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Recent advances in the treatment of colonic diverticular disease and prevention of acute diverticulitis

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Abstract

The incidence of diverticulosis and diverticular disease of the colon is increasing worldwide. Although the majority of patients remains asymptomatic long-life, the prevalence of diverticular disease of the colon, including acute diverticulitis, is substantial and is becoming a significant burden on National Health Systems in terms of direct and indirect costs. Focus is now being drawn on identifying the correct therapeutic approach by testing various treatments. Fiber, non-absorbable antibiotics and probiotics seem to be effective in treating symptomatic and uncomplicated patients, and 5-aminosalicylic acid might help prevent acute diverticulitis. Unfortunately, robust evidence on the effectiveness of a medical strategy to prevent acute diverticulitis recurrence is still lacking. We herein provide a concise review on the effectiveness and future perspectives of these treatments.

Keywords Diverticular disease, 5-aminosalicylic acid, acute diverticulitis, high-fiber diet, nonabsorbable antibiotics, probiotics

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Introduction

Diverticular disease (DD) is characterized by the presence of sac-like protrusions (diverticula) which form when colonic mucosa and submucosa herniate through defects in the muscle layer of the colon wall [1]. DD is commonly found in developed countries, slightly more frequently in the USA than in Europe, and is a rare condition in Africa. However, some indication is available that the prevalence of colonic diverticulosis is increasing throughout the world, probably because of changes in lifestyle [1]. Although most people with colonic diverticulosis remain asymptomatic about 20% of patients will develop symptoms, developing so-called DD [2], of whom 15% will ultimately develop diverticulitis [3,4], with or without complications (Fig. 1).

Terminology

To aid in the discussion about DD, it is important to first define some key terms, including DD, diverticulosis and symptomatic uncomplicated DD (SUDD). According to currently accepted definitions, the following terminology is used in describing different scenarios in which diverticula may be detected.

'Diverticulosis' is merely the presence of colonic diverticula; these may, or may not, be symptomatic or complicated.

'DD' is defined as clinically significant and symptomatic diverticulosis; this may be due to true diverticulitis or to other less well-understood manifestations (e.g. visceral hypersensitivity in the absence of verifiable inflammation). The overarching term DD implies that the pathologic lesion (diverticulosis) rises to the level of an illness.

'SUDD' is a subtype of DD in which there are persistent abdominal symptoms attributed to diverticula in the absence of macroscopically overt colitis or diverticulitis.

'Diverticulitis' is the macroscopic inflammation of diverticula with related acute or chronic complications. Diverticulitis can be uncomplicated or complicated. It is uncomplicated when computed tomography (CT) shows colonic wall thickening with fat stranding, while it is complicated when CT demonstrates complicating features of abscess, peritonitis, obstruction, fistulas or hemorrhage.

'Segmental colitis associated with diverticulosis (SCAD)' is a unique form of inflammation that occurs in areas marked by diverticulosis. Endoscopic and histological characteristics describe it as a forerunner of inflammatory bowel disease (IBD).

Clinical picture of DD

Clinical classification of DD is still currently based on the 1999 EAES (European Association for Endoscopic Surgery)

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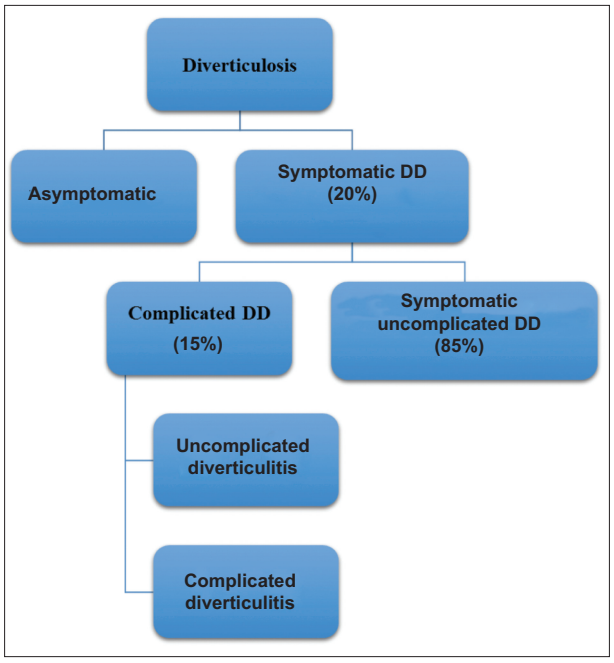

