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REVIEW

Treatment of diverticular disease: an update on latest evidence and clinical implications

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Abstract

Background: Diverticular disease (DD) is a common condition, especially in Western countries. In about 80% of patients, colonic diverticula remain asymptomatic (diverticulosis), while approximately 20% of patients may develop abdominal symptoms (symptomatic uncomplicated diverticular disease, SUDD) and, eventually complications as acute diverticulitis (AD). The management of this condition has been improved, and in the last five years European countries and the USA have published guidelines and recommendations.

Scope: To summarize the latest evidence and clinical implication in treatment of DD focusing the attention either on the treatment of diverticulosis, SUDD and AD together with the primary and secondary prevention of diverticulitis.

Findings: The present review was based on the latest evidence in the treatment of DD in the last 10 years. In the last 5 years, six countries issued guidelines on DD with differences regarding covered topics and recommendations regarding treatments. At present there is a lack of rationale for drug use in patients with asymptomatic diverticulosis, but there are limited indications to suggest an increase in dietary fibre to reduce risk of DD. To achieve symptomatic relief in SUDD patients, several therapeutic strategies with fibre, probiotics, rifaximin and mesalazine have been proposed even if a standard therapeutic approach remained to be defined. Agreement has been reached for the management of AD, since recent guidelines showed that antibiotics can be used selectively, rather than routinely in uncomplicated AD, although use of antibiotics remained crucial in the management of complicated cases. With regard to treatment for the primary and secondary prevention of AD, the efficacy of rifaximin and mesalazine has been proposed although with discordant recommendations among guidelines.

Conclusion: Treatment of DD represented an important challenge in clinical practice, especially concerning management of SUDD and the primary and secondary prevention of AD.

Keywords: acute diverticulitis, diverticulosis, fibre, guidelines, mesalazine, probiotics, rifaximin, symptomatic uncomplicated diverticular disease, treatment.

Citation

Carabotti M, Annibale B. Treatment of diverticular disease: an update on latest evidence and clinical implications. Drugs in Context 2018; 7: 212526. DOI: 10.7573/dic.212526

Introduction

In Western countries, colonic diverticula are significantly frequent, affecting up to 50–66% of individuals aged 80 years or older [1]. The majority of individuals with colonic diverticula remain asymptomatic (i.e., colonic diverticulosis), whereas about one-fifth of subjects may develop abdominal symptoms, as abdominal pain, changes in bowel habits and bloating, a condition termed symptomatic uncomplicated diverticular disease (SUDD). This condition might resemble irritable bowel syndrome (IBS), but features of abdominal pain and presence of pain lasting for more than 24 hours might help to differentiate patients with SUDD from those with IBS [2–6]. About 4% of patients with colonic diverticula develop acute diverticulitis (AD), an inflammatory process that may result in complications in about 15% of patients, with the development of abscesses, perforation, fistula, obstruction or peritonitis [7]. Recurrence of diverticulitis after the first episode has been reported to occur in 15–30% of patients [8,9].

Recently, the Western scientific community has focused more attention to DD and, in the last 5 years, many European countries [10–15] and the USA [16] have published guidelines and recommendations, but the topics discussed were not the same among countries (Table 1). All cited guidelines focused their attention on AD, with less attention to diverticulosis and SUDD treatments (Table 1).

Table 1. Comparison among European and US guidelines: covered topics.

	Andersen et al. [10], Denmark	Andeweg et al. [11], Holland	Kruis et al. [12], Germany	Pietrzak et al. [13], Poland	Cuomo et al. [14], Italy	Binda et al. [15], Italy	Stollman et al. [16], USA
Diverticulosis	Only definition	Only definition	Only definition	√	√	√	
Symptomatic uncomplicated diverticular disease				√	√	√	
Acute diverticulitis	√	√	√	√	√	√	√
Treatment of diverticulosis				√	√	√	
Treatment for symptomatic uncomplicated diverticular disease	√		√	√	√	√	
Treatment for acute diverticulitis	√	√	√	√	√	√	√
Prevention of acute diverticulitis		√	√	√	√	√	√

The aim of this review is to summarize the latest evidence and clinical implications for the treatment of DD focusing on the treatment of diverticulosis, SUDD and AD together with the primary and secondary prevention of diverticulitis.

