants**

Patients of 18 years or older diagnosed with diverticulitis were included. The diagnosis of diverticular disease had to be confirmed by radiologic evidence (Barium enema or CT scan) or colonoscopy. A diagnosis of diverticulitis on clinical grounds was allowed.

**Types of interventions**
All studies (prospective, retrospective, case-controlled, cohort) that assessed medical treatment to prevent recurrence were searched.

Types of outcome measures
Primary endpoint parameters for inclusion were the occurrence of recurrent diverticulitis.

RESULTS

Systematic review
The first search resulted in a combined total of 84 articles. After reviewing the abstracts, 12 articles were retrieved for more detailed information. Only three articles met our inclusion criteria and were used for this systematic review (Fig. 1).

Dietary fibre
No dietary fibre study met the inclusion criteria of this systematic review.

5-Aminosalicylic acid and probiotics
In a study in 2002, a total of 218 consecutive patients (131 males, 87 females age 64.3 years, range 51–79) with recurrent diverticulitis, after two attacks of diverticulitis in the
same year, were monitored [12]. Diagnosis of diverticulitis, defined as inflammation and/or infection associated with diverticula of the colon, was done by colonoscopy (123 patients) or by double contrast X-ray study of the colon (95 patients), by the presence of abdominal pain, bowel disorders and/or fever and leukocytosis.

The intensity of the symptoms and bowel habits were quantified with a scale from 0 to 4. After assessment of the acute diverticulitis attacks, patients were randomly assigned to two different groups, after giving informed consent:

Group A (109 patients): rifaximin 400 mg bid plus mesalazine 800 mg tid for 7 days, followed by rifaximin 400 mg bid plus mesalazine 800 mg bid for 7 days every month;

Group B (109 patients): rifaximin 400 mg bid for 7 days, followed by rifaximin 400 mg bid for 7 days every month.

Colonoscopy was performed after 3, 6 and 12 months of therapy. At end of follow-up, 193 patients were fully compliant to therapy. Recurrence of diverticulitis was evaluated on the basis of clinical and endoscopic examination. Neither diagram to show enrolment and randomization process nor sample size calculation were given. Severity of symptoms and bowel habits improved significantly in group A compared to group B, and symptomatic recurrence of diverticulitis occurred significantly less in group A (Table 1). In 2004, the effect of probiotics on recurrent diverticulitis has been compared to no treatment after an acute attack [13]. The study was carried out on 83 consecutive patients (31 males, 52 females; mean age 64.3, range 49–78) suffering from recurrent diverticulitis and with at least two attacks in the previous year. The diagnosis of diverticular disease was performed by colonoscopy or double contrast X-ray study, or both. The diagnosis of diverticulitis was based on clinical grounds. All patients were treated during the acute period of diverticulitis with oral rifaximin or with intravenous ciprofloxacin for 7–14 days, until the complete remission of laboratory findings and symptoms improvement. After clinical recovery, 43 patients were randomly assigned to receive (group A) an oral polybacterial lysate suspension containing 80x10^9 Escherichia coli (strains 01, 02, 055 and 0111) and 1x10^9 Proteus vulgaris (Colifagina S). The study medication was administered as a twice-daily 5 ml oral medication for 2 weeks every month, within 3 months after an acute attack. The other patients were the control group. All patients received adequate dietary rules. The patients were to fill in a score-point schedule for abdominal symptoms and the intensity of symptoms was quantified on a scale from 0 to 3. The diagnostic criteria for recurrence were the same as for inclusion. Seven out of the total 83 patients (8.4 %) had a recurrence within the 3 months of the study. Two patients belonged to group A (4.6 %) and 5 to group B (12.5 %). The authors state that the difference between the recurrence rates in the two groups was significant
Using a Student's t test for paired data. However, in statistical comparison of proportions a chi-square test should be used. The chi-square test of the difference is not significant (P=0.28). Complete results are summarized in Table 2. In a recent small study by Tursi et al., 30 consecutive patients (19 males, 11 females; mean age 60 years, range 47–75 years) affected by uncomplicated diverticulitis of the colon were monitored [14]. The aim was to investigate whether a combination of Balsalazide and/or VSL#3, a probiotic mixture containing several billions of different bacterial strains (mainly Lactobacillus and Bifidobacteria), is effective in preventing diverticulitis recurrence. After obtaining remission, the patients were randomly assigned to: group A, Balsalazide 2.25 g daily for 10 days every month plus VSL#3 450 billions per day for 15 days every month and group B, VSL#3 alone 450 billions per day for 15 days every month. Primary end-point was remission throughout a 12-month follow-up. Diverticulitis recurrence was evaluated on the basis of clinical and/or endoscopic examination. Secondary end-points were overall scores at the end of the follow-up and the effect on symptom score component. The intensity of the symptoms was quantified on a scale of 0–10 according to worsening of symptoms.

In Table 3, the results at the end of follow-up are summarized. No side effects were recorded throughout the follow-up in both groups. The authors have concluded that the combination of probiotic/Balsalazide is better than probiotic treatment alone in the prevention of recurrent diverticulitis. This conclusion is inappropriate since no significant difference was found. Antibiotics No study evaluating the use of antibiotics meeting the inclusion criteria of this systematic review was found. Quality assessment of the included studies This assessment is shown in Table 4 and demonstrates the moderate quality of the available evidence (Jadad score 2 out of 5).