Figure 1 Classification of diverticular disease of the colon
DD, diverticular disease

criteria, which subdivided DD as SUDD, recurrent symptomatic disease and complicated disease [5]. SUDD is characterized by nonspecific attacks of abdominal pain without evidence of an inflammatory process. This pain is typically colicky in nature, but can be constant, and is often relieved by passing flatus or having a bowel movement. Bloating and changes in bowel habits also can occur due to bacterial overgrowth, and constipation is more common than diarrhea. Fullness or tenderness in the left lower quadrant, or occasionally a tender palpable loop of the sigmoid colon, is often discovered on physical examination. Recurrent symptomatic disease is associated with the recurrence of the symptoms described above, and it may occur several times per year. As recently underlined, these symptoms may resemble irritable bowel syndrome (IBS) [6]. Moreover, it has been recently described that IBS occurs 4.7-fold more likely in patients after an episode of acute diverticulitis than controls. Several factors seem to explain persistence of symptoms in those patients, such as significant attenuation in serotonin-transporter expression [7], increased neuropeptide expression in colonic mucosa [8], and persistence of low-grade inflammation [9]. Hence, in this way, it seems to be appropriate to speak of IBS-like symptoms rather than IBS in those patients. On the contrary, it may be quite difficult to differentiate SUDD from IBS. Clinical and laboratory parameters may be useful. Cuomo *et al* recently found that only a minority of DD patients (10%) fulfilled the criteria for IBS diagnosis and that abdominal pain >24 h was more prevalent in SUDD than in IBS patients (P<0.01). It was also demonstrated that, compared with IBS, DD patients had more episodes of pain lasting 24 h requiring medical attention (P<0.01) [10]. More recently, we investigated 72 patients suffering from abdominal pain with diverticula identified on colonoscopy, of whom 42 were classified as having SUDD (abdominal pain for at least 24 consecutive h in the left lower abdomen), and 30 were classified as having IBS-like symptoms fulfilling Rome III criteria. All patients underwent fecal calprotectin (FC) determination and it was found that FC levels were elevated in 64.3% of SUDD patients and in none of the patients in the IBS-like group (P<0.0001). Moreover, the severity of the abdominal pain and the FC score correlated significantly in SUDD patients (P=0.0015) [11]. FC is particularly useful in this setting, because raised FC may be detected in SUDD, acute diverticulitis and SCAD but not in IBS. Hence, the characteristic of abdominal pain (left lower quadrant pain lasting >24 h), and the detection of raised FC are very useful in achieving a correct differential diagnosis between IBS and DD in a patient with diverticulosis of the colon [12].

The development of inflammation in these diverticula results in acute diverticulitis. It has been suggested that in the same way, obstruction by fecal material causes appendicitis, that fecal matter becomes trapped in the diverticula and as a result, low-grade inflammation develops due to abrasion of the mucosa, allowing access of fecal microbiota to the lamina propria, leading to acute inflammation of the mucosa, which usually begins at the apex of the sac [13,14]. This can be associated with acute inflammation of the mesenteric and pericolic fat with the formation of a diverticular abscess. Another postulated mechanism for the development of acute diverticulitis is a micro-perforation at the fundus of the diverticulum leading to inflammation [15].

Acute diverticulitis of the colon represents a significant burden for National Health Systems so far, in terms of direct and indirect costs [16]. Moreover, this disease seems to relapse more frequently than previously thought. In fact, a recent study found that overall disease relapse during a 10-year follow up is up to 40% [17]. Until recently the guideline was based on the assumption that recurrent episodes (two or more) of diverticulitis will lead to complicated diverticulitis and higher mortality [18]. However, 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 favorably with a mortality rate of 10% for patients with a first presentation of complicated diverticulitis [19]. In addition, 78% of patients with perforated diverticulitis had no prior history of diverticulitis [20]. Elective sigmoid resection for diverticulitis is associated with risks of mortality and colostomy as high as 2.3% and 14.2% respectively [21-23]. Furthermore, the risk of recurrent diverticulitis is not eliminated after sigmoid resection, with recurrence rates between 2.6% and 10.4%. In this way, the American Society of Colon and Rectal Surgeons revised their recommendations in 2006 and recommended an individualized approach to patients after an attack of acute diverticulitis [24].