Methods

The present review was based on the most relevant topics related to the latest evidence and clinical implications in the treatment of DD. These include the following topics: (i) treatment of colonic diverticulosis; (ii) treatment of SUDD; (iii) treatment of AD; (iv) treatment for the primary prevention of AD; (v) treatment for the secondary prevention of AD. Each topic was dealt with according to the best evidence available, with particular reference to the most recent European and US guidelines on diverticular disease. A comprehensive search of the PubMed and Scopus database up to December 2017 was performed. Reports published in English, during the last 10 years were considered. Colonic diverticular bleeding and the surgical treatment of DD were not addressed in this review.

Results

Colonic diverticulosis

Colonic diverticulosis represents an incidental finding in asymptomatic patients undergoing gastrointestinal evaluation for other indications. After 50 years of age, colonic diverticulosis is the most commonly reported finding reported on colonoscopy usually performed for colon cancer screening [17]. One of the most frequently asked questions is whether these asymptomatic patients should be treated. Polish [13] and Italian [14,15] guidelines addressed the issue of pharmacological treatment of diverticulosis, suggesting that no rationale for treatment or monitoring asymptomatic colonic diverticulosis subsist (Table 1). As for dietetic counselling, there are limited indications to suggest an increase in dietary fibre to reduce the risk of DD in this setting [10,14,15] (see paragraph 'Treatment for the primary prevention of acute diverticulitis').

Symptomatic uncomplicated diverticular disease

SUDD represents a 'grey' clinical condition characterized by recurrent abdominal symptoms such as recurrent abdominal pain, bloating and changes in bowel habits attributed to diverticula in the absence of macroscopical alterations other than diverticula. Abdominal complaints observed in SUDD may be similar from those of IBS, but some abdominal pain features would be helpful to differentiate these two disorders [2–6,18]. A key difference between pain associated with SUDD and IBS is the localisation of the pain: IBS patients typically complained of diffuse/generalised pain, whereas SUDD patients have a pain often localised in left iliac fossa. During pain, IBS patients may experience either diarrhoea or constipation, while in DD, diarrhoea is slightly more frequent. Another diagnostic feature in IBS is the relief of pain by defecation or flatulence, while SUDD patients did not present this picture. In addition, SUDD presented more frequently a long-lasting pain, lasting more than 24 hours [2–6,18].

International guidelines partially address the definition [13,14,15] and treatment [10,12–15] of SUDD (Table 1). The main purpose in the management of SUDD is the relief of abdominal symptoms. Even if a standard therapeutic approach still remained to be defined, several dietary and pharmacologic strategies have been proposed in this condition. DD is a complex, multifactorial disorder, in which the gut microbiota could play a pathogenetic key role. In fact, Barbara and colleagues recently reported that patients with DD showed depletion of microbiota members with anti-inflammatory properties, including *Clostridium* cluster IV, *Clostridium* cluster IX, *Fusobacterium* and Lactobacillaceae, with microbiota

changes being related with mucosal immune activation [19]. On these basis, treatments having gut microbiota as therapeutic targets, such as fibres, probiotics or rifaximin have been proposed in SUDD [20].