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<thead>
<tr>
<th>Table 1 Result of Tursi et al (12). Significant less recurrence in the Mesalazine group.</th>
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<tr>
<td>Group A (Mesalazine + Rifaximin) n=104 After 12 months</td>
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<td>Regular bowel habits</td>
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<td>Symptom free</td>
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<td>Recurrence of diverticulitis</td>
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<th>Table 2 Result of Tursi et al (13). No significant difference between the Balsalazide and the VSL3# group.</th>
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<tr>
<td>Group A (Balsalazide + VSL#3) after 12 month, n=15</td>
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<tr>
<td>Recurrent diverticulitis</td>
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<td>Symptom free</td>
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New medical treatment options have been introduced to lower recurrence rates after an episode of diverticulitis [5, 6]. In this systematic review, we present an overview of medical therapy options for the prevention of recurrence of diverticulitis. With 5-aminosalicylic acid (mesalazine) significant less disease recurrence and fewer symptoms were found [12]. Probiotics decreased symptoms without an effect on diverticulitis recur-
ence [13]. No effect was seen when Balsalazide was added to probiotics compared to probiotics only [14]. Dietary therapy for uncomplicated diverticular disease is based on the theory that decreased fibre intake may result in decreased intestinal contents and decreased size of the lumen. This results into increased pressure on the wall which leads to the formation of diverticula at the weakest point in the wall, the so-called vasa recta being the site of penetration by blood vessels [15]. Dietary therapy will increase stool transit time and decrease pressure and hypothetical therefore may prevent recurrence.

In our literature search, no dietary fibre study was found enrolling patients with acute diverticulitis. A study of Hyland et al. [16] enrolled 100 patients with acute diverticular disease of which 25 patients had been operated. It is not clear from that publication whether patients had diverticulitis or symptomatic diverticular disease, suggesting a mixed study population. Patients were reviewed 5 to 7 years after admission and 91% of the patients on high fibre diet had remained symptom-free during that period. It was concluded that high fibre diet may have a protective role and prevent further complications. The last few decades, the pathogenesis theory of diverticular disease has changed [17]. It has been suggested that the type of inflammation is similar to that occurring in chronic idiopathic inflammatory bowel disease, suggesting that patients may benefit from anti-inflammatory medication [18–20]. Some studies have evaluated this theory [21–24]. All studies included patients with symptomatic uncomplicated diverticular disease and excluded patients with diverticulitis. These studies reveal that mesalazine may improve symptoms and bowel habits significantly and maybe a new medical therapy for diverticular disease.

Balsalazide is a pro-drug needing bacterial action to liberate the active 5-ASA molecules. Thus far, one low quality study has evaluated the effect of Balsalazide on recurrence after an episode of acute diverticulitis and showed no advantage [14].

The theory that inflammation is chronic in the formation of diverticulitis also raises the hypothesis that probiotics could be effective by stimulating immunologic processes that restore an altered microflora of the colon. This alteration of the microbial environment could result in a lowgrade colitis, which has then a potential to progress to acute diverticulitis [25–28]. There is only one comparative study studying the effect of probiotics on recurrence of diverticulitis [13]. This low quality study (Jadad <3) has shown no clear benefit of probiotics. Antibiotics are commonly used in the treatment of inflammatory complications of diverticular disease. Apart from recommendations in several guidelines there is no evidence mandating the routine use of antibiotics in mild diverticulitis. Antibiotics have also been studied for their effect on prevention of recurrent diverticulitis. Several clinical studies suggest a role of long-term cyclic administration of the non-absorbable antibiotic drug rifaximin in the management of symptomatic uncomplicated diverticular disease of the colon [29–32]. Only one study was found that studied the cyclic administration of rifaximin to prevent recurrence of lower rate of
operations of 73 % in the antibiotic group. The proportion of patients with primary or recurrent diverticulitis is not given, thereby prohibiting definitive conclusions on the effectiveness of rifaximin to prevent recurrence of diverticulitis.

Another possible bias is that all studies included patients on mostly clinical grounds. It is known that the clinical diagnosis of acute diverticulitis is in only 43–68% of the patients correct [33, 34]. This could be a reason for the difference in recurrence rates (12 %, 13 % vs 18 %) in the three studies. An explanation for this variance can be the clinical interobserver variation of the diagnosis diverticulitis.

In conclusion, the evidence of medical treatment to prevent recurrence of diverticulitis is scarce. Studies are of poor quality. It is too early to promote the medical options such as mesalazine, probiotics or antibiotics. Future patients could benefit from the results of prospective trials [35]. Until then, the treatment of choice after a first episode of acute diverticulitis remains a wait and see policy.
References

35. Phase III, randomised double blind dose–response stratified placebo controlled study of evaluating the safety and efficacy of SPD476 versus placebo over 104 weeks in the prevention of recurrence of diverticulitis (PREVENT 2). Clinical.Trials.gov Identifier (http://www.clinicaltrials.gov): NCT00545103. Principal Investigator: Raskin JB, University of Miami Miller School of Medicine, USA