Medical treatment of diverticular disease

SUDD

Fiber

According to current WGO Guidelines, many clinicians advise spasmolytics and a high-fiber diet or fiber supplementation, which

still represent the first-line treatment for SUDD [25]. However, a recent systematic review found that high-quality evidence for a high-fiber diet in the treatment of DD is lacking, and most recommendations are based on inconsistent level 2 and mostly level 3 evidence [26]. Only three randomized, placebo-controlled trials of adequate quality were identified, giving contradictory results [27,28]. This systematic review did not found a significant difference between soluble versus insoluble fiber. Only one randomized, placebo-controlled study compared insoluble (bran, 6.99 g/day) with soluble fiber (ispaghula 9.04 g/day) and placebo (2.34 g/day), taken for 16 weeks. There were no significant differences in pain, lower bowel symptoms or total symptom scores taking crisp bread, ispaghula drink and placebo. Surprisingly, Peery *et al* recently found that high intake of soluble fiber had a higher risk of diverticulosis occurrence (P=0.038) [29]. Nevertheless, a high-fiber diet is still recommended. Adequate quality controlled studies in using fiber in such patients are reported in Table 1.

Antibiotics

Since 1992, the use of rifaximin has been investigated in the treatment of SUDD. This is a poorly absorbable antibiotic with a broad spectrum of action, including action against Gram-positive and -negative bacteria, aerobes and anaerobes [30]. It has been successfully used in recent years in the treatment of SUDD, and also seems to be effective in maintaining SUDD remission. A recent meta-analysis examined four prospective randomized trials (only one conducted in double-blind placebo-controlled fashion) including 1660 patients. The pooled rate of difference for symptom relief was 29.0% in favor of rifaximin (rifaximin vs. control; 95% CI 24.5-33.6; P<0.0001) with a clinically significant Number Needed to Treat (NNT=3) [31]. Controlled studies of rifaximin in such patients are reported in Table 2.

Mesalazine

Controlling inflammation with mesalazine is another option for the treatment of SUDD. Although this drug has been effectively used for many years in the treatment of IBD, the mechanisms of action are not yet well understood. Mesalazine acts in the gastrointestinal epithelium through N-Ac-5-ASA, the active metabolite of 5-ASA (mesalazine), but the molecular mechanisms of its action are not clear. It is thought

Table 1 Fiber in diverticulosis and symptomatic diverticular disease

Study	Trial design	No of patients	Randomization	Outcomes assessed	Length of follow up	Results
Brodibb	Double-blind	18	Wheat crispbread 0.6 g/day vs. bran crisp bread 6.7 g/day	Reduction in global symptom score in SUDD	3 months	High-fiber vs. low-fiber group has significant reeuction in symptoms score (34.3-8.1 vs. 42.0-35.1, P<0.002
Ornstein *et al*	Randomized, cross-over, double-blind, placebo	58	Bran (6.99 g/day) vs. ispaghula (9.04 g/day) vs. placebo (2.34 g/day)	Reduction in global symptom score in SUDD	16 weeks	No difference was found between the three arms (from 16.3, 18.4 and 15.6-5.9, 6.7 and 6.3, P=n.s.) No difference between bran and ispaghula consumption (5.9 vs. 6.7)
Hodgson	Double-blind, randomized, Placebo controlled	30	Methylcellulose 2 tablets/day vs. placebo 2 tablets/day	Reduction in global symptom score in SUDD	3 months	Symptom score decreased significantly in the methylcellulose group (from 19+6 to 13+4, P<0.01) but not in the placebo group (from 21+7 to 17+9, P=n.s.)
Crowe *et al*	Prospective, cohort study	47.033	Vegetarian vs. non vegetarian diet (>25.5 g/day for women and >26.1 g/day for men) vs. lower fiber consumption	Occurrence of DD; Hospital admission for DD complications	11.6 years	Vegeterians had a 31% lower risk of DD occurrence (P=0.001) high-fiber intake had a 25% lower risk of developing DD (P=0.018). Hospital admission of death for DD was 4.4% for meat eaters and 3.0% in vegetarian of vegans
Peery *et al*	Cross-sectional study	2104	Fiber or high-fiber consumption (>50 g/day) vs. normal diet	Diverticulosis occurrence	12 years	High-fiber consumption had higher risk to develop diverticulosis (P=0.004) Soluble fiber had higher risk to develop diverticulosis (P=0.038)
Strate *et al*	Prospective cohort study	47.228	Lower (less than once per month) vs. higher (at least twice per week) nut, corn, or popcorn consumption	Diverticulitis occurrence Diverticulitis bleeding occurrence	18 years	Higher nut, corn or popcorn consumption had lower risk of diverticulitis occurrence (P=0.034). No difference in diverticular bleeding occurrence between higher or lower consumption of nut, corn or popcorn (P=0.56, 0.64 and 0.52 respectively)
Leahy *et al*	Prospective case-control	56	Lower (<25 g/day) vs. high (>25/day) fiber diet	Symptoms recurrence occurrence of complications surgery due to DD	66 months	High-fiber diet has significantly lower symptom recurrence (19.35% vs. 44%, P<0.05), occurrence of complications (6.45% vs. 20.25%, P<0.05) and surgery due to DD (6.45% vs. 32%) than low-fiber diet