Fibre

Although dietary and supplementary fibre have been proposed for the symptomatic relief in SUDD patients, the therapeutic benefit is not yet fully understood. In SUDD patients, fibres might act through: (i) conferring benefits by increasing faecal mass and promoting the regularity of bowel movements; (ii) capability to act as prebiotics in the colon, by favouring health-promoting species of the intestinal microbiota, especially bifidobacteria and lactobacilli [21]. The gut microbiota, indeed, shifts rapidly in response to dietary changes, particularly with fibre intake [22]. However, evidence for a therapeutic benefit of a high-fibre diet in the treatment of DD is poor. Five years ago, a systematic review assessed whether a high-fibre diet can improve symptoms or prevent complications of DD. Few studies (three randomised control trials [RCTs] and one case–control study) were identified, and the authors concluded that high-quality evidence for a high-fibre diet in the treatment of DD is lacking [23]. A more recent systematic review aimed to update the evidences on the efficacy of fibre treatment, both dietary and supplemental, in terms of a reduction in symptoms and the prevention of AD in SUDD patients [24]. Nineteen studies were included, nine with dietary fibre and ten with supplemental fibre, with a high heterogeneity concerning the quantity and quality of fibres employed. Authors concluded that, even single low-quality studies suggest that fibres, both dietary and supplemental, could be beneficial in the treatment of SUDD, the presence of substantial methodological limitations, the heterogeneity of therapeutic regimens employed, and the lack of *ad hoc* designed studies, do not permit a summary of the outcome measures. On the basis of these data, fibre supplements are suggested in Danish [10] and Polish [13] guidelines, whereas Italian guidelines argue that fibre supplementation alone provides controversial results in terms of symptom relief [14,15].

Probiotics

Probiotics may modify the gut microbial balance leading to health benefits due to their anti-inflammatory effects and capability to enhance anti-infection defences by maintaining an adequate bacterial colonization in the gastrointestinal tract and by inhibiting colonic bacterial overgrowth and metabolism of pathogens [25–27]. A recent systematic review aimed to summarize data on the efficacy of probiotics in DD in terms of remission of abdominal symptoms and prevention of AD [28]. Eleven studies (two were double-blind, randomized, placebo-controlled; five were open, randomized; four were non-randomized open studies) were selected. Authors concluded that even the efficacy of probiotics reported in the single-controlled studies seemed to show a trend toward a positive clinical response on abdominal symptoms or their recurrence; however, several limitations – largely arising from the nature of the included studies – impair the results of this systematic review [28]. As a consequence, available data do not allow conclusions to be made. Based on these data, Italian guidelines argued that there is insufficient evidence that probiotics are effective in reducing symptoms [14].

Rifaximin

Rifaximin is a poorly absorbable oral antibiotic for the treatment of several gastrointestinal diseases (i.e., acute bacterial diarrhoea, portal systemic encephalopathy). This drug exerts its gastrointestinal activity because of its peculiar pharmacological activities, *viz.*: non-systemic absorption, thus high faecal concentration and a broad spectrum of antimicrobial activity [29]. Furthermore, rifaximin acts through different mechanisms: (i) inhibition of bacterial growth; (ii) increase of resistance to bacterial infection; (iii) modulatory effect of some bacterial species, such as *Lactobacillus* spp and *Bifidobacterium* spp, leading to the so-called *eubiotic effect*; (iv) modulation of bacterial metabolism; (v) anti-inflammatory activity [29–31]. For these reasons, rifaximin is often used in European countries for symptomatic relief in SUDD patients and for the prevention of AD. Use of rifaximin in DD has been recently summarised in two systematic reviews [32,33], one of which is a meta-analysis [32]. The meta-analysis found that 64% of patients treated with rifaximin plus fibre supplements were symptom-free at one-year follow-up compared with 34.9% of patients treated with fibre alone. The pooled rate difference for symptom relief was 29.0% (rifaximin *vs* control; 95% CI: 24.5–33.6; $p<0.0001$; number needed to treat [NNT]=3) [32]. A non-interventional study, in an outpatient setting, evaluated the efficacy of rifaximin (400 mg b.i.d. for 7–10 days) for 3 months. The authors confirmed the beneficial effect of rifaximin on global gastrointestinal symptoms and showed a good safety profile of cyclic administration [34]. A more recent 'real-life' study conducted in an outpatient setting, evaluated the effect of the same therapeutic regimen in 142 SUDD patients: after 3 months, a significant reduction in symptoms was observed, and severity score symptoms reduced from 1.7±0.7 to 0.3±0.1 ($p<0.001$) [35].

