



Position Paper

Rifaximin and diverticular disease: Position paper of the Italian Society of Gastroenterology (SIGE)

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ABSTRACT

Management of diverticular disease has significantly improved in the last decade. Antibiotic treatment is used for symptom relief and prevention of complications. In Italy, the non-absorbable antibiotic rifaximin is one of the most frequently used drugs, and it is perceived as the reference drug to treat symptomatic diverticular disease. Its non-systemic absorption and high faecal concentrations have oriented rifaximin use to the gastrointestinal tract, where rifaximin exerts eubiotic effects representing an additional value to its antibiotic activity. This position paper was commissioned by the Italian Society of Gastroenterology governing board for a panel of experts (RC, GB, BA) to highlight the indications for treatment of diverticular disease. There is a lack of rationale for drug use for the primary prevention of diverticulitis in patients with diverticulosis; thus, rifaximin use should be avoided. The cyclic use of rifaximin, in association with high-fibre intake, is safe and useful for the treatment of symptomatic uncomplicated diverticular disease, even if the cost-efficacy of long-term treatment remains to be determined. The use of rifaximin in the prevention of diverticulitis recurrence is promising, but the low therapeutic advantage needs to be verified. No evidence is available on the efficacy of rifaximin treatment on acute uncomplicated diverticulitis.

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1. Introduction

The management of diverticular disease (DD) has significantly improved over the course of the last decade. Nonetheless, several unmet demands remain. It is now clear whether clinical manifestations of diverticular disease are not uniquely represented by acute diverticulitis. Indeed, physicians in primary and specialist care are more often confronted with the management of uncomplicated patients complaining of recurrent abdominal symptoms and changes in bowel habits [1,2]. An appropriate diagnosis, classification and management of these patients is mandatory to improve their quality of life and reduce the social and economic burden of this condition. In Italy, the Scientific Association for the Study of Diverticular Disease (GRIMAD) and the Italian Society of Colorectal Surgery (SICCR) have respectively published a consensus document with a Delphi approach [3] and a guideline document for the man-

agement of DD [4]. Similar efforts have been made by Danish and Polish associations and other groups in Europe [4–6] as well as in the USA [7]. Through the critical reading of these documents, it appears evident that there is an urgent need for robust data on the epidemiology, risk factors and medical and surgical evidence-based approaches in the management of DD to create the basis for modern unifying international recommendations that overcome the limitations of loco-regional approaches.

The treatment of DD represents a significant part of the gastroenterologist's daily practice, as noted in the national and international guidelines [3–7]. Antibiotic treatment for symptom relief and the prevention of acute complications is generally used for this condition [3–7]. In Italy, the non-absorbable antibiotic rifaximin is one of the most frequently used drugs in DD, and it is perceived as the reference drug to treat symptomatic DD. This position paper was commissioned by the Italian Society of Gastroenterology governing board for a panel of experts (RC, GB, and BA) to illustrate the current evidence and indications for the use of the non-absorbable antibiotic rifaximin in DD.

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1.1. Clinical scenarios of DD

DD is the fifth most important gastrointestinal disease in terms of health-care costs in Western countries, with the highest rates in the United States and Europe. All age groups can be affected, but prevalence increases with age, and cases in younger individuals are more likely to be complicated [8–10]. In the vast majority of individuals, colonic diverticula remain asymptomatic (diverticulosis) over their lifetime, while approximately 20% of subjects with colonic diverticula develop symptoms, including recurrent abdominal pain or discomfort, bloating, and changes in bowel habits (symptomatic diverticular disease). Only approximately 4% of patients develop acute diverticulitis, contradicting the common belief that diverticulosis has a high rate of progression [1,11].

DD is classified into four clinical stages that take into account symptoms, colonic tissue changes and complications [12,13]. STAGE I is an early phase characterized by the progressive development of colonic diverticula. In STAGE II, the patient has developed diverticula, but remains asymptomatic, a condition termed diverticulosis, which represents the most common entity. In STAGE III, approximately 20% of individuals with diverticula develop symptoms, including abdominal pain and changes in bowel habits, often indistinguishable from those of irritable bowel syndrome [14–16], which is a condition termed symptomatic uncomplicated diverticular disease (SUDD). In STAGE IV, only approximately 4% of patients develop complicated DD, including diverticulitis [1,11]. Fig. 1 shows the clinical scenarios in patients with DD, illustrating its possible natural history and estimating the prevalence for each DD stage; however, this stage classification does not imply a mandatory progression from one stage to another.

1.2. SUDD

SUDD is described by the concomitant presence of diverticula and a symptom complex characterized by abdominal pain and bloating, bowel habit changes, including diarrhoea and constipation or a mixed bowel habit. The severity and frequency of symptoms is variable and ranges from mild and rare episodes to a severe, chronic, recurrent and debilitating disorder that impacts daily activities and severely affects the quality of life of patients who have reduced vitality and emotional health [17,18]. In these patients, DD may be experienced as a chronic debilitating illness [1,17].