SUDD, symptomatic uncomplicated diverticular disease; DD, diverticular disease

Table 2 Controlled trials in using rifaximin in treating divertucular disease

Study	Trial design	No of patients	Randomization	Outcomes assessed	Length of follow up	Results
Papi *et al*	Open-label, prospective, randomized	217	RFX 800 mg/plus GM 2 g/day for 7 days vs. GM 2 g/day for 7 days each month	Reduction in global symptomatic score in SUDD	12 months	RFX+GM 63.9% reduction score vs. GM alone 47.6% (P<0.001)
Papi *et al*	Double-blind, randomized, placebo-controlled	168	RFX 800 mg/plus GM 2 g/day for 7 days vs. placebo plus GM 2 g/day for 7 days each month	Reduction in global symptomatic score in SUDD prevention of diverticulitis occurrence	12 months	RFX+GM 68.9% reduction score vs. placebo+GM 39.5% (P=0.001). No difference in preventing diverticulitis occurrence (1.3% vs. 1.5%, P=n.s.)
Latella *et al*	Prospective, randomized, open-label	968	RFX 800 mg/plus GM 4 g/day for 7 days vs. GM 4 g/day for 7 days each month	Reduction in global symptomatic score in SUDD prevention of DD complications (acute diverticulitis and diverticular bleeding)	12 months	RFX+GM 56.5% reduction score vs. GM alone 29.2% (P<0.001). RFX+GM 1.34% occurrence of DD complications vs. GM alone 3.22% (P<0.05)
Lanas *et al*	Open-label, prospective, randomized	165	RFX 800 mg/plus fiber 7 g/day for 7 days vs. fiber 7 g/day for 7 days each month	Prevention of diverticulitis recurrence	12 months	RFX/fiber 10.4% diverticulitis recurrence vs. fiber alone 19.3% (P=0.025)

RFX, rifaximin; GM, glucomannan; SUDD, symptomatic uncomplicated diverticular disease; DD, diverticular disease

that mesalazine inhibits some key factors of the inflammatory cascade (cyclo-oxygenase, thromboxane-synthetase and PAF-synthetase); inhibits the production of interleukin-1 and free radicals; and has intrinsic antioxidant activity [32]. In the light of new data on the role of inflammation in the pathogenesis of SUDD, it was inevitable that researchers would attempt to apply mesalazine based on this indication. Although limited by the open-label design, the favorable effect of mesalazine on SUDD has been demonstrated by several open-label studies [33,34].