Danish [10], Polish [13] and Italian [14,15] concur that cyclic rifaximin plus fibre supplementation should be used for SUDD patients for symptom relief. Furthermore, the position paper of the Italian Society of Gastroenterology on use of rifaximin in DD, supported its use together with fibre in SUDD, with a moderate grade of evidence [31]. However, the efficacy of rifaximin in SUDD needed to be further investigated in larger RCT placebo-controlled, in order to assess the best therapeutic dosage, the modality of administration (continue *vs* cyclic) and its efficacy alone or in association with probiotics.

Mesalazine

5-aminosalicylic acid (mesalazine) is an anti-inflammatory drug primarily used as a first-line therapy for patients with

inflammatory bowel disease. Its anti-inflammatory effect is not fully understood, but several mechanisms are likely involved: (i) reduction in synthesis of prostaglandins and pro-inflammatory cytokines; (ii) inhibition of the chemotaxis of neutrophils and inhibition of activation of nuclear factor kB transcription family (important for pro-inflammatory cytokines production); (iii) activation of nuclear receptor that downregulate inflammation; (iv) change in luminal pH (favouring growth of beneficial colonic bacteria) [36–38].

In SUDD, the rationale for the use of mesalazine is based on the recognition of inflammation as a therapeutic target [39]. Regarding the efficacy of mesalazine in SUDD, only two studies are double-blind and placebo controlled. Kruis and colleagues investigated the efficacy of mesalazine in a double-blind, placebo-controlled, multicentre, 6-week trial, where patients were randomized to mesalazine 3 g/day (Salofalk® granules, which differ from other mesalazine by combining both delayed and extended-release mechanisms) or placebo, in uncomplicated DD [40]. Regarding the primary endpoint, the change in lower abdominal pain with mesalazine compared with placebo was not different in the intent-to-treat (ITT) population (p=0.374), but better results were reached in the per-protocol (PP) population (p=0.053). *Post hoc* adjustment for confounding factors resulted significant in the PP population (p=0.005) [40]. In Italy, a multicentre, double-blind, placebo-controlled study investigated the efficacy of cyclic treatment (10 days/month for one year) with mesalazine 1.6 g/day with or without *Lactobacillus casei* subspecies *DG* 24 billion/day, in maintaining clinical remission of SUDD after a first episode [41]. Recurrence of SUDD occurred in 0% of patients treated with mesalazine and probiotics (group LM), in 13.7% of patients treated with mesalazine (group M), in 14.5% of patients treated with probiotics (group L) and in 46.0% of patients treated with placebo (group P) (p<0.001 for group LM, L and L *vs* P) [41].

Furthermore, the efficacy of mesalazine in SUDD has been evaluated in several open randomized trials, which results are summarised in recent reviews [32,38]. Even if some positive results have been found, the data presented different endpoints, different dosage and modality of treatments (continue *vs* cyclic) appearing heterogeneous, and no valid conclusion can be drawn. These discrepancies have led to different recommendations in Western guidelines, since Italian guidelines contend that there is no clear evidence that mesalazine alone is effective in reducing symptoms [14,15], whereas German guidelines [12] state that this condition can be treated with mesalazine. Further larger placebo-controlled RCTs are needed to establish if mesalazine represents a useful therapy in this condition and its therapeutic regimen.

