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Hot Topics in Medical Treatment of Diverticular Disease: Evidence Pro and Cons

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ABSTRACT

Symptomatic Uncomplicated Diverticular Disease (SUDD) is the most common clinical form of Diverticular Disease (DD). The therapy should be aimed at reducing both the intensity and frequency of symptoms as well as preventing complications. The pharmacological treatments include fibers, not absorbable antibiotics (for example rifaximin), anti-inflammatory drugs (for example 5-amino-salycilic acid) and probiotics, alone or in combination with other drugs. Although some of these treatments seem to be effective in treating SUDD, but their efficacy in preventing complications of the disease is still uncertain. It has been hypothesized that microbial imbalance associated with bacterial overgrowth of the colon, may be the key to the development of diverticular disease (DD). Therefore, drugs that can manipulate gut microbiota such as probiotics or rifaximine are considered as a potential key therapy. Rifaximine is able to modulate the intestinal ecosystem, restoring eubiosis. Traditionally, DD of the colon is thought to be related to low grade of inflammation. By analogy with other inflammatory bowel diseases mesalazine has been studied also in DD. There are several evidences that may support the use of mesalazine in the SUDD. Unfortunately, mesalazine cannot be used to prevent diverticulitis because of the paucity of high-quality studies. Currently, mesalazine has a limited place for the management of SUDD. In SUDD probiotics have been proven as an effective therapy in reducing abdominal symptoms, but unfortunately there has been limited number of relevant studies regarding efficacy of this therapy.

Key words: diverticulosis – diverticular disease – diverticulitis – rifaximin – mesalazine – probiotics .

Abbreviations: AUD: acute uncomplicated diverticulitis; CDD: complicated diverticular disease; CRP: C reactive protein; CT: computer tomography; DD: diverticular disease; FC: Fecal calprotectin; SUDD: symptomatic uncomplicated diverticular disease.

ANTIBOTICS: PRO AND CONS

Pro

The pathogenesis of symptomatic uncomplicated diverticular disease (SUDD) is complex, multifactorial, and still under discussion. New insights have emerged in recent years regarding irreversible changes in the intestinal microbiota, which appear to be crucial for the occurrence and persistence of symptoms [1-3].

Why to use rifaximin in SUDD? Because in patients with SUDD there is often the presence of small intestinal bacterial overgrowth (SIBO), and rifaximin is able to control the symptoms [4]. Bacteria-induced immune activation will generate a low-grade mucosal inflammation. This alteration will lead to development and/or persistence of symptoms [5].

Rifaximin is a poorly absorbed oral antibiotic and it has activity against anaerobic, gram-positive, and gram-negative bacteria, including Clostridium difficile. It is not systemically absorbed and is active only in the gastrointestinal tract. It may work by reducing bacterial byproducts and altering intestinal microbiota. Serious adverse effects from rifaximin are rare (less than 1%). It should not be used in patients with severe hepatic impairment and rarely causes C. difficile–associated colitis [6].

Rifaximin is also known for its direct and indirect anti-inflammatory mechanisms via inhibition of transcription factors and cytokines through the pregnane X receptor and reduction of bacterial virulence, adhesion, and translocation [7, 8].

Some studies showed that rifaximin treatment promotes the growth of beneficial bacteria, such as Bifidobacteria and Lactobacillus. Recent data support the hypothesis that rifaximin produces an "eubiotic" effect [9]. This important effect on Lactobacillus could have significant clinical consequences. In fact, this bacterial species has been reported to be able to down-regulate pro-inflammatory cytokines and TNF production, to inhibit translocation of pathogenic bacteria and consequently to restore impaired intestinal permeability [9, 10].

In patients with SUDD, the therapy with rifaximin - plus soluble or insoluble fibers - is more effective in reducing symptoms than fiber alone. This has been shown by several RCTs and their meta-analyses [11], but only one of the included studies was placebo-controlled. The best results were obtained using rifaximin (given for 1 week every month) with soluble fibers [12].

Data concerning the optimal treatment (in terms of treatment duration and dose) after an exacerbation of SUDD is still unsatisfactory [11, 13, 14]. According to the guidelines, treatment with rifaximin should last for at least 12 monthly cycles [11]; however, we do not know for sure what the minimum and maximum number of treatment cycles should be in the different patient groups (first episode, relapse, post-diverticulitis) to maintain the benefits of this regimen. To date, two studies confirming the effectiveness and progressive gain after three treatment cycles in patients with the first episode of SUDD have been published [15, 16].

Cons

Patients with SUDD should not be treated with antibiotics for pathophysiological, clinical and pharmacological reasons. In fact, as these patients do not have a demonstrable infection, there could be many other options to treat them, and the inappropriate use of antibiotics leads to the onset of bacterial resistances.