Three double-blind, placebo-controlled studies have also recently assessed the role of mesalazine in treating those patients. The first trial investigated the efficacy and safety of mesalazine granules 3 g/day vs. placebo in patients with lower abdominal pain as a symptom of SUDD. Change in lower abdominal pain to week 4 (baseline defined using pain score from 7 days pre-treatment) was significantly lower in the mesalazine group (P=0.05) in the per-protocol (PP) but not on intention-to-treat (P=0.374) population. *Post hoc* adjustment for confounding factors resulted in P=0.005 (PP). Safety was comparable [35]. The second trial assessed the effectiveness of mesalazine, with or without probiotic, vs. placebo in maintaining remission in SUDD patients. Four groups were randomly enrolled: Group M (active mesalazine 1.6 g/day plus *Lactobacillus casei* (*L. casei*) subsp. DG placebo), Group L (active *L. casei* subsp. DG 24 billion/day plus mesalazine placebo), Group LM (active *L. casei* subsp. DG 24 billion/day plus active mesalazine), Group P (*L. casei* subsp. DG placebo plus mesalazine placebo). SUDD recurred in none (0%) of the patients in group LM, in 7 (13.7%) patients in group M, in 8 (14.5%) patients in group L, and in 23 (46.0%) patients in group P (LM group vs. M group, P=0.015; LM group vs. L group, P=0.011; LM group vs. P group, P=0.000; M group vs. P group, P=0.0001; L group vs. P group, P=0.0001). No adverse events were recorded during the study [36]. Another double-blind, placebo-controlled trial not yet published assessed the efficacy of mesalazine in controlling abdominal pain in SUDD as a secondary endpoint. Patients with SUDD underwent flexible sigmoidoscopy and biopsies at baseline and after 12-week treatment, completing diaries of pain and bowel habits. Patients were randomized to receive mesalazine 3 g/day (group M) or placebo (group P) for 12 weeks with follow-up visits at 2 and 4 weeks. In Group M but not in Group P there was a significant reduction in the duration of abdominal pain (P=0.0413) [37]. Controlled studies of mesalazine use in such patients are reported in Table 3.

Probiotics

Using probiotics is a third choice for the treatment of SUDD. Probiotics are living micro-organisms, which can exert host health benefits beyond those of inherited basic nutrition [38]. The pathophysiological actions of probiotics include pathogen adherence inhibition, increasing IgA secretion in Peyer's patches, increasing immune system activity inhibiting the release of anti-inflammatory cytokines and inhibiting pro-inflammatory cytokines. However, some bacteria may provide specific health benefits when consumed as a food component or in the form of specific preparations of viable micro-organisms, without the risk of antibiotic resistance. Recent studies investigated the effect of probiotics on the course of SUDD. All found different probiotic strains effective in treating SUDD patients [39-41] but the open-label designs limited the usefulness of these results. Finally, in the double-blind, placebo-controlled trial, already mentioned, the combinations of mesalazine with *L. casei* subsp. DG (group LM) or *L. casei* subsp. DG alone (group L) were significantly better than placebo in preventing SUDD recurrence (LM group vs. P group, P=0.000; L group

Table 3 Fully published placebo-controlled trials in using mesalazine in diverticular disease

Study	Trial design	No of patients	Randomization	Outcomes assessed	Length of follow up	Results
Kruis *et al*	Double-blind, randomized, placebo controlled	117	Mesalazine granules 3 g/day vs. placebo in SUDD	Pain control in SUDD	3	Mesalazine had higher percentage of pain control (62.5% vs. 50.81%, P=0.374 on ITT and P=0.05 on PP)
Tursi *et al*	Double-blind, randomized, placebo controlled	210	Mesalazine Eudragit L 2.4 g/day vs. mesalazine 2.4 g/day+*Lactobacillus casei* 750 mg/day vs. *Lactobacillus casei* 750 mg/day vs. placebo in SUDD	Reducing gastrointestinal symptoms in SUDD preventing diverticulitis occurrence	12	Mesalazine, alone or in combination, had high remission rate (93.33% and 85.45% vs. 54%, P=0.0001)* Mesalazine, alone or in combination, had lower diverticulitis occurrence (0% and 1.81% vs. 12%, P=0.003)*
Stollman *et al*	Double-blind, randomized, placebo controlled	117	Mesalazine eudragit L 2.4 g/day vs. Mesalazine 2.4 g/day+ *Bifidobacterium infantis* 35624 vs. placebo following acute diverticulitis	Reducing gastrointestinal symptoms preventing diverticulitis recurrence	12	Mesalazine, alone or in combination, had higher symptoms' improvement rate (59.3% and 54.8% vs. 27.3%, P=0.0346).* Mesalazine, alone or in combination, had no higher remission rate in preventing diverticulitis recurrence (28.1%, 37% vs. 31% placebo, P=n.s.)*
Parente *et al*	Double-blind, randomized, placebo controlled	92	Mesalazine eudragit L 2.4 g/day for 10 days/ month vs. placebo following acute diverticulitis	Preventing diverticulitis recurrence improvement quality of life	24	Mesalazine had higher but no significant remission rate in preventing diverticulitis recurrence (13% vs. 28%, P=0.1011).* Mesalazine had higher quality of life score (P=0.022)*
Raskin *et al*	Double-blind, randomized, placebo controlled	1182 (590 in PREVEN T1 and 592 in PREVEN T2)	Mesalazine MMX 1.6 g/day vs. 2.4 g/day vs. 4.8 g/day vs. placebo following acute diverticulitis	Preventing diverticulitis recurrence	24	Mesalazine did not reduce the rate of diverticulitis recurrence both in PREVENT 1 (53-63% vs. 65%, P=n.s.)* and in PREVENT 2 (59-69% vs. 68%, P=n.s.)*