Treatment of acute diverticulitis

AD is an inflammatory condition affecting at least one colonic diverticula, often associated with pericolonic inflammation [42]. Patients with AD usually complain of abdominal pain in the left lower quadrant, fever and leukocytosis, even if some patients do not present all these symptoms at the same time [43]. Furthermore, patients might have change in bowel habits, nausea, vomiting, urinary symptoms and elevated inflammatory markers. Contrast-enhanced computerised tomography (CT) should be considered as the first-line colonic examination since it offers a more comprehensive evaluation of uncomplicated and complicated forms [14,15]. In fact, the severity of diverticulitis is graded with the use of modified Hinchey's Criteria, based on CT imaging and on preoperative findings [44]. An important role in AD diagnosis is also provided by abdominal ultrasound (US), which in the hands of experienced investigators can be used as a sensitive and specific diagnostic technique [11,12,14,15]. A multicentre study evaluating the accuracy of US compared with CT in unselected patients referred for acute abdominal pain to the emergency department, showed that CT have higher sensitivity compared to US in detecting AD (81 *vs* 61%; p=0.048) [45]. Presently, a strategy providing CT after negative or inconclusive US has been proposed [11,14,15].

The majority of AD episodes are uncomplicated, with about 15% presenting complications as abscesses, fistulas, obstructions and perforations; even if a recurrence of AD has been reported in 15–30% of patients, generally the first episode is the most severe [8,9]. In a retrospective cohort study it has been showed that, during a follow-up period of 8.9 years, recurrence of AD appeared in 13.3% of patients and only 3.9% had a second recurrence. In this cohort, non-operative treatment was used in 80.6% of patients, whereas emergency colectomy was performed in 19.4% [9]. During follow-up, elective colectomy was performed in 7.3% of patients, with all re-recurrences were treated non-operatively [9].

Some lifestyle factors such as smoking, physical activity, dietary habits and especially fibre consumption have been associated to the development of diverticulitis [46].

Until 10 years ago, antibiotics were considered mandatory in the treatment of AD, even in mild episodes. This practice was based on the belief that diverticulitis was due to obstruction of a diverticulum leading to mucosal abrasions, microperforation and bacterial translocation [42]. However, this concept has been changed with newer hypotheses highlighting that AD may be an inflammatory rather than an infectious condition [47]. In fact, prospective randomized [48,49], case–control [50] and retrospective cohort study [51] shown no benefit for the use of antibiotics in the treatment of uncomplicated AD, suggesting that its use should be reserved for the treatment of complicated disease. The most recent RCT, was a multicentric observational study compared with antibiotic treatment (amoxicillin plus clavulanic acid 1.2g four times daily intravenously (i.v.) for at least 48 h, after which the route was switched to oral administration of 625 mg three times daily) for a first episode of CT-proven uncomplicated AD [49]. Regarding the primary endpoint, no differences about the median time to recovery were found: 14 days (6–35 days) for the observational and 12 days (7–30 days) for the antibiotic treatment strategy with a hazard ratio

Table 2. Recommended medical treatment of acute diverticulitis: comparison among European and US guidelines.

	Andersen et al. [10], Denmark	Andeweg et al. [11], Holland	Kruis et al. [12], Germany	Pietrzak et al. [13], Poland	Cuomo et al. [14], Italy	Binda et al. [15], Italy	Stollman et al. [16], USA
Treatment of acute uncomplicated diverticulitis	Not routine use of antibiotics	Not routine use of antibiotics	Not routine use of antibiotics	Not routine use of antibiotics	Not routine use of antibiotics	Not routine use of antibiotics	Not routine use of antibiotics
Treatment of acute complicated diverticulitis	Antibiotics	Antibiotics	Antibiotics	Antibiotics	Antibiotics	Antibiotics	NR
Primary prevention of acute diverticulitis	NR	NR	NR	Rifaximin+ fibre	Rifaximin+ fibre	Rifaximin+ fibre	NR
Secondary prevention of acute diverticulitis	NR	Rifaximin or Rifaximin+ Mesalazine or Mesalazine± Rifaximin or probiotics	Neither rifaximin or mesalazine or probiotics are recommended	Rifaximin+ fibre	Rifaximin+ fibre	Rifaximin+ fibre	Neither rifaximin or mesalazine or probiotics are recommended

Antibiotics: broad-spectrum antibiotics; NR: not reported.