There are many trials in favor of this indication: the AVOD trial [17], enrolling 623 patients with uncomplicated left-sided diverticulitis, demonstrated that patients untreated with antibiotics had a similar median hospital stay and the same rate of readmission to hospital of patients receiving antibiotics.

Also, the DIABOLO study [18] comparing patients with uncomplicated diverticulitis, treated or not with antibiotics, showed overlapping results, and moreover hospital stay was shorter in the observation group (2 vs 3 days; p=0.006). A trend of increased rate of elective sigmoid-resection was observed at 2-year follow-up in patients untreated with antibiotics but without achieving statistical significance.

Mesalazine, on the contrary, could play an important role in the management of patients with SUDD. A systematic review by Picchio et al. [19] demonstrated a better outcome of mesalazine, in terms of symptoms relief, compared to placebo, higher-fiber diet and low-dose rifaximin.

At last, occurrence of antibiotics resistance is a critical issue, especially in patients with IBS chronically treated with rifaximin, a drug also diffusely used to prevent diverticulitis. There is a lack of evidence on absence of antibiotic resistance to rifaximin use over the long-term, even though poor systemic absorption suggests a limited implication with resistance. However, is known that rifaximin-resistant Clostridium difficile strains were isolated from symptomatic patients [20], and many studies report the development of rifampin-resistant staphylococcal infections after treatment with rifamixin for other reasons.

MESALAZINE: PRO AND CONS

Pro

In the present understanding DD physiopathology is a consequence of dysbiosis or bacterial overgrowth that would provoke a low-grade inflammation in the intestinal mucosa. This inflammation would cause sensitization of primary afferent nerves with consequent neuromuscular dysfunction, changes in visceral sensitivity and abdominal symptoms [22].

Mesalazine does not have a completely known mechanism of action. The major evidence relates to its anti-inflammatory, antioxidant and an antibiotic effect [23,24]. Therefore, these properties would justify at least from the pharmacochemical point of view its use in DD, which is a consequence of intestinal inflammation and dysbiosis.

When we analyzed the evidence from clinical studies on mesalazine and SUDD, we found in the literature several papers of prospective or retrospective series of cases, non-randomized case control studies, and randomized control studies. A large majority of them prove the beneficial use of mesalazine in SUDD. Recently, systematic reviews and meta-analyzes (only with randomized control studies) have been published indicating that mesalazine was better than placebo in relieving symptoms and reducing symptoms recurrence of SUDD. These meta-analyzes also conclude that mesalazine may be able to prevent the first episode of diverticulitis [4, 25-29].

With regard to safety, mesalazine has been in use worldwide for more than 30 years. Some adverse events were noted. Nephrotoxicity possibly linked to hypersensitivity is the major concern. Pharmacovigilance studies including systematic reviews point to a good safety profile, some of them no higher than placebo [30].

Cons

Diverticular disease has been classified into different subgroups [31]. Most important is the differentiation between SUDD without clear inflammation and with inflammation (diverticulitis), both entities can be acute or chronic. A review on treatments in DD has definitely to consider definitions. The number of high-quality studies with Mesalazine for DD is sparse. In 2018, three systematic reviews considered only RCT´s [29, 32, 33].

Symptomatic uncomplicated diverticular disease is characterized by persisting (> 24 hrs) abdominal pain (mainly located in the left lower quadrant) and altered bowel habits [28]. Thus, aim of treatments of acute SUDD is symptom relief. Pain was significantly reduced in two placebo-controlled studies.

The first fully published RCT in acute SUDD showed therapeutic superiority after 28 days [26], which was confirmed in an abstract [26].

Long-term application of Mesalazine (one week every month) was shown in a placebo-controlled trial beneficial on symptoms and in prevention of acute pain attacks [34].

Acute uncomplicated diverticulitis (AUD) is not only defined by symptoms but also by objective signs of inflammation such as C-reactive protein (CRP) and fecal calprotectin (FC). Cross sectional imaging (computer tomography, ultrasound) must demonstrate morphologic inflammation of the bowel wall and around diverticulas [31]. A placebo-controlled study in AUD could not prove significant effects of mesalazine [35].

Probably the most intensively studied indication for mesalazine and diverticular disease is prevention of recurrent diverticulitis. Four placebo-controlled studies showed no effects [35, 36].