*All results reported are on ITT analysis

ITT, intention-to-treat analysis; PP, per-protocol analysis; SUDD, symptomatic uncomplicated diverticular disease

vs. P group, P=0.000) [36]. Controlled studies of probiotics in such patients are reported in Table 4.

Prevention of acute diverticulitis

Primary prevention of acute diverticulitis is a very important topic. Acute diverticulitis, defined as acute inflammation of a colonic diverticulum, is a common emergency presentation managed by both surgeons and physicians. Factors predisposing to the development of acute diverticulitis include obesity, smoking, lack of physical activity and medication use such as non-steroidal anti-inflammatory drugs.

There have been advances in the medical treatments offered to patients in recent years. Patients with uncomplicated diverticulitis are generally treated as outpatients with a clear liquid diet and antibiotics [42]. In outpatients, broad-spectrum antibiotics are usually given for 7-10 days. If opioid analgesics are required for pain control, meperidine is the preferred option since morphine causes colonic spasm and may accentuate colonic hyper-segmentation.

Outpatient treatment is effective in most cases, and less than 10% of patients are readmitted at the emergency room for diverticulitis within 60 days of the initial evaluation. Hospitalization with intravenous antibiotic treatment is usually recommended by current guidelines if the patient: is unable to take oral therapy; is affected by severe comorbidity; fails to improve with outpatient therapy; or is affected by complicated diverticulitis. Clinical improvement in patients affected by acute diverticulitis is generally observed within 3-4 days. If patients are hospitalized, a 7-10 day course of oral antibiotics is usually given following discharge. However, results of studies investigating such prevention are often conflicting.

Fiber

Data on the role of fiber in primary prevention of diverticulitis are particularly conflicting [43-45]. Patients with a history of diverticulosis or DD commonly seek dietary and lifestyle recommendations to reduce their risk of occurrence/recurrence of the disease and/or complications. The traditional recommendation has been to consume a high-fiber diet. Using data from a single case-control study that included 56 participants, it is estimated that a high-fiber diet might reduce the number of complications (by 52 cases per 1000 patients treated) and the need for surgery (by 100 cases per 1000 patients treated [43]). Based on a prospective cohort

Table 4 Controlled trials in using probiotics for symptomatic diverticular disease

Study	Trial design	No of patients	Randomization	Outcomes assessed	Length of follow up	Results
Annibal *et al*	Prospective, randomized, open-label	50	Group A, high-fiber diet alone; Group B, twice daily 1 sachet of probiotic lactobacillus paracasei sub paracasei F19 for 14c days/month+high-fiber diet). Group C twice daily 2 sachets of probiotic *Lactobacillus paracasei* sub, *paracasei* F19 for 4 days/month+high-fiber diet	Decrease in VAS score after treatment in SUDD	6 months	Bloating decreased significantly in Groups B and C (group B: 4.6+2.6 vs. 2.3+2.0, P<0.05, group C: 3.9+2.9 vs. 1.8+2.1, P<0.05)
Dughera *et al*	Prospective, randomized, open-label	83	Polybacterial lysate suspension of *Escherichia coli+Proteus vulgaris* for 2 weeks every month plus fiber 15 g/day vs. fiber 15 g/day alone	Prevention of diverticulitis recurrence	3 months	Polybacterial lysate plus fiber had significant superiority to fiber alone at 1 and 3 months in controlling symptoms and preventing diverticulitis recurrence (P<0.05 and P<0.01 respectively)
Lahner *et al*	Prospective, randomized, open-label	30	Methylcellulose 2 tablets/day vs. placebo 2 tablets/day		3 months	Symptom score decreased significantly in the methylcellulose group (from 19+6 to 13+4, P<0.01) but not in the placebo group (from 21+7 to 17+9, P=n.s.)
Tursi *et al*	Double-blind, randomized, placebo-controlled	210	Mesalazine 800 mg twice a day and mesalazine 800 mg twice a day+*Lactobacillus casei* 750 mg a day vs. *Lactobacillus casei* 750 mg a day vs. placebo		12 months	Remission was maintained in 93.33% in combined treatment group. 85.45% in probiotic group and 54% of placebo group (P=0.0001) acute diverticulitis occurred in 0% in combined treatment group. 1.82% in probiotic group and 12% in the placebo group (P=0.003)
Tursi *et al*	Prospective, randomized, open-label	30	Balsalazide 2.25 g daily for 10 days every month plus probiotic mixture VSL #3 450 billion/day for 15 days every month (Group A) vs. VSL#3 alone 450 billion /day for 15 days every month (Group B)		12 months	6.66% of group A and 13.33% of group GB pts had recurrence of the disease (P=n.s.)

