Mesalazine for the Treatment of Symptomatic Uncomplicated Diverticular Disease of the Colon and for Primary Prevention of Diverticulitis

A Systematic Review of Randomized Clinical Trials

Marcello Picchio, MD, Walter Elisei, MD,† Giovanni Brandimarte, MD,‡ Francesco Di Mario, MD,§ Peter Malfertheiner, MD, PhD,‖ Carmelo Scarpignato, MD, DSc, PharmD, MPH, FRCP, FACP, FACG, AGAF,¶ and Antonio Tursi, MD#*

Background: Symptomatic uncomplicated diverticular disease (SUDD) is a common gastrointestinal disease, because it affects about one fourth of the patient harboring colonic diverticula.

Goal: To assess the effectiveness of mesalazine in improving symptoms (namely abdominal pain) and in preventing diverticulitis occurrence in patients with SUDD.

Study: Only randomized clinical trials (irrespective of language, blinding, or publication status) that compared mesalazine with placebo or any other therapy in SUDD were evaluated. The selected endpoints were symptom relief and diverticulitis occurrence at maximal follow-up. Absolute risk reduction (ARR, with 95% confidence interval) and the number needed to treat were used as measures of the therapeutic effect.

Results: Six randomized clinical trials enrolled 1021 patients: 526 patients were treated with mesalazine and 495 with placebo or other therapies. Symptom relief with mesalazine was always larger than that with placebo and other therapies. However, absolute risk reduction was significant only when mesalazine was compared with placebo, a high-fiber diet, and low-dose rifaximin. The incidence of diverticulitis with mesalazine was lower than that observed with placebo and other treatments, being significant only when compared with placebo.

Conclusions: Mesalazine is effective in achieving symptom relief and primary prevention of diverticulitis in patients with SUDD.

Key Words: controlled trials, diverticular disease, diverticulitis, mesalazine, systematic review

(*J Clin Gastroenterol* 2016;50:S64–S69)

From the *Division of Surgery, "P. Colombo" Hospital, ASL RMH, Velletri; †Division of Gastroenterology, ASL RMH, Albano Laziale; ‡Division of Internal Medicine and Gastroenterology, "Cristo Re" Hospital, GIOMI Group, Rome; §Department of Clinical & Experimental Medicine, Gastroenterology Unit; ¶Department of Clinical & Experimental Medicine, Clinical Pharmacology & Digestive Pathophysiology Unit, University of Parma; #Gastroenterology Service, ASL BAT, Andria (BT), Italy; and ‖Department of Gastroenterology, Hepatology and Infectious Diseases, University of Magdeburg, Magdeburg, Germany.

C.S. is member of the Speakers' Bureau and of the Scientific Advisory Board of Alfa Wassermann. F.D.M. was member of the Speakers' Bureau and of the Scientific Advisory Board of Sofar and Nathura. P.M. is member of Speakers' Bureau of Biohit and Infai. The remaining authors declare that they have nothing to disclose.

Address correspondence to: Antonio Tursi, MD, Gastroenterology Service, ASL BAT, Via Torino, 49, 76123 Andria (BT), Italy (e-mail: antotursi@tiscali.it).

DOI: 10.1097/MCG.0000000000000669

Diverticular disease of the colon is one of the most common gastrointestinal diseases, with its prevalence increasing with age and affecting almost 50% of the people by the fifth decade.[1,2] However, a growing body of knowledge is changing the epidemiologic pattern of the disease. Overall, annual age-adjusted admissions for acute diverticulitis are increasing rapidly.[3]

Although most patients remain asymptomatic for their lifetime, about one fifth or one fourth of them will experience symptoms related to the presence of diverticula, a condition referred to as "diverticular disease."[1,2] Diverticular disease can be classified into symptomatic uncomplicated diverticular disease (SUDD), recurrent symptomatic disease, or complicated disease.[4,5]

SUDD is characterized by abdominal pain (mainly located in the left lower quadrant) and altered bowel habits.[4,5] It is thought that among patients with diverticular disease, 25% develops complications, 1% to 2% require hospitalization, and 0.5% require surgery.[3,6] An endoscopy-based study found a lower rate (ie, 5%) of diverticulitis at 5 years and only 1.5 per 1000 patient-years, using strict criteria in diverticulosis-proven patients.[7] However, the recurrence of acute diverticulitis was found to be higher, involving up to 20% of the patients after the first episode.[8]

Concerning medical therapy, current guidelines actually recommend only the use of fibers and spasmolytics in treating SUDD.[9] Clinical trials have recently provided evidence of the substantial benefit of mesalazine in SUDD, reducing symptoms and maintaining remission in most patients.[10–19] However, its value in modifying the clinical course of the disease and in primary prevention of diverticulitis needs to be fully assessed.