PROBIOTICS: PRO AND CONS

Pro

Overgrowth and alteration of the intestinal microbiota represents today a possible key step in development of DD and possible inflammation [37-39]. They act through several mechanisms including competitive inhibition of proinflammatory and pathogenic bacterial overgrowth, decrease in bacterial translocation, downregulation of inflammatory cytokines and improvement of mucosal defense by enhancing tight junctions' integrity [37-39]. Therefore, the rationale for the use of probiotics in order to restore healthy colonic microenvironment is very strong [39-42].

Lahner et al. [39] conducted a systematic review and meta-analysis that included 11 studies that investigated patients with SUDD, SUDD in remission and complicated diverticular disease (CDD) or acute diverticulitis. That was the first systematic review and meta-analysis that collected all available data of the use of probiotics in DD [43-45]. Some studies showed possible positive effect on abdominal symptoms or their recurrence in patients with SUDD. A very recent double-blinded trial showed that in the group with the probiotic supplementation and in the placebo group the decrease in abdominal pain, the most prominent symptom in DD and the primary endpoint of the study, was observed, but interestingly with no significant difference. Reduction of other symptoms such as diarrhea, constipation and back pain was significantly present in probiotic group [46].

Numerous studies showed that combination therapies, with aminosalicylates, or high fiber diet are usually more effective than probiotic therapy alone or placebo. A multicenter, controlled study in 52 patients with SUDD treated with either high-fiber diet alone or in combination with symbiotic product showed efficacy of both in reducing symptoms, but combination had faster and more accentuated effect [24]. Two randomized studies investigated the efficacy of probiotic strain Lactobacillus casei alone or with mesalamine [47, 48]. The combination therapy was more effective in maintenance of long-term remission. Tursi et al. [26] conducted a randomized double-blind placebo-controlled trial comparing the combination of mesalazine and probiotics with single therapies and placebo. The results were consistent with previous smaller trials indicating that combination therapy is the most effective in maintaining remission in patients with SUDD. Not a single patient had a SUDD recurrence in a combination therapy group, followed with 13.7%, 14.5% and 46% recurrence rate in mesalazine, probiotics and placebo groups, respectively. Moreover, another study from the same authors [49] showed that combination therapy with anti-inflammatory drugs was also more effective in maintaining remission in patients with previous attack of acute uncomplicated diverticulitis.

Also, the results of the two placebo-controlled studies pound probiotics effective in treating SUDD. Tursi et al [26] found Lactobacillus casei subsp. paracasei DG, with or without mesalazine, significantly better than placebo in controlling several symptoms (ranging from abdominal pain to diarrhea) [26]; Kvasnovsky found a multi-strain probiotic mixture in improving significantly constipation, diarrhea, mucorrhea and back pain [46].

Cons

A recent consensus of experts stated with 97% level of agreement that there is insufficient data regarding efficacy of probiotics in managing symptoms in DD [43,44]. Studies regarding the use of probiotics, not only in DD, are very difficult to analyze and to conduct a reliable meta-analysis because there are no established protocols; different strains are being used, alone or in combination, probiotics are often used in combination with high fiber diet, antibiotics or with aminosalicylates and the timing and dosage differ as well as the follow-up periods.

A double-blind, randomized, placebo-controlled study enrolled 117 patients with acute diverticulitis treated with either mesalamine alone or in combination with B. infantis 35624 showed improvement in global symptoms in all groups, including placebo, but the addition of mentioned probiotic strain did not increase efficacy [34]

Probiotics are generally considered safe; adverse effects are usually minor such as flatulence and changes in bowel habit. Only rare episodes of Lactobacillus bacteriemia and Saccharomyces fungemia have been reported in literature, but only in immunosuppressed patients and in intensive care patients due to the probable central venous catheter contamination [45, 50, 51]. However, there are no available data of safety of probiotic therapy in long term because there are no established protocols that define the exact strain, dosage nor period of usage.

It is also questionable if the probiotics are really needed as supplementation therapy, because probiotic strains are present in yogurt or other fermented dairy products, as well as in variety nutritional supplements and functional food and therefore very accessible to people [53].

It is not possible to perform a valid meta-analysis due to the heterogenicity of data and small sample studies [54].

Nowadays, there is no standard approved therapeutic approach for SUDD, even though high fiber diet is recommended by American guidelines for diverticulitis treatment in order to increase fecal mass and bowel movements [55].

Therefore, double-blind, randomized, placebo-controlled studies are needed to investigate different probiotic strains separately in patients with SUDD and DD in general in order to determine most beneficial strain for each group of patients and possibly to establish probiotics as a treatment option.

All things considered, it is fair to say that probiotics may be promising treatment option for SUDD, especially in combination with anti-inflammatory drugs, but the fact is

that nowadays enthusiasm for probiotics has outpaced the scientific evidence.

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