(HR) for recovery of 0.91 (lower limit of one-sided 95% CI: 0.78; p=0.151). The same occurred for secondary endpoints – that is, no significant differences found: complicated diverticulitis (p=0.377), recurrent diverticulitis (p=0.494), sigmoid resection (p=0.323), readmission (p= 0.148), adverse events (p=0.221) and mortality (p=0.432) [49]. Also, a Cochrane review evaluating the antibiotic use in uncomplicated AD, found no significant difference between antibiotics compared with no antibiotics in the treatment of uncomplicated diverticulitis [52]. These findings supported the most recent European and US guidelines that suggested nonroutine use of antibiotics in patients with uncomplicated AD (Table 2). Use of antibiotics in uncomplicated AD should be made individually, and with indications for possible cases of severe infection or sepsis, severe comorbidities or in immunosuppressed patients [10–16].

The need of hospitalization has been also revised, since the safety of outpatient management of uncomplicated AD is emerging: a recent systematic review updating the evidence about the outpatient treatment of uncomplicated AD, concluded that this approach is safe, effective and economically efficient [53].

The management of complicated AD depends on its severity and complexity, and if it requires hospitalization, bowel rest and surgery in selected cases. Antibiotic therapy is part of the management of complicated diverticulitis and recent guidelines are in accordance at recommending broad-spectrum antibiotics (Table 2). Antibiotics that are more often used in AD include: ciprofloxacin (500 mg twice daily orally or 200 twice daily i.v.) combined with metronidazole (250–500 mg three times daily orally or 500 mg three times daily i.v.); amoxicillin-clavulanic acid (650 mg–1 g twice daily orally or 1, 2, 3, 4 times per day i.v.) [13]. Also clindamycin or metronidazole combined with trimethoprim/sulfamethoxazole or gentamicin, are used [13]. Biondo and colleagues evaluated 92 papers in a systematic review, concluding that patients with severe AD without need of emergency surgery, should be treated with hospitalisation, parenteral fluids and a single intravenous antibiotic active against aerobic and anaerobic bacteria [54].

Treatment for the primary prevention of acute diverticulitis

Treatment for the primary prevention of AD is partially covered by recent guidelines, because only Polish [13] and Italian [14,15] guidelines deal with this topic (Table 2). Here, we summarised the most recent evidence about use of fibre, rifaximin and mesalazine in the primary prevention of AD.

Fibre

Available data suggest that people with a higher intake of dietary fibre than a lower intake have a lower risk of DD.

A large prospective cohort study examined the associations between a vegetarian diet and dietary fibre intake with risk of DD. After a mean follow-up time of 11.6 years, vegetarians had a 31% lower risk (relative risk [RR] 0.69, 95% CI: 0.55–0.86) of DD compared with meat eaters. DD risk is inversely associated with dietary fibre consumption; participants consuming the highest quantity of fibre had a 41% lower risk of DD (0.59, 0.46–0.78; $p<0.001$ trend) compared with those consuming less fibre [55]. A more recent prospective study conducted on a cohort of middle-aged women confirmed this observation, reporting that the association with DD risk varied by the source of fibre, the reduced risk being strongest for cereal and fruit fibre [56]. Based on these data, recent European guidelines support the use of a high-fibre diet for the prevention of acute diverticulitis [11–15].