The aim of the present systematic review was to compare the efficacy of mesalazine, alone or in combination with other treatments, against placebo or other therapies on symptom improvement and the occurrence of diverticulitis in patients with SUDD.

METHODS

Methods for the analysis and the generation of inclusion criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA) recommendations.[20]

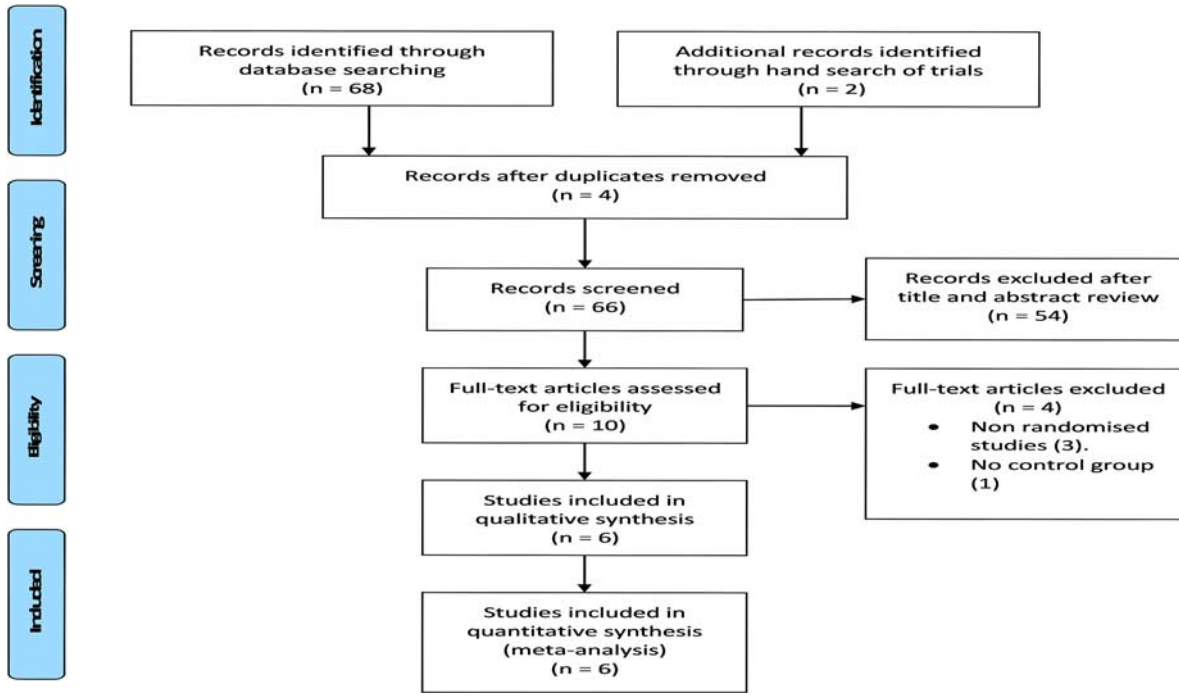

FIGURE 1. Article identification and selection algorithm. full color online

Types of Studies, Participants, and Interventions

Randomized clinical trials (RCTs) (irrespective of language, blinding, or publication status) that compared mesalazine (irrespective of the associated therapies and dosage regimens) with placebo or any other therapy (fibers, rifaximin, or probiotics) in SUDD were evaluated. Cohort studies, case series, and case reports were excluded.

Types of Outcome Measures

The selected primary outcome was the percentage of patients with symptom relief at maximal follow-up. The secondary outcome was diverticulitis occurrence at maximal follow-up.

Literature Search

The RCTs were identified by searching MEDLINE and the Cochrane Central Register of Controlled Trials from 1966 to April 2016. No language limits were imposed. A search of the abstract books from the British Society of Gastroenterology (2000 to 2015), the American Gastroenterological Association (2000 to 2015), the American College of Gastroenterology (2004 to 2015), and the United European Gastroenterology Federation (2000 to 2015) was also performed. Bibliographies of all identified relevant studies were used to perform a recursive search. In addition, authors were contacted to obtain unpublished data from their studies, whenever deemed necessary.

