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Preventing Diverticulitis Recurrence by Selecting the Right Therapy for a Complex Disease

See "Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials," by Raskin JB, Kamm MA, Jamal MM, et al, on page 793.

Diverticulosis of the colon is an anatomic alteration commonly found in those residing in developed countries, slightly more frequent in the United States than in Europe.[1] Diverticulitis is the most common complication of diverticulosis: The majority of patients suffer from an "uncomplicated" form of the disease, generally undergoing outpatient medical management, whereas the "complicated" form is generally managed with inpatient medical-surgical treatment.[1] It has been thought that diverticulitis affects $\leq$15% of patients with symptomatic diverticular disease.[1] However, a colonoscopy-based study hypothesized that the actual rate of diverticulitis occurrence is lower, occurring in only 5% of patients harboring simple diverticulosis.[2]

There is little evidence regarding appropriate management of diverticulitis after an acute episode, even though the long-term recurrence rate of diverticulitis is $\leq$20%.[3] In this issue of *Gastroenterology*, Raskin et al present the results of 2 phase III, randomized, double-blind, placebo-controlled studies (PREVENT 1 and PREVENT 2) conducted to examine role of mesalamine in preventing recurrence of diverticulitis. More than 1,000 adult patients (590 in PREVENT1and 592 in PREVENT2) with $\geq$1 episode of acute diverticulitis in the previous 24 months that resolved without surgery were randomised to receive 1 of 3 dose regimens of MMX mesalamine (1.2, 2.4, or 4.8 g/d) or placebo.[4] The primary endpoint was the proportion of patients free of recurrent diverticulitis, defined as surgical intervention at any time for diverticular disease or presence of computed tomography (CT) results demonstrating bowel wall thickening (>5 mm) and/or fat stranding consistent with diverticulitis. The authors found that any dose of MMX mesalamine was not better than placebo for reducing diverticulitis recurrence at week 104 by using a CT-only definition of recurrent diverticulitis (recurrence-free rates for PREVENT1: Mesalamine, 53%–63% vs placebo, 65%; recurrence-free rates for PREVENT2: Mesalamine 59%–69% vs placebo 68%).[4] Thus, mesalamine does not seem to be effective in preventing diverticulitis recurrence.

Given that these controlled trials suggest that mesalamine does not work, how can we prevent diverticulitis recurrence in clinical practice?

Once the acute episode has resolved, patients are generally advised to maintain a high-fiber diet to optimize their bowel movements.[1] However, the collective literature investigating the role of dietary modification in preventing diverticular disease or a recurrence of diverticulitis is inconsistent, with conflicting results, and does not provide consistent support for recommending a high-fiber diet.[5] Another interesting point is related to the typical advice to avoid consuming seeds, popcorn, and nuts, which is based on the assumption that such substances could theoretically enter, block, or irritate a diverticulum and result in diverticulitis, and possibly increase the risk of perforation. However, there is no evidence to date to support this practice.[6]

Several treatments have been proposed and are used in clinical practice (Figure 1). Given the potential involvement of microbial imbalance in the pathogenesis of diverticular disease,[1] 1 option to prevent recurrence after an acute episode may be to use a single, broad-spectrum antibiotic that has activity against both Gram-negative and anaerobic bacteria. Recently, an open-label, pilot study found cyclic administration of rifaximin (800 mg/d for 10 days every month) to be effective for improving symptoms, but not for prevention of acute diverticulitis.[7] However, the lack of a placebo-controlled arm is a limitation; therefore, the role of rifaximin in preventing diverticulitis recurrence needs definitive confirmation.