VAS, visual analogic scale; DD, diverticular disease; SUDD, symptomatic uncomplicated diverticular disease

study that examined the association of dietary fiber intake and risk of incident hospitalization for DD, it is estimated that a high-fiber diet may reduce the risk of acute diverticulitis by 59 cases per 1000 patients [45]. We rated the quality of this evidence as very low based on substantial differences between our target population (those with a history of diverticulitis) and those in the cohort study (those without a history of diverticulitis). Only three randomized trials analyzed the role of fiber in preventing diverticulitis occurrence in those patients. Unfortunately, their sample size was far too small to demonstrate a significant effect of high-fiber supplementation on the prevention of acute uncomplicated diverticulitis or other complications of DD (e.g. abscess, perforation, stenosis, fistula or bleeding).

Rifaximin

Data from three open randomized trials (comprising a total of 1492 patients) and four comparing rifaximin plus glucomannan or fiber supplementation vs. glucomannan or fiber alone, reported that rifaximin led to a slight benefit in preventing acute diverticulitis, but only the largest study showed significant results. Cumulative data from placebo-controlled and unblinded trials 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) [46-49]. According to these results, the number needed to be treated to prevent an attack of acute diverticulitis in 1 year with the rifaximin plus fiber supplementation regimen reached is 57 (NNT: 57). Only one double-blind, placebo-controlled trial assessed the prevention of acute diverticulitis as a secondary endpoint. This was a 1-year follow-up trial in which all patients received glucomannan (2 g/day); one arm received rifaximin (400 mg b.i.d. for 7 days each month), and the other arm received a placebo. Rifaximin failed to show superiority over placebo in preventing acute diverticulitis, which occurred in 2.4% of patients in both study arms [48].

Mesalazine

Data from five randomized open trials (comprising more than 400 patients) comparing mesalazine alone or in combination with probiotics, and probiotics alone in