Data Extraction

Two reviewers (A.T. and M.P.) extracted all data independently, using a paper data extraction form. A third author (W.E.) further confirmed the accuracy of the extracted data. The information collected from each study was as follows: study design, definition of primary and secondary outcomes, and frequencies of each endpoint.

To have homogenous groups, different doses of mesalazine and rifaximin were pooled. This helps analyze the data, but it is noteworthy that this may be a confounding factor, as different drug doses may have different efficacies.

Assessment of the Risk of Bias

Two raters (A.T. and M.P.) independently assessed the methodological quality of the included studies according to the Cochrane Collaboration guidelines.[21] A third investigator (C.S.) arbitrated in the event of a lack of agreement.

Statistical Analysis

The percentage of absolute risk reduction (ARR) and the number needed to treat (NNT) were assessed as a measure of the therapeutic effect because these parameters are relevant from a clinical standpoint. ARR describes the difference in the rates of events between study and control populations, whereas NNT (defined as the inverse of the ARR) is the average number of patients who need to be treated to prevent 1 additional bad outcome.[21]

RESULTS

Figure 1 illustrates the PRISMA flow chart for study inclusion and exclusion. The search retrieved 68 records. Two further records were identified in the reference lists. After deleting duplicate results, 66 records remained for title and abstract review. Of these, 10 trials were selected for full-text examination. Three studies were excluded because patients were not randomized.[11,16,17] One study was excluded because no control group was present.[15] At the end, 6 studies fulfilled the inclusion criteria and were suitable for the analysis.[10,12–14,18,19]

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Characteristics of the Included Studies

References	Patients	Randomization	Follow-up (mo)	Clinical Evaluation	Main Results	Adverse Events
Trespi et al[10]	166	Mesalazine (400 mg bid per 8 wk) (n = 81) High fiber diet (≥ 30 g/d) (n = 85)	48	Recurrence of symptoms	The likelihood of remaining symptom free during follow-up favored treatment with mesalazina	Epigastric pain in 13 patients Epigastric pain in 4 patients
Di Mario et al[12]	170	Mesalazine 400 mg bid (n = 40) Mesalazine 800 mg bid (n = 48) Rifaximin 200 mg bid (n = 39) Rifaximin 400 mg bid (n = 43)	3	A questionnaire on 11 clinical variables (upper/lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria), scored from 0 = no symptoms to 3 = severe (incapacitating symptoms with inability to perform normal activities)	In all treatments but rifaxim 200 mg bid group 3 of the 11 symptoms improved. The global score decreased in all groups but rifaxim 200 mg bid group. Mesalazine-treated patients had the lowest global score at 3 mo. Mesalazine was as effective as rifaximin 400 mg bid for relieving some symptoms, but appeared to be better than rifaximin in improving the global score in those patients. No cases of diverticulitis occurred during follow-up	
Tursi et al[13]	90	Mesalazine 800 mg bid (n = 30) Mesalazine 800 mg bid + *Lactobacillus casei* 750 mg a day (n = 30) *Lactobacillus casei* 750 mg a day (n = 30)	12	Recurrence of symptoms	In both mesalazine and *Lactobacillus casei* group 76.7% of patients were symptom free. In the group that used both medications together, the number of patients, who were symptom free, was significantly greater than in the other groups. One case of acute uncomplicated diverticulitis occurred in *Lactobacillus. casei* group	Transitory epigastric pain occurred in 2 patients and reansitory pain in 1 patient
Comparato et al[14]	268	Mesalazine 400 mg bid (n = 66) Mesalazine 800 mg bid (n = 67) Rifaximin 200 mg bid (n = 66) Rifaximin 400 mg bid (n = 69)	12	A questionnaire on 12 clinical variables (upper abdominal pain/discomfort, lower abdominal pain/discomfort, bloating, tenesmus, diarrhea, abdominal tenderness, fever, general illness, nausea, emesis, dysuria, and bleeding) graded on a quantitative scale from 0 (no symptoms) to 3 (severe, incapacitating symptoms with inability to perform normal activities)	All the treatment regimens, but rifaximin 400 mg bid, were effective in reducing symptoms scores. Patients treated with mesalazine 800 mg bid had the significantly lowest scores for symptoms. Diverticulitis occurred in 2 patients in the group treated with rifaximin 400 mg bid and in 1 patient in the group treated with rifaximin 800 mg bid	Nausea, headache, and asthenia were observed in 5 patients in rifaximin groups and in 4 patients in mesalazine groups
Kruis et al[18]	117	Mesalazine 1 g tid (n = 56) Placebo (n = 61)	1	Change in lower abdominal pain at week 4 (baseline defined using pain score from 7 d pretreatment)	Median change in lower abdominal pain was similarly	Adverse events occurred in 13 patients randomized to mesalazine and in 17 in the placebo group. The most frequently reported adverse events were headache and diarrhea
Tursi et al[19]	210	Mesalazine 800 mg bid (n = 51) Mesalazine 800 mg bid + *Lactobacillus casei* 750 mg a day (n = 54) *Lactobacillus casei* 750 mg a day (n = 55) Placebo(n = 50)	12	Recurrence of SUDD was defined as the reappearance of abdominal pain during follow-up, scored as ≥ 5 (0: best; 10: worst) for at least 24 consecutive hours	Recurrence of SUDD occurred in no patient in *Lactobacillus casei* + mesalazine group, in 7 (13.7%) patients in mesalazina group, in 8 (14.5%) patients *in Lactobacillus casei* group and in 23 (46.0%) patients in placebo group. Acute diverticulitis occurred in 6 patients in the placebo group and in 1 patient in the *Lactobacillus casei* group	No adverse events related to study drugs were reported

