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

Walter Elisei, Antonio Tursi
ASL Roma H, Albano Laziale, Rome; ASL Bat, Andria, Italy

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

Ann Gastroenterol 2016; 29 (1): 24-32

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)
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 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

![Classification of diverticular disease of the colon](image)

**Figure 1** Classification of diverticular disease of the colon

**DD, diverticular disease**
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 find 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 1.

**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 et al     | 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 reduction 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.) |
| Hodgson et al     | 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           | Vegetarians 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

26 W. Elisei and A. Tursi
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 2: Controlled trials in using rifaximin in treating diverticular 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
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

\[28.61, 29.03\]
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

---

### 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 lyase 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 lyase 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 | 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.) | 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 | Remission was maintained in 93.3% in combined treatment group, 85.4% 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) | 12 months          | Remission was maintained in 93.3% in combined treatment group, 85.4% 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) | 6.66% of group A and 13.33% of group GB pts had recurrence of the disease (P=n.s.) | 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
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 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

| 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 1                                | From 1 to 3 points |
| DICA 2                                | From 4 to 7 points |
| DICA 3                                | >7 points    |

SCAD, segmental colitis associated with diverticulosis
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.

**References**

1. Tursi A, Papagrigroriadis S. Review article: the current and evolving treatment of colonic diverticular disease. *Aliment Pharmacol Ther* 2009;30:532-546.
2. Weizman AV, Nguyen GC. Diverticular disease: epidemiology and management. *Can J Gastroenterol* 2011;25:385-389.
3. Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiological and clinical insights. *Am J Gastroenterol* 2012;107:1486-1493.
4. Tursi A. New physiopathological and therapeutic approaches to diverticular disease: an update. *Expert Opin Pharmacother* 2014;15:1005-1017.
5. Kohler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: result of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. *Surg Endosc* 1999;13:430-436.
6. Yamada E, Inamori M, Uchida E, et al. Association between the location of diverticular disease and the irritable bowel syndrome: a multicenter study in Japan. *Am J Gastroenterol* 2014;109:1900-1905.
7. Aldoorni WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. Prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr* 1994;60:757-764.
8. Costedio MM, Coates MD, Danielson AB, et al. Serotonin signaling in diverticular disease. *J Gastrointest Surg* 2009;12:1439-1445.
9. Tursi A, Elisei W, Giorgetti GM, et al. Detection of endoscopic and histological inflammation after an attack of colonic diverticulitis is associated with higher diverticulitis recurrence. *J Gastrointestin Liver Dis* 2013;22:3-9.
10. Cuomo R, Barbara G, Andreozzi P, et al. Symptom patterns can distinguish diverticular disease from irritable bowel syndrome. *Eur J Clin Invest* 2013;43:1147-1155.
11. Tursi A, Brandimarte G, Elisei W, Giorgetti GM, Inchingolo CD, Aiello F. Faecal calprotectin in colonic diverticular disease: a case-control study. *Int J Colorectal Dis* 2009;24:49-55.
12. Tursi A. Diverticular disease and irritable bowel syndrome: it's time to differentiate. *Am J Gastroenterol* 2015;110:774-775.
13. Humes D, Simpson J, Spiller RC. Colonic diverticular disease. *BMJ Clin Evid* 2007 pii:0405.
14. Simpson J, Scholefield JH, Spiller RC. Origin of symptoms in diverticular disease. *Br J Surg* 2003;90:899-908.
15. von Rahden BA, Germer CT. Pathogenesis of colonic diverticular disease. *Langenbecks Arch Surg* 2012;397:1025-1033.
16. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive disease in the United States. *Gastroenterology* 2002;122:1500-1511.
17. Lahat A, Avidan B, Sakhnini E, Katz L, Fidder HH, Meir SB. Acute diverticulitis: a decade of prospective follow-up. *J Clin Gastroenterol* 2013;47:415-419.
18. Stollman N, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;94:3110-3121.
19. Chautems R, Ambrosetti P, Ludwig A, Mermillod B, Morel P, Soravia C. Long term follow-up after first acute episode of sigmoid diverticulitis: is surgery mandatory? A prospective study of 118 patients. *Dis Colon Rectum* 2002;45:962-966.
20. Chapman J, Dozois EI, Wolff BG, Gullerud RE, Larson DR. Diverticulitis: a progressive disease? Do multiple recurrences predict less favourable outcomes? *Ann Surg* 2006;243:876-880.
21. Hart AR, Kennedy HJ, Stebbings WS, Day NE. How frequently do large bowel diverticula perforate? An incidence and cross-sectional study. *Eur J Gastroenterol Hepatol* 2000;12:661-665.
22. Richards R, Hammitt JK. Timing of prophylactic surgery in prevention of diverticulitis recurrence: a cost-effectiveness analysis. *Dig Dis Sci* 2002;47:1903-1908.
23. Salem L, Veenstra DL, Sullivan SD, Flum DR. The timing of elective colectomy in diverticulitis: a decision analysis. *J Am Coll Surg* 2004;199:904-902.
24. Rafferty J, Shellito P, Hyman NH, Buie WD; Standards Practice Committee of the American College of Gastroenterology. *Practice guidelines for sigmoid diverticulitis.* *Dis Colon Rectum* 2006;49:939-944.
25. World Gastroenterology Organisation (WGO) Practice Guidelines. Diverticulitis, disease, 2007. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/07_diverticular_disease_pdf 2007.
26. Ünlü C, Daniels L, Vrouenraets BC, Boermeester MA. A systematic review of high-fibre dietary therapy in diverticular disease. *Am J Gastroenterol* 2012;107:247-257.
27. Brodribb AJ. Treatment of symptomatic diverticular disease with a high fibre diet. *Lancet* 1977;1:664-666.
28. Hodgson WJ. The placebo effect. Is it important in diverticular disease? *Int J Colorectal Dis* 2012;27:419-427.
29. Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology* 2012;142:266-267.
30. Lamanna A, Orsi A. In vitro activity of rifaximin and rifampicin against some anaerobic bacteria. *Chemioterapia* 1984;3:365-367.
31. Bianchi M, Festa V, Moretti A, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticulitis. *Aliment Pharmacol Ther* 2011;33:902-910.
32. MacDermott RP. Progress in understanding the mechanisms of action of 5-aminosalicylic acid. *Am J Gastroenterol* 2000;95:3343-3345.
33. Trespi E, Colla C, Panizza P, et al. Therapeutic and prophylactic
role of mesalazine (5-ASA) in symptomatic diverticular disease of the large intestine. 4 year follow-up results. Minerva Gastroenterol Dietol 1999;45:245-252. (Article in Italian)

34. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Mesalazine and/or Lactobacillus casei in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. Hepatogastroenterology 2008;55:916-920.

35. Kruijs W, Meier E, Schumacher M, Mickisch O, Greinwald R, Mueller R; German SAG-20 Study Group. Randomised clinical trial: mesalazine (Salofalk granules) for uncomplicated diverticulitis of the colon – a placebo-controlled study. Aliment Pharmacol Ther 2013;37:680-690.

36. Tursi A, Brandimarte G, Elisei W, et al. Randomised clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease – a double-blind, randomised, placebo-controlled study. Aliment Pharmacol Ther 2013;38:741-751.

37. Smith J, Humes D, Garsed K, et al. Mechanistic randomised control trial of mesalazine in symptomatic diverticular disease. Gut 2012;61:A51-A52.

38. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A. Probiotic mechanism of action. Ann Nutr Metab 2012;61:160-174.

39. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Mesalazine and or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticulitis of the colon: a prospective, randomized, open-label study. J Clin Gastroenterol 2006;40:312-316.

40. Annibale R, Maconi G, Lahner E, De Giorgi F, Cuomo R. Efficacy of Lactobacillus paracasei sub. paracasei F19 on abdominal symptoms in patients with symptomatic uncomplicated diverticulitis: a pilot study. Minerva Gastroenterol Dietol 2011;57:13-22.

41. Lahner E, Esposito G, Zullo A, et al. High-fiber diet and Lactobacillus paracasei B21060 in symptomatic uncomplicated diverticular disease. World J Gastroenterol 2012;18:5918-5924.

42. Feingold D, Steele SR, Lee S, et al. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum 2014;57:284-294.

43. Leary AI, Ellis RM, Quill DS, Peel AL. High fiber diet in symptomatic diverticular disease of the colon. Ann R Coll Surg Engl 1985;67:173-174.

44. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. BMJ 2011;343:d4131.

45. Ornstein MH, Littlewood ER, Baird IM, Fowler J, North WR, Cox AG. Are fiber supplements really necessary in diverticular disease of the colon? A controlled clinical trial BMJ 1981;282:1353-1356.

46. Papi C, Ciaco A, Koch M, Capurso L. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double-blind placebo-controlled trial. Aliment Pharmacol Ther 1995;9:33-39.

47. Latella G, Pimpo MT, Sottoli S, et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. Int J Colorectal Dis 2003;18:55-62.

48. Papi C Ciaco A, Koch M, Capurso L. Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon: a pilot multicentre open trial. Diverticular Disease Study Group. Ital J Gastroenterol 1992;24:452-456.

49. Colecchia A, Vestito A, Pasqui F, et al. Efficacy of long term cyclic administration of the poorly absorbed antibiotic rifaximin in symptomatic, uncomplicated colonic diverticular disease. World J Gastroenterol 2007;13:264-269.

50. Cohen E, Fuller G, Bolus R, et al. Increased risk for irritable bowel syndrome after acute diverticulitis. Clin Gastroenterol Hepatol 2013;11:1614-1649.

51. Di Mario F, Aragona G, Leandro G, et al. Efficacy of mesalazine in the treatment of symptomatic diverticular disease. Dig Dis Sci 2005;50:581-586.

52. Comparato G, Fanigliulo L, Cavallaro LG. Prevention of complications and symptomatic recurrences in diverticular disease with mesalazine: a 12-month follow-up. Dig Dis Sci 2007;52:2934-2941.

53. Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Continuous versus cyclic mesalazine therapy for patients affected by recurrent symptomatic uncomplicated diverticular disease of the colon. Dig Dis Sci 2007;52:671-674.

54. Ghorai S, Ulbright TM, Rex DK. Endoscopic findings of diverticular inflammation in colonoscopy patients without clinical acute diverticulitis: prevalence and endoscopic spectrum. Am J Gastroenterol 2003;98:802-806.

55. Tursi A, Elisei W, Giorgetti GM, Aiello F, Brandimarte G. Inflammatory manifestations at colonoscopy in patients with colonic diverticular disease. Aliment Pharmacol Ther 2011;33:358-365.

56. Tursi A, Brandimarte G, Di Mario F, et al. Development and validation of an endoscopic classification of diverticular disease of the colon: The DICA classification. Dig Dis 2015;33:68-76.