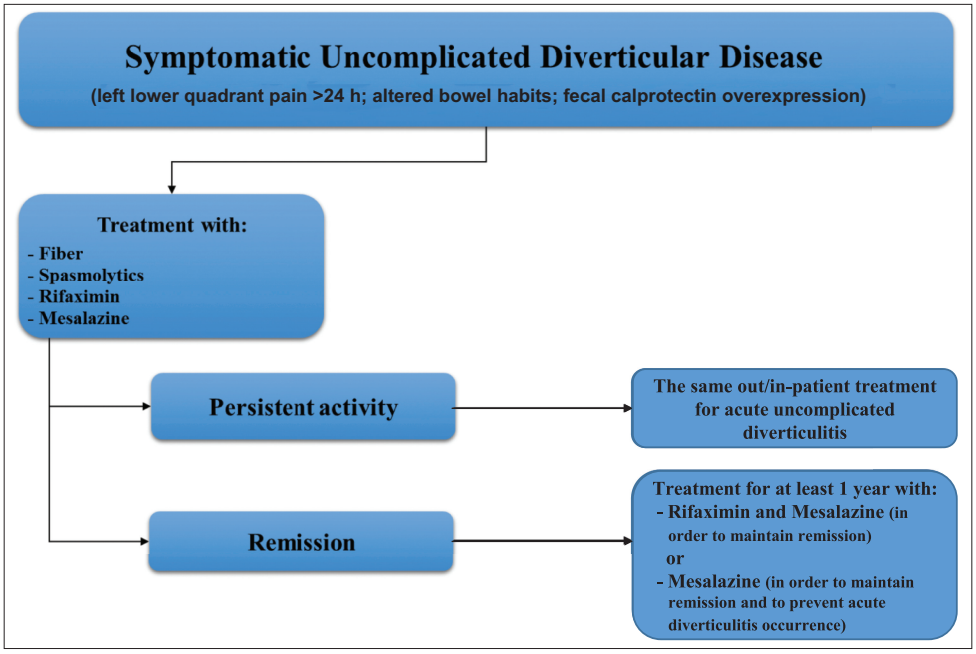

Figure 2 Management of symptomatic uncomplicated diverticular disease

preventing acute diverticulitis, did not show any significant difference. However, there were only seven episodes of acute diverticulitis per year (yearly incidence rate of 2%) [33,34,50-52]. More recently, a double-blind, double-dummy placebo-controlled trial assessed the prevention of acute diverticulitis occurrence as secondary endpoint. This was a 1-year follow-up trial in which patients received mesalazine (1.6 g/day for 10 days/month), a probiotic (*L. casei* subsp. DG 24 billion/day for 10 days/month), mesalazine plus probiotic, or placebo. This study found mesalazine significantly better than placebo in preventing acute diverticulitis, which occurred in none of the patients in the mesalazine group, in 1.78%, and in 12% of patients in the probiotic and placebo study arms respectively [36]. Fig. 2 shows advice on how to manage such patients based on the above-mentioned data.

Diverticular inflammation and complications assessment (DICA) classification: Is the solution around the corner?

Several radiological and clinical approaches are currently available to classify DD. Surprisingly, an endoscopic classification of the disease is still lacking, considering the high number of colonoscopies performed in our centers and the percentage of signs of diverticular inflammation detected by colonoscopy in everyday practice [53,54]. Selecting patients according to the colonic characteristics may be an option to increase therapeutic efficacy. To this end, an endoscopic classification of DD has been recently developed and validated [55]. This classification, called DICA, assesses four main items (diverticulosis extension, number of diverticula in each district, presence of inflammation, and presence of complications) and some sub-items, and scores the disease

Table 5 Diverticular inflammation and complication assessment (DICA) classification

Items	Points
Diverticulosis extension	
Left colon	2
Right colon	1
Number of diverticula (in each district)	
Up to 15: grade I	0
>15: grade II	1
Presence of inflammatory signs	
Edema/hyperemia	1
Erosions	2
SCAD	3
Presence of complications	
Rigidity of the colon	4
Stenosis	4
Pus	4
Bleeding	4

DICA classification	Numerical value
DICA 1	From 1 to 3 points
DICA 2	From 4 to 7 points
DICA 3	>7 points

SCAD, segmental colitis associated with diverticulosis

in three grades: DICA 1, DICA 2 and DICA 3 (Table 5). Preliminary retrospective data found that this classification is able to predict the outcome of the disease according to the severity of the score. In other words, simple and/or asymptomatic diverticulosis does not appear to need any

maintenance treatment to prevent occurrence of complications, while a colon with signs of recurrent inflammatory attack may be unresponsive to maintenance treatment to prevent recurrence of complications. On the contrary, DICA 2 seems to be very responsive to scheduled treatment. In other words, symptomatic diverticulosis with/without signs of inflammation responds very well to maintenance treatment for the prevention of occurrence/recurrence of complications. If further, prospective studies confirm these results, then we will have a clear subgroup of patients that can be expected to benefit from scheduled maintaining treatment.

Concluding remarks

DD is a multifactorial disease in which optimal patient stratification according to the severity of the disease may guarantee therapeutic success. DICA classification is a new and practical instrument that can be used by clinicians for the objective description of the colon harboring diverticula. The simplicity of this classification, its excellent reproducibility and its correlation with biochemical and clinical disease markers make it very attractive in clinical practice. Of course, further studies are needed to validate this classification and to assess its reproducibility in clinical trials, as well as to assess whether its use may impact upon the natural history of DD.

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