SUDD indicates symptomatic uncomplicated diverticular disease.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Description of the Included Studies

The included studies are described in Table 1.

Analysis of Data

Risk of Bias

Only 2 trials[18,19] were of high quality. All the other studies had inadequate generation of randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and the risk of selective reporting. Incomplete outcome data were present in the study of Comparato et al.[14]

Symptom Relief

All studies provided data on symptoms, according to the definition. As shown in Table 2, symptom relief with mesalazine was always larger than that with placebo and other therapies. However, ARR and NNT were significant only when mesalazine was compared with placebo and a high-fiber diet and rifaximin with long-term follow-up.

Globally, symptom relief was achieved in 440 of 526 (83.6%) patients, a proportion higher than that observed with placebo (58/111, 52.3%) or any other treatment.

Prevention of Diverticulitis Occurrence

Four studies provided information about the occurrence of diverticulitis during follow-up.[10,13,14,19] Table 2 shows that the incidence of this complication with mesalazine was lower than that observed with placebo and other treatments. However, ARR and NNT were significant only when compared with placebo.

Globally, diverticulitis occurred in 4 of 382 patients (1.1%) given mesalazine and in 6 of 50 patients (12.0%) given placebo.

DISCUSSION

SUDD is the most common clinical form of symptomatic diverticular disease. Several symptoms describe this specific subtype of the disease, ranging from abdominal pain to alteration of bowel habits, often resembling irritable bowel syndrome. It has been recently suggested that pain in the left lower quadrant (especially its duration) is the best pathognomonic symptom of SUDD, which is able to differentiate it from irritable bowel syndrome.[22,23]

Despite the large epidemiological impact of SUDD, the "standard of care" for the treatment of symptoms and for the prevention of diverticulitis occurrence is not yet established. Consistent evidence indicates that dietary fiber, especially the insoluble fiber found mostly in fruits and vegetables rather than cereals, decreases the risk of diverticula development, but evidence with respect to SUDD and diverticulitis is still lacking.[24,25]

The administration of the nonabsorbable antibiotic rifaximin is able to reduce most of the clinical manifestations of diverticular disease and, when compared with fiber supplementation alone, has been reported to improve the clinical benefits of dietary fiber in SUDD.[26] A systematic review assessed the long-term efficacy of rifaximin plus fiber supplementation against fiber supplementation alone on symptoms and complications in patients with SUDD.[27] A meta-analysis of data found that treatment with rifaximin and fiber supplementation is effective in obtaining symptom relief and preventing complications.

Mounting evidence underlines the role of inflammation in the pathogenesis of diverticular disease, ranging from increased inflammatory infiltrate to the enhanced expression of proinflammatory cytokines (such as TNF).[28] Hence, diverticular disease may be considered as a chronic inflammatory process, in which mesalazine may represent an appealing therapeutic tool. Recently, Smith et al[29] found that besides decreasing the duration of abdominal pain, mesalazine reduced important inflammation and pain genes.