The symptoms of SUDD resemble those of irritable bowel syndrome (IBS) [19,20] and it is still a matter of debate whether a separation between these two conditions is always possible, as both conditions lack clear-cut diagnostic biomarkers. As a matter of fact, patients with SUDD fulfill the Rome criteria for the diagnosis of IBS in 71% of the cases [21], and the high prevalence of both IBS and colonic diverticula makes it highly probable to find the two conditions associated by chance, as shown in a cross-sectional study that reported an increased risk for diverticulosis in patients with IBS compared to those without IBS [14]. In some patients, SUDD may also follow a bout of acute diverticulitis, as shown by a recent study [22]. This condition has been termed post-diverticulitis IBS analogously to the well-known post-infectious IBS, characterized by the development of IBS symptoms in the aftermath of acute infectious gastroenteritis [22,23]. From a pathogenic standpoint, both conditions share common factors, including the participation of microbiota [20,24,25], low-grade inflammation [20], visceral hypersensitivity, gut motor dysfunction and psychological factors such as anxiety and depression [24].

A study addressing the abdominal pain patterns in DD reported that episodes of prolonged pain were frequently followed by recurrent, short-lived pain similar to that seen in IBS [25], suggesting that acute mucosal inflammation might lead to prolonged changes in

gut motility and sensitivity, as described in post-infective IBS [23]. Altered patterns of colonic motility and visceral sensation similar to IBS have been described in patients with diverticulosis [26,27].

A multicentre nationwide survey reported an updated clinical picture of SUDD that was mainly characterized by unspecific symptoms, such as short-lived abdominal pain (lasting less than one day) and abdominal bloating, suggesting that SUDD has a clinical presentation similar to that of IBS [28]. An age- and gender-matched case controlled study reported that abdominal pain lasting for more than 24 h was more prevalent in patients with SUDD than in patients fulfilling the Rome III criteria for IBS (22% vs. 7%; $p < 0.01$), thus helping to discriminate a subset of patients with diverticular disease from those with IBS [29].

1.3. Acute diverticulitis

Acute diverticulitis (AD) is an inflammatory process involving one or more colonic diverticula and it is often associated with pericolic inflammation. Complicated diverticulitis is characterized by the presence of one or more abscesses, perforations, fistulae, or colonic obstruction. Approximately 4% of patients with diverticulosis develop acute diverticulitis in their lifetime, and approximately 15% of them develop further complications such as abscesses and fistulae [11]. It has been reported that after the first episode of diverticulitis, 15–30% of patients will experience a recurrence [30–33].

Usually, the patient with AD presents with pain in the left lower quadrant of the abdomen, fever, and leukocytosis, even if many patients do not present all these symptoms at the same time [8]. Other possible symptoms or signs might include changes in bowel habits, nausea, vomiting, urinary symptoms, and elevated C reactive protein (CRP). Although diverticulitis is considered a disease of the elderly, a USA survey between 1998 and 2005 showed a marked increase in the prevalence of diverticulitis in subjects younger than 40 years [34]. In these age groups, diverticulitis predominates in males, while in those older than 65 years of age, diverticulitis appears to be more common in women [35]. According to the guidelines, in the case of a patient presenting in an acute setting with fever and laboratory findings of active inflammation, computed tomography (CT) scanning should be used to confirm the diagnosis and assess the severity of the disease as well as ruling out other disorders that can mimic diverticulitis, such as malignancy, ischaemic colitis, inflammatory bowel disease, appendicitis, and gynaecological disorders [7].

Taking into consideration the large impact of DD in Western countries and the economic burden of acute episodes, some have suggested employing therapeutic strategies aimed at preventing the first episode of diverticulitis (primary prevention), even if the cost-efficacy strategy remains largely to be determined.

1.4. Recurrent diverticulitis

In up to 25–30% of cases, AD recurs after the first episode [1,36], potentially increasing the risk of future development of recurrent abdominal pain and disturbed bowel habits (i.e., post-diverticulitis SUDD) [22]. The rate of recurrence of diverticulitis is far from being established because of the paucity of well-conducted prospective longitudinal studies. A recent retrospective longitudinal study has been carried out in the USA from 1995 to 2009, based on an analysis of the patient discharge database. In this study, 85% of patients who were managed with bowel rest and antibiotics did not have any recurrence, further suggesting that recurrent diverticulitis occurs in a minority of patients and that probably the concept that episodes of diverticulitis often recur was overemphasized in the past [37]. Generally, recurrence occurs early in the first months after the initial bout of diverticulitis and decreases thereafter [38]. Nonetheless,

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