Rifaximin

Bianchi and colleagues, in a meta-analysis, summarised the results of four RCTs (only one of which was double-blind) that have evaluated the efficacy of rifaximin with fibre supplementation to prevent AD in patients with colonic DD. They found that the pooled RD=rate difference in the treatment group was –2% (95% CI: –3.4 to –0.6; $p=0.0057$; NNT=50) [32]. However, the only double-blind, placebo-controlled trial assessing the efficacy of rifaximin (400 mg twice daily for 7 days a month plus glucomannan 2 g/day) compared with glucomannan alone, found that both treatments showed the same effectiveness, since AD occurred in 2.4% of both group [57]. Maconi and colleagues evaluated data from placebo-controlled and unblended trials showing that AD was less frequent in patients treated with rifaximin plus fibre supplementation (1.1%) in comparison to fibre alone (2.9%) ($p=0.012$). Based on these data, the NNT to prevent an episode of AD in 1 year was 57 [33]. A recent retrospective study evaluated the efficacy of rifaximin (400 mg twice daily for 7 days a month, every 3 months) for 1 year in preventing AD [58]. Authors observed that AD rate between the 6th and 12th month was lower in the rifaximin group ($p=0.0001$), with a further improvement of quality of life [58]. Although with a low grade of evidence, the position paper of the Italian Society of Gastroenterology, suggested that rifaximin when administrated with fibre reduces the occurrence of diverticulitis (primary prevention) in patients with SUDD [31].

Finally, some evidence suggests that rifaximin may reduce the risk of occurrence of AD when associated with fibre intake, as advised in Polish [13] and Italian [14,15] guidelines, even though there is a high NNT and only a low number of RCT available.

Mesalazine

Tursi and colleagues, in a placebo-controlled trial designed to evaluate the effectiveness of mesalazine and/or probiotics in maintaining remission in SUDD, assessed the efficacy in prevention of AD as secondary endpoint [41]. In their study, mesalazine was more effective than placebo in preventing AD, since diverticulitis occurred in six cases of patients treated with placebo, in one of patients treated with probiotics, but no patients treated with mesalazine developed AD ($p=0.003$). Furthermore, as summarised by Maconi and colleagues [33], four open trials evaluated the efficacy of mesalazine, balsalazide, alone or in combination with probiotics, and probiotics alone in prevention of AD [59–62]. Considering together these four studies, 350 patients were included, reporting seven episodes of AD per year (yearly incidence rate=2%), and no significant difference among treatments were found [33].

More studies are needed to assess the efficacy of mesalazine alone in preventing occurrence of AD. At present, there is no clear evidence that mesalazine reduces episodes of AD in SUDD patients as per Italian guidelines [14].

Treatment for the secondary prevention of acute diverticulitis

Treatment for the secondary prevention of AD is discussed in almost all recent guidelines, although with discordant recommendations (Table 2). We now summarize the most recent evidence about use of rifaximin and mesalazine in the secondary prevention of AD.

Rifaximin

Several randomized trials evaluated the efficacy of rifaximin in secondary prevention of AD as summarised in a recent systematic review [33]. The most recent by Lanas and colleagues evaluated the efficacy of 1-year intermittent rifaximin (400 mg twice daily 7 days a month) plus fibre (*Plantago ovata* 3.5 g twice daily) in a multicentre open RCT to prevent AD recurrence [63]. After randomization, this study was switched from evidence-gathering to proof-of-concept because the recruitment rate did not reach the minimum anticipated. In this study, rifaximin was more effective compared to fibre alone in the secondary prevention of AD, because its recurrence occurred in 10.4% compared with 19.3% of patients, respectively ($p=0.033$). A small open trial by Tursi and colleagues compared rifaximin 800 mg/day for 10 days a month compared with mesalazine 1.6 g/day for 24 months, showing that 25 and 5% of patients, respectively, have a recurrence of diverticulitis ($p=0.002$) [64].

These weak data have led to different recommendations in Western guidelines with European guidelines advising that rifaximin seems to reduce the risk of recurrence of diverticulitis [11,13–15], whereas German [12] and US guidelines [16] suggest against the use of rifaximin. Available evidences are based on only a few studies with methodological limitations and heterogeneity of therapeutic regimens. Further placebo-controlled RCTs are needed to determine

the real benefit of rifaximin for the secondary prevention of diverticulitis.