Results of the current systematic review show that mesalazine administration achieves symptomatic relief and reduce the occurrence of diverticulitis in a larger proportion of patients with SUDD when compared with other treatments and placebo controls.

Obviously, this study has limitations related to the underlying literature on the topic. First, the number of RCTs included is low. This is because mesalazine is now out of patent and it is unlikely that any large RCT in SUDD might ever be sponsored, at least for conventional formulations. Although the RCTs included had a similar patient population and endpoint, the comparator was different, including high-fiber treatment, placebo treatment, probiotic treatment, or rifaximin treatment. Overall, mesalazine was found to be significantly more effective than other treatments. In particular, mesalazine proved to be better than placebo in both endpoints analyzed. Moreover, the ARR over placebo, observed by Tursi et al,[19] is higher than that achieved in the Kruis trial.[18] The same holds true when mesalazine was studied against low-dose rifaximin.[12,14] One possible explanation for this apparent quantitative difference is the duration of mesalazine treatment, which was considerably longer in trials achieving better results. It is conceivable that the longer the treatment, the better the control of low-grade mucosal inflammation.

The quality of the trials included in this systematic review is poor. This could lead to an overestimation of the treatment effect of mesalazine. Blinding and a placebo-controlled group were guaranteed only in 2 studies.[18,19] The present study assessed only the effectiveness of mesalazine in patients with SUDD. Therefore, the role of mesalazine in preventing diverticulitis recurrence was not an endpoint of this study, because SUDD and diverticulitis seem to show different responses to medical treatment.[28] In particular, mesalazine seems to be effective in preventing primary diverticulitis occurrence from SUDD but not secondary diverticulitis recurrence.[30–32] A potential explanation for this dichotomy is that SUDD and diverticulitis are 2 different diseases. SUDD is characterized by mucosal inflammation, whereas acute diverticulitis is characterized by transmural inflammation, leading to fibrosis. Fibrosis may be the key feature explaining mesalazine effectiveness in SUDD but not in diverticulitis.[33,34] If the patients are at the first episode of diverticulitis, it is likely that the disease still has low-grade fibrosis but marked inflammation: in these patients, mesalazine could still be able to control inflammation and, as a consequence, symptoms and recurrence of the disease. In contrast, >2 attacks of acute diverticulitis are able to cause fibrosis, limiting mesalazine absorption across the colonic wall and making it inefficacious.

With the exception of the study of Kruis et al,[18] all the trials included in the present analysis used a pH-dependent formulation of mesalazine, which has stood the test of time

TABLE 2. Symptom Relief and Diverticulitis Occurrence at Maximal Follow-up

References	Randomization	Symptom Relief	ARR (95% CI)	NNT (95% CI)	Diverticulitis Occurrence	ARR (95% CI)	NNT (95% CI)
Trespi et al[10]	Mesalazine (400 mg bid per 8 wk) (n = 81)	69/81 (85.2)	31.1 (17.9-44.2)	3.2 (2.3-5.6)	2/81 (2.4)	8.6 (1.1-11.2)	11.6 (6.2-92.2)
	High fiber diet (≥ 30 g/d) (n = 85)	46/85 (54.1)	Reference	Reference	9/85 (11.0)	Reference	Reference
Di Mario et al[12]	Mesalazine 400 mg bid (n = 40) and mesalazine 800 mg bid (n = 48)	82/88 (93.2)	5.4 (−3.5 to 14.2)	18.6 (7.0-infinity)	—	—	—
	Rifaximin 200 mg bid (n = 39) and rifaximin 400 mg bid (n = 43)	72/82 (87.8)	Reference	Reference			
Tursi et al[13]	Mesalazine 800 mg bid (n = 30) and mesalazine 800 mg bid + *Lactobacillus casei* 750 mg a day (n = 30)	52/60 (86.7)	10.0 (−7.41 to 27.41)	10.0 (3.6-infinity)	0/60 (0)	3.3 (−4.6 to 11.2)	30.0 (8.9-infinity)
	Lactobacillus casei 750 mg a day (n = 30)	23/30 (76.7)	Reference	Reference	1/30 (3.3)	Reference	Reference
Comparato et al[14]	Mesalazine 400 mg bid (n = 66) and mesalazine 800 mg bid a day (n = 67)	96/133 (72.2)	33.7 (2.5%-44.9%)	3.0 (2.2-4.5)	1/133 (0.7)	1.5 (−1.4 to 4.4)	68.0 (22.9-infinity)
	Rifaximin 200 mg bid (n = 66) and rifaximin 400 mg bid (n = 69)	52/135 (38.5)	Reference	Reference	3/135 (2.2)	Reference	Reference
Kruis et al[18]	Mesalazine 1 g tid (n = 56)	41/56 (73.2)	7.6 (6.2%-29.5%)	13.1 (24.3-infinity)	—	—	—
	Placebo (n = 61)	40/61 (65.6)	Reference	Reference			
Tursi et al[19]	Mesalazine 800 mg twice a day (n = 51) and mesalazine 800 mg bid + *Lactobacillus casei* 750 mg a day (n = 54)	98/105 (93.3)	39.3 (24.7-53.9)	2.5 (1.9-4.0)	0/105 (0%)	12.0 (2.9.6-21.0)	8.3 (4.8-33.4)
	Lactobacillus casei 750 mg a day (n = 55)	47/55 (85.4)	31.5 (14.8-48.1)	3.2 (2.1-6.8)	1/55 (1.8%)	10.2 (0.5-19.8)	9.8 (5.0-197.3)
	Placebo (n = 50)	27/50 (54.0)	Reference	Reference	6/50 (12.0%)	Reference	Reference