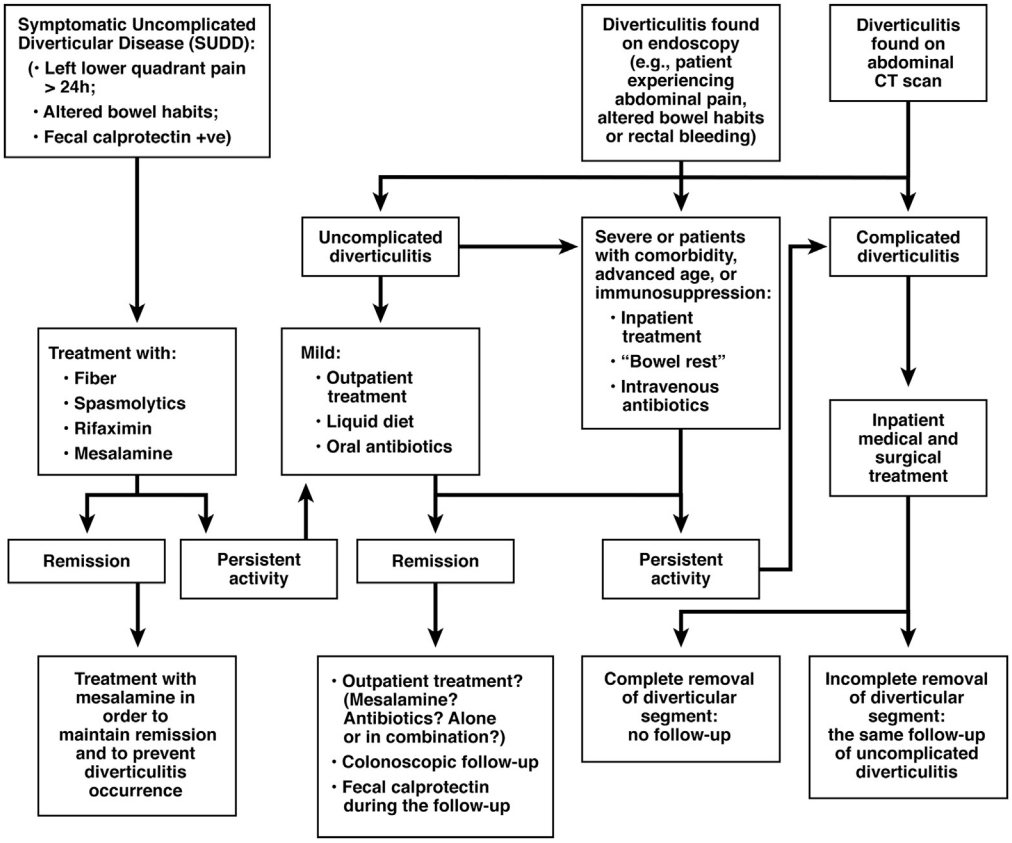

Figure 1. Proposed algorithm in managing diverticular disease. Mild uncomplicated diverticulitis, thickening of colonic wall ≥5 mm on computed tomography (CT); severe uncomplicated diverticulitis, thickening of colonic wall ≥5 mm with involvement of pericolic fat on CT. Amount of fiber consumption advised is 24–30 g/d. Rifaximin in preventing symptomatic uncomplicated diverticular disease (SUDD) recurrence is advised at 400 mg twice daily for 7 days every month. Mesalamine in preventing SUDD recurrence and diverticulitis occurrence is advised at 1.6 g/d for 10 days every month. Combination antibiotic treatment with fluoroquinolones (1 g/d) and metronidazole (1 g/d) for 7 days is generally advised either by oral (mild uncomplicated disease diverticulitis) or intravenous routes (severe uncomplicated or complicated diverticulitis). A further 10 days of antibiotic treatment with fluoroquinolones (1 g/d) or metronidazole (1 g/d) is generally advised after resolution of episode of severe uncomplicated diverticulitis. Otherwise, β-lactamase inhibitors (eg, amoxicillin-clavulanic acid or ampicillin-sulbactam) may be used instead of the combination of fluoroquinolones-metronidazole.

Surgery is considered a therapeutic option after an attack of diverticulitis. According to the current guidelines,[8,9] elective resection should be considered after 1 or 2 well-documented attacks of diverticulitis, depending on the severity of the attack and age and medical fitness of the patient. However, abdominal symptoms persist in up to 25% of patients after elective surgery for diverticulitis,[10] although the recurrence rate of diverticulitis after surgery is currently considered quite low.[3] Neither the stage of disease (complicated or uncomplicated) nor the surgical technique (laparotomy or laparoscopy) were significantly related to the occurrence of symptoms after surgery.[10]

Because diverticulitis pathogenesis is driven by inflammation, it seems logical that control of inflammation could be a relevant therapeutic option. Indeed, in diverticular disease there is a significant microscopic inflammatory infiltrate,[11] overexpression of fecal calprotectin (relative to the disease severity),[12] and an enhanced expression of proinflammatory cytokines as tumor necrosis factor-α at mucosal sites.[13]

Therefore, diverticular disease may be considered as a chronic inflammatory process ranging from low-grade inflammation that is localized within the colonic mucosa to a full-blown acute diverticulitis resulting in expanding inflammation to the colonic wall. In this way, mesalamine may be an interesting therapeutic tool. Two recent double-blind, placebo-controlled studies found mesalamine effective in treating symptomatic uncomplicated diverticular disease (SUDD). The first trial, conducted in Germany, found that mesalamine is better than placebo in improving abdominal pain in SUDD patients.[14] The second trial, conducted in Italy, found that mesalamine alone or in combination with probiotic strain *Lactobacillus casei* subsp. DG is superior to placebo not only in preventing SUDD recurrence, but also in preventing the occurrence of diverticulitis.[15]

Because mesalamine was effective in controlling SUDD and in preventing the occurrence of diverticulitis from SUDD, it was considered that it may be a useful therapeutic option for preventing recurrence of diverticulitis. Several double-blind, placebo-controlled studies have recently been completed to assess the role of mesalamine in preventing recurrence of diverticulitis. Unfortunately, most did not find mesalamine to be superior to placebo in preventing

diverticulitis recurrence.[16] On the other hand, in the DIVA and DIV/4 trials mesalamine was found significantly better than placebo in reducing abdominal symptoms after acute diverticulitis (DIVA trial: $P = .045$; DIV/04 trial: $P = .021$).[16,17] Only a trial conducted in Romania found mesalamine superior to placebo in reducing the risk of developing diverticulitis as well as the number of diverticulitis flares and the need for surgery. The relative risk of developing diverticulitis was 2.47 times higher (95% CI, 1.38-4.43) in the placebo group than in the mesalamine group.[18]