Mesalazine

Recently, the efficacy of mesalazine in the secondary prevention of AD has been evaluated in large RCTs. Stollman and colleagues evaluated – in a 1-year double-blind, randomized, placebo-controlled study – the efficacy of mesalazine or mesalazine+*Bifidobacterium infantis* 35624, in the prevention of AD [65]. In this trial, mesalazine alone, or in combination with probiotics, did not prevent recurrence; the proportion of diverticulitis was comparable between the two groups [65]. Raskin and colleagues investigated the efficacy of mesalazine in preventing recurrence of diverticulitis in two identical but separate Phase III, randomized, double-blind, placebo-controlled, multicenter trials, involving 590 (PREVENT1) and 592 (PREVENT2) patients, respectively [66]. Patients were randomized to receive mesalazine (1.2, 2.4 or 4.8 g) or placebo once daily for 104 weeks. Authors reported that, among patients in PREVENT1, 53–63% did not have disease recurrence, compared with 65% of those given placebo, whereas among patients in PREVENT2, 59–69% of patients did not have disease recurrence, compared with 68% of those given placebo; thus without differences between groups [66]. More recently two Phase III, randomised, placebo-controlled, double-blind multicentre trials (SAG-37 and SAG-51) investigated the efficacy of mesalazine granules in the prevention of recurrence [67]. Patients were randomised to receive either 3 g of mesalazine once daily or placebo (SAG-37, n=345) or to receive either 1.5 g mesalazine once daily, 3 g once daily or placebo for 96 weeks (SAG-51, n=330). Mesalazine did not increase the proportion of recurrence-free patients compared to placebo, being proportion of recurrence-free patients 67.9% compared with 74.4% (p=0.226) and 46, 52 and 58% (p=0.86) in SAG-37 and SAG-51, respectively, over 48 weeks [67]. Also a recent Cochrane review (not including Kruis and colleagues' study), concluded that the effects of mesalazine on recurrence of diverticulitis are uncertain owing to the small number of heterogeneous trials available [68].

Based on the available evidence, guidelines showed some discrepancies, since Dutch [11] guidelines suggested its use, whereas German [12], Polish [13], Italian [14] and US guidelines [16] did not recommend use of mesalazine in the secondary prevention of acute diverticulitis.

Discussion

Data emerging from this review suggests the potential use of fibre, probiotics, rifaximin and mesalazine and their possible combination in treatment of DD. In the last 5 years, six countries have issued guidelines that differ with regard to topics covered and recommendations regarding treatment. Recent evidence regarding the treatment of SUDD and the primary and secondary prevention of AD are conflicting, and often based on uncontrolled trials. However, guidelines agreement has been reached with regard to the management of AD, since recent strong data showed that antibiotics can be used selectively, rather than routinely, in uncomplicated AD, though use of antibiotics remains crucial in the management of complicated cases.

This review suggests the need of robust well-designed placebo-controlled RCTs that take into consideration of the clinical history of patients (i.e., asymptomatic *vs* symptomatic/with or without previous episode of AD) in order to achieve clearer evidence for each patient's DD categories and to optimize clinical practice.

Contributions: Marilia Carabotti performed the data extraction and collection, and wrote the manuscript. Bruno Annibale contributed to the conception and design of the study and to the final revision of the manuscript. Both authors approved the final draft submitted.

Disclosure and potential conflicts of interest: Marilia Carabotti has no conflict of interest to declare; Bruno Annibale reports grants and personal fees from Alfa Wassermann, grants and personal fees from Allergan, personal fees from Malesci, and grants from Biohit. These are all outside of the submitted work. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2018/02/dic.212526-COI.pdf

Funding declaration: No funding was provided.

Article URL: http://www.drugsincontext.com/treatment-of-diverticular-disease-an-update-on-latest-evidence-and-clinical-implications

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Provenance: invited; externally peer reviewed.

Submitted: 17 January 2018; **Peer review comments to author:** 21 February 2018; **Revised manuscript received:** 23 February 2018; **Accepted:** 23 February 2018; **Publication date:** 21 March 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

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