Values are expressed as number (%)
ARR indicates absolute risk reduction; CI, confidence interval; NNT, number needed to treat.

for the treatment of inflammatory bowel disease. The impact and the efficacy of newer mesalazine formulations (eg, granules and MMX-based technology) is almost unknown. Actually, the site and the amount of mesalazine released might well influence the therapeutic response in SUDD.

Finally, although the trials included apparently similar patient populations (namely patients with colonic diverticula and related symptoms), the imaging (whether endoscopic or radiologic) criteria were not strictly standardized. Future studies should overcome these limitations by enrolling patients with the same endoscopic findings. The first endoscopic classification of colonic diverticular disease (ie, DICA, Diverticular Inflammation and Complication Assessment) has been recently developed and validated.[35] It is advisable that future trials enroll homogeneous populations to better define the correct management strategy for this complex disease. The therapeutic role of mesalazine might then be assessed more precisely.

In conclusion, the present systematic review shows that mesalazine is more effective in obtaining symptom relief and in preventing diverticulitis occurrence in comparison with placebo and other therapies in SUDD. However, larger and well-designed studies are needed to assess the long-term impact of this treatment on diverticular disease outcomes.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

ACKNOWLEDGMENTS

The authors are indebted to Professor Alex Ford (Leeds Institute of Biomedical and Clinical Sciences, Leeds, UK) for his useful suggestions and to the Authors (Drs Aragona and Comparato, Professor Kruis) who provided us with some unpublished data.

