Use of antibiotics in diverticular disease: are we embracing a schizophrenic approach?

Angelo Zullo,[1] Vincenzo De Francesco[2]

[1]Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, Rome; [2]Gastroenterology Section, Department of Medical Sciences, University of Foggia, Foggia, Italy

Dear Editor,

Diverticular disease (DD) includes clinical conditions ranging from the presence of colonic diverticula to diverticulitis with peritonitis.[1] Despite insights on DD improved, several aspects remain controversial, including the use of antibiotics. The presence of abdominal symptoms in patients with diverticula is a condition classified as a symptomatic uncomplicated diverticular disease (SUDD). Italian guidelines define SUDD as *a syndrome characterized by recurrent abdominal symptoms* - i.e*., abdominal pain and bloating resembling or overlapping symptoms of irritable bowel syndrome (IBS) - attributed to diverticula in the absence of macroscopically evident alterations other than the presence of diverticula*.[2] Therefore, it is difficult to distinguish the two conditions clinically. It was proposed that the presence of long-lasting (>24 h) abdominal pain may discriminate SUDD from IBS, prolonged symptoms being present in 22.2%, and 6.7% of DD and IBS patients.[3] Although statistically significant, this difference is small. The prevalence of this symptom is too low to be used for differential diagnosis in clinical practice between SUDD and IBS, as well as other benign conditions.[4] Symptoms' pathogenesis in SUDD - as well in IBS - patients remains unclear, and increased gas production by colonic bacteria was hypothesized.[5] Patients perceive bloating as a *hot air balloon* in the abdomen and physicians are generally convinced that bowel of SUDD patients is overflowing by gas. Nonetheless, gas content in the bowel increases by only 22 mL from basal condition to bloating sensation, at least in IBS patients.[6] Nonetheless, this small amount of gas induces paradoxical relaxation of abdominal muscles with increased abdomen circumference of 21±4 mm.[7] Therefore, bloating sensation is caused by a reduced compliance with the small increase of gas content in the bowel.[7] Neither specific pathogens nor a particular bacterial pattern of bowel microbiota have been identified for tailoring antibiotic therapy. Despite these observations, a 7-day, monthly, life-long rifaximin therapy - a poorly absorbable antibiotic - plus fibers is advised by Italian guidelines for SUDD.[2] This was based on a meta-analysis results, including data of only 1 double-blind and 3 open-label, studies, whose consistency was questioned.[8] Therefore, rifaximin is largely used in clinical practice for long-term SUDD therapy, and a recent Italian study showed that this therapy is even administered to as many as 20.6% of subjects with asymptomatic diverticulosis.[9] In Italy, rifaximin was in 7th position among the most prescribed drugs (624,535 boxes containing 12 tablets) and in 13th in terms of pharmaceutical expense (5,195,406.08 euros) in 2018.[10] Likewise, these prescriptions also include an off-label use in SUDD patients, since rifaximin is not approved for such therapy in Italy. The *enteric neuropathy* due to the cholinergic denervation hypersensitivity,[11] leads to disturbed motility and visceral hypersensitivity in the sigmoid tract, which, in turn, may be responsible for some abdominal symptoms - particularly pain - in DD patients.[1] Experimental data have clearly demonstrated that hyper-contractions of circular

Correspondence: Angelo Zullo, Gastroenterology and Digestive Endoscopy, Nuovo Regina Margherita Hospital, via Emilio Morosini 30, 00153 Rome, Italy.
Tel.: +39.06.588446608 - Fax: +39.06.58446533.
E-mail: angelozullo66@yahoo.it

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muscle in the sigmoid tract with DD are reduced by anticholinergic drugs.[1] Unfortunately, such therapy is often neglected in clinical practice without a clear justification.

The exact mechanism of diverticulitis still remains hypothetical. Diverticulitis is considered as an acute inflammation due to the traumatic lesion of diverticular mucosa caused by fecalith impaction in a diverticular sac.[12] Besides this *trauma*, an *ischaemic* pathogenesis was recently proposed, based on compression of vasa recta due to prolonged and/or recurrent contractile spikes related to neuromuscular alterations in the diverticular tract.[13] Therefore, a micro-perforation develops, causing peritoneal participation (acute pain, fever, leukocytosis), and a subsequent infection in damaged diverticular sac may develop since billions of bacteria contaminate the bowel. Patients with acute diverticulitis were typically treated with systemic, widen broad antibiotics, to prevent a secondary infection, rather than eliminate a specific pathogen. However, some recent data suggest that acute diverticulitis might be treated with only bowel rest and conservative therapy without antibiotics, at least in patients with stage Ia-Ib Hinchey disease and without relevant comorbidities. A meta-analysis found no difference in treatment outcome between diverticulitis patients treated with or without antibiotics.[14] However, there were only two randomized trials, whilst the other 6 studies were retrospective. Therefore, data should be interpreted with caution, since patients enrolled in the latter studies were no comparable upon arrival to the hospital for several clinical characteristics, based on which the clinician arbitrarily performed the choice of treatment. Anyway, the AGA guideline suggests that antibiotics should be used case by case,[15] although antibiotic therapy accounted for only 2.1% of the total cost for management of in-patients with diverticulitis.[16]

Based on these observations, the use of antibiotics in DD patients appears at least controversial. Indeed, we should avoid a short-term use of antibiotics in the few patients (near 4% of DD patients) with well-documented diverticulitis at risk of developing - if not with an ongoing - bacterial infection in a micro-perforated colon, whilst we should administer a long-life antibiotic therapy to patients with SUDD (near 20% of DD patients) without an ongoing infection. Therefore, at best of current knowledge, it would appear wise and advantageous for patients and health-care resources to continue antibiotic administration in patients with documented diverticulitis - until definitive data on its useless are available - and to stop antibiotic therapy in SUDD patients. Otherwise, as in the famous story by Robert Louis Stevenson, the gastroenterologist should undertake a *schizophrenic* behavior where Dr. Jekyll administers a cyclic antibiotic therapy for reducing *abdominal bloating* in SUDD patients without an infection, and Mr. Hyde avoids antibiotics for preventing an infection in a micro-perforated colon.

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