These conflicting results raise some key questions. First of all, are all the patients enrolled in the studies similar, or has the placebo effect altered the results? Heterogeneity in the population enrolled, the different endpoint used, and heterogeneity in the type of mesalamine investigated suggest that the studies are quite different. But the question of why mesalamine seems to be effective in treating SUDD and in preventing diverticulitis occurrence, but not in preventing diverticulitis recurrence, remains. A potential explanation 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 point explaining mesalamine effectiveness in SUDD but not in diverticulitis.[19] We can speculate that, if the patients are at the first episode of diverticulitis, it is probable that the disease still has lower levels of fibrosis and greater inflammation: In those patients, mesalamine is still able to control inflammation and therefore symptoms and recurrence of the disease. On the contrary, >2 attacks are able to cause fibrosis, limiting the mesalamine absorption across the colonic wall, and therefore mesalamine is ineffective.[20] Disease history, and the number of previous attacks with potential different degrees of fibrosis, could therefore help to explain in part the difference across trials. Parente et al[16] enrolled only patients at the first attack of diverticulitis and the vast majority of patients enrolled in the Stollman et al[17] trial were at the first or second attack of diverticulitis. Although most of patients enrolled in the PREVENT 1 and PREVENT 2 were at the first or second attack of diverticulitis, about 15% of the enrolled patients suffered from multiple attacks of diverticulitis and, unfortunately, the authors did not assess whether there was a difference in preventing diverticulitis recurrence according to the number of prior attack of diverticulitis.[4]

Another key point is in relation to the potential differences among mesalamine formulations. Indeed, the mechanism of mesalamine discharging through the colon, both from distal to proximal colon both transmural discharging (Eudragit L, granules, MMX),[21] could in part explain the differences in the literature for symptom control.

Further studies are therefore needed to overcome these limits, for example, enrolling patients with the same endoscopic and/or radiologic finding of the disease. However, objective measures of diverticular disease are still lacking in terms of inflammation or grading. For this purpose, the first endoscopic classification of diverticular disease of the colon, the Diverticular Inflammation and Complication Assessment (DICA) classification, has been developed and validated.[22] This classification considers 4 endoscopic items on which classify the patients: (a) Diverticulosis extension, (b) number of diverticula (≤15, grade I; >15, grade II), (c) presence of inflammatory signs (edema/hyperemia, erosions, segmental colitis associated with diverticulosis), and (d) presence of complications (rigidity of the colon, stenosis, pus, bleeding). Points in constructing final DICA were assigned according to the severity of the anatomic/inflammatory findings and patients are therefore classified as DICA 1, DICA 2, and DICA 3. Preliminary data found DICA classification able to predict patient outcomes during a 1-year follow-up, as well as found higher DICA scores at higher risk of developing diverticulitis occurrence/recurrence.[22]

It is advisable that in the future trials will enroll homogeneous populations to define a correct therapeutic strategy for this complex disease.

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The Increasing Diversity of KRAS Signaling in Pancreatic Cancer

See "Ribonucleoprotein HNRNPA2B1 interacts with and regulates oncogenic KRAS in pancreatic ductal adenocarcinoma cells," by Barceló C, Etchin J, Mansour MR, et al, on page 882.

Approximately 30% of all tumors harbor oncogenic mutations in the RAS gene family members HRAS, NRAS, and KRAS, which are among the longest studied oncogenic drivers in malignant diseases. Despite their predominant role in tumor development and their ability to drive hallmark characteristics of cancer such as proliferation, antiapoptosis, and metabolic reprogramming, little is known about regulatory interactions of RAS family members, and in particular, the modulation of RAS activity.

RAS oncogenes encode small GTPases, which cycle between an active GTP-bound and an inactive GDP-bound state. The active and inactive states of RAS are promoted by guanine nucleotide exchange factors and GTPase-activating proteins, respectively. Of the different RAS isoforms, KRAS is the most commonly mutated family member, with mutations present in >90% of pancreatic ductal adenocarcinoma (PDAC) and 30%–40% in lung and colorectal adenocarcinomas. To date, there are more than 300 different KRAS mutations in human cancer, most of which shift the ratio to active RAS:GTP complexes at the expense of inactive RAS:GDP complexes through diminished intrinsic GTPase activity and interfering with the action of GTPase-activating proteins. Mutations in codons 12, 13, and 61 are the most common base-pair substitutions and the codon 12 mutations G12D and G12V are predominant in PDAC, occurring in ≤75% of cases. Interestingly, other endodermal tumor types such as lung and colon cancer display different spectra of predominant KRAS mutations, arguing for a context- and tissue-dependent role of individual mutations and KRAS activity. Other mechanisms leading to increased RAS activity include amplification of receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR) in lung cancer or alterations in GTPase-activating proteins in hepatocellular carcinoma. Thus, although increased KRAS activity is seen in many tumors, specific modes of increased activity are observed in distinct tumor entities.

Early occurrence of KRAS mutations in preneoplastic lesions has led to the assumption that increased KRAS