REFERENCES

1. Tursi A, Papagrigoriadis S. Review article: the current and evolving treatment of colonic diverticular disease. *Aliment Pharmacol Ther*. 2009;30:532–546.
2. Humes DJ, Spiller RC. Review article: the pathogenesis and management of acute colonic diverticulitis. *Aliment Pharmacol Ther*. 2014;39:359–370.
3. Etzioni DA, Mack TM, Beart RW Jr, et al. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. *Ann Surg*. 2009;249:210–217.
4. Petruzziello L, Iacopini F, Bulajic M, et al. Review article: uncomplicated diverticular disease of the colon. *Aliment Pharmacol Ther*. 2006;23:1379–1391.
5. Humes D, Simpson J, Spiller R. Colonic diverticular disease. *Clin Evid (Online)*. 2007;2007. pii: 0405.
6. Haglund U, Hellberg R, Johnsen C, et al. Complicated diverticular disease of the sigmoid colon. An analysis of short and long-term outcome in 392 patients. *Ann Chir Gynaecol*. 1979;68:41–46.
7. Shahedi K, Fuller G, Bolus R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol*. 2013;11:1609–1613.
8. Binda GA, Arezzo A, Serventi A, et al. Multicentre observational study of the natural history of left-sided acute diverticulitis. *Br J Surg*. 2012;99:276–285.
9. Köhler L, Sauerland S, Neugebauer E. Diagnosis and treatment of diverticular disease: results of a consensus development conference. The Scientific Committee of the European Association for Endoscopic Surgery. *Surg Endosc*. 1999;13:430–436.
10. Trespi E, Panizza P, Colla C, 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.
11. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit*. 2004;10:PI70–PI73.
12. 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.
13. Tursi A, Brandimarte G, Giorgetti GM, et al. Mesalazine and/or *Lactobacillus casei* in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol*. 2006;40:312–316.
14. Comparato G, Fanigliulo L, Cavallaro LG, et al. Prevention of complications and symptomatic recurrences in diverticular disease with mesalazine: a 12-month follow-up. *Dig Dis Sci*. 2007;52:2934–2941.
15. Tursi A, Brandimarte G, Giorgetti GM, et al. Continuous versus cyclic mesalazine therapy for patients affected by recurrent symptomatic uncomplicated diverticular disease of the colon. *Dig Dis Sci*. 2007;52:671–674.
16. Tursi A, Brandimarte G, Giorgetti GM, et al. Mesalazine and/or *Lactobacillus casei* in maintaining long-term remission of symptomatic uncomplicated diverticular disease of the colon. *Hepatogastroenterology*. 2008;55:916–920.
17. Gatta L, Di Mario F, Curlo M, et al. Long-term treatment with mesalazine in patients with symptomatic uncomplicated diverticular disease. *Intern Emerg Med*. 2012;7:133–137.
18. Kruis W, Meier E, Schumacher M, et al. Randomised clinical trial: mesalazine (Salofalk granules) for uncomplicated diverticular disease of the colon—a placebo-controlled study. *Aliment Pharmacol Ther*. 2013;37:680–690.
19. 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.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151:65–94.
21. Higgins JPT, Green S. eds. Cochrane handbook for systematic reviews of interventions, version 5.1.0. 2011. Available at: http://cochrane-handbook.org. Accessed May 24, 2016.
22. 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.
23. Tursi A, Elisei W, Picchio M, et al. Moderate to severe and prolonged left lower-abdominal pain is the best symptom characterizing symptomatic uncomplicated diverticular disease of the colon: a comparison with fecal calprotectin in clinical setting. *J Clin Gastroenterol*. 2015;49:218–221.
24. Peery AF, Barrett PR, Park D, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. *Gastroenterology*. 2012;142:266–272.
25. Ünlü C, Daniels L, Vrouenraets BC, et al. A systematic review of high-fibre dietary therapy in diverticular disease. *Int J Colorectal Dis*. 2012;27:419–427.
26. Latella G, Scarpignato C. Rifaximin in the management of colonic diverticular disease. *Expert Rev Gastroenterol Hepatol*. 2009;3:585–598.
27. Bianchi M, Festa V, Moretti A, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. *Aliment Pharmacol Ther*. 2011;33:902–910.
28. Tursi A. New physiopathological and therapeutic approaches to diverticular disease: an update. *Expert Opin Pharmacother*. 2014;15:1005–1017.
29. Smith J, Humes D, Garsed K, et al. Mechanistic randomised control trial of mesalazine in symptomatic diverticular disease. *Gut*. 2012;61:A51–A52.
30. Stollman N, Magowan S, Shanahan F, et al. A randomized controlled study of mesalamine after acute diverticulitis: results of the DIVA trial. *J Clin Gastroenterol*. 2013;47:621–629.
31. Parente F, Bargiggia S, Prada A, et al. Intermittent treatment with mesalazine in the prevention of diverticulitis recurrence: a randomised multicentre pilot double-blind placebo-controlled study of 24-month duration. *Int J Colorectal Dis*. 2013;28:1423–1431.
32. Raskin JB, Kamm MA, Jamal MM, et al. Mesalamine does not prevent recurrent diverticulitis in phase 3 controlled trials. *Gastroenterology*. 2014;147:793–802.
33. Tursi A, Elisei W, Giorgetti GM, et al. Expression of basic fibroblastic growth factor, syndecan 1 and tumour necrosis factor α in resected acute colonic diverticulitis. *Colorectal Dis*. 2014;16:O98–103.
34. Tursi A, Elisei W, Inchingolo CD, et al. Chronic diverticulitis and Crohn's disease share the same expression of basic fibroblastic growth factor, syndecan 1 and tumour necrosis factor-α. *J Clin Pathol*. 2014;67:844–846.
35. 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.