Diverticular disease

Current physiopathologic, diagnostic, prognostic and therapeutic issues
# Table of contents

- **Introduction** ......................................................................................................................... 4
- **Definition and clinical classification of DD** .............................................................................. 4
- **Epidemiology and risks factors** ............................................................................................. 5
- **Pathophysiology** ....................................................................................................................... 6
  - Role of the gut microbiota ........................................................................................................ 6
  - Neuromuscular function abnormalities ..................................................................................... 7
  - Inflammation .............................................................................................................................. 7
  - Genetic factors .......................................................................................................................... 8
- **Prognosis and DICA score** ....................................................................................................... 9
- **Focus on SUDD** ...................................................................................................................... 10
- **Diagnosis** ............................................................................................................................... 10
  - Endoscopy .................................................................................................................................. 10
  - Ultrasonography ....................................................................................................................... 11
  - Computer tomography colonography (CTC) .......................................................................... 11
  - Markers ..................................................................................................................................... 11
- **Issues in primary care diagnosis** ............................................................................................ 12
- **Therapy** .................................................................................................................................. 12
  - Surgery ..................................................................................................................................... 12
  - Dietary fiber .............................................................................................................................. 12
  - Non-absorbable antibiotics: Rifaximin-α ................................................................................... 12
  - Aminoglicosilates ....................................................................................................................... 13
  - Probiotics ................................................................................................................................... 14
- **Guidelines** .............................................................................................................................. 15
- **Conclusion** .............................................................................................................................. 15
- **References** .............................................................................................................................. 16
Introduction

Diverticulosis is a very common condition in the Western World, affecting more than 70% of subjects in some age ranges. Yet, most of this population will remain asymptomatic, while 20% of subjects will develop symptoms, the so-called Diverticular Disease (DD).

Being diverticulosis common and its prevalence steadily increasing as population ages, the economic burden involved for the diagnosis and treatment of this condition is significant: DD is in fact the fifth most important disease in terms of direct and indirect costs in western countries [Tursi A, Di Mario F, Scarpignato C et al., 2016].

Despite these facts, DD is a relatively unknown pathology; its underlying mechanisms are still being investigated, partially because its clinical patterns are often overlapping other gut diseases.

The 2nd International Symposium: Diverticular Disease of the Colon, held in Rome in April 2016, provided the current state of the art: several key and breakthrough aspects of DD were presented and issues were carefully analyzed, as well as approaches concerning physiopathology, diagnosis, prognosis and therapy were considered.

Clinical research is moving towards a preventive approach and an early identification of the diseases, in order to treat patients adequately before the development of life-threatening clinical pictures.

In diagnostics, an increasing emphasis is currently given to minimally invasive methods such as use of ultrasound or serum markers identification.

Moreover, the scientific community is unanimously looking forward the development of internationally recognized Guidelines, in order to make the modus operandi of specialists and general practitioners (GPs) simple, and their intervention as proper and effective as possible, correctly evaluating the many variables related to each single patient.

In this vibrant context, rifaximin is receiving an important consensus in the treatment of subjects suffering from Symptomatic Uncomplicated Diverticular Disease (SUDD), as an effective therapy for symptoms relief and prevention of recurrences and complications. These results are due not only to its well-known antibiotic effect, but also thanks to its modulating action on microbiota, whose alteration have an important pathological role in this disease.

Definition and clinical classification of DD

Diverticulosis is an acquired deformity of the colon wall, characterized by the development of pseudo diverticula, i.e. protrusions of the mucosa and submucosa through the muscular wall, typically 5 to 10 mm in diameter, but at times, they can exceed 20 mm (Figure 1).

![The area of the bowel commonly affected by diverticular disease](image)

Figure 1. Location and aspect of diverticula.
In Western populations, diverticulosis occurs primarily in the sigmoid and descending colon (more than 90% of patients). It may be prevalent in varying degrees in the different region of the colon [Gargallo, 2016]; while being relatively uncommon in subjects under 40 years of age, it increases up to 65% in those aged 65 years or more; consequently 80% of patients who present with diverticulosis are 50 or older.

Eighty percent of patients with diverticulosis will remain asymptomatic for their lifespan, while about 20% will develop symptoms and/or complications and will be defined as Diverticular Disease (DD) patients; 3-5% of patients with diverticula will have an episode of acute diverticulitis (AD), 1-2% will require hospitalization and 0.5% will require surgery. Diverticula are also responsible for the majority of episodes of lower gastrointestinal bleeding [Stollman, 2004].

Among patients presenting DD, the vast majority will have Symptomatic Uncomplicated Diverticular Disease (SUDD) with colicky abdominal pain, but no inflammation. The remaining ones will have complicated DD, also called “diverticulitis”, and a minor percentage of them will develop severe complications (perforation, fistulas, obstruction and/or bleeding). There is also chronic diverticulitis, because of recurrent diverticulitis or because of the development of a segmental colitis associated with the diverticula (SCAD) [Humes, 2014]. This condition is a chronic inflammatory process localized in the colonic area presenting diverticulosis, mainly in the sigmoid colon [Harpaz, 2006]. Recent data have hypothesized that SCAD may be a pathology itself within the IBD set of diseases (Figure 2).

Therefore, DD represents the most common disease affecting the colon in the western societies and its prevalence is increasing because of changes in lifestyle, overweight, physical inactivity and low fiber diet.

**Epidemiology and Risk Factors**

Diverticular disease and its complications represent a burden for the health systems all over the world. Recent data, obtained from the 2010 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey (United States), report that DD is the eighth, among most frequent outpatient gastrointestinal diagnosis, with 2.7 million of medical consultation [Peery, 2015]. In addition, the 2012 Nationwide Inpatients Sample (NIS) reported that diverticulitis without hemorrhage admissions are more than 200,000 with an increase of 21% when compared to 2003 data, with an aggregate cost of 2.2 billion of USD [Peery, 2015]. Diverticular hemorrhage (included in gastrointestinal hemorrhage diagnosis) has an adjunctive burden of admissions and costs. When we consider the causes of death for gastrointestinal, liver and pancreatic disease in the US in 2012, the rank of diverticular disease is 16 with a crude rate of 0.9 per 100,000 patients [Peery, 2015]. Data obtained from the Scottish Morbidity Records confirm that DD is an increasing burden on health service resources, even in younger age groups [Paterson, 2014], whereas the prevalence of asymptomatic diverticulosis increases with age. Lifestyle, dietary and environmental factors are important in both the development of diverticulosis and subsequent symptomatic disease [Spiller, 2013]; among these factors, low dietary fiber intake is considered the major risk factor for DD, as it leads to a prolonged fecal transit time and reduced stool volume. An abnormal colonic motility leads to changes in intracolonic pressure, and localized high pressure leads to the formation of diverticula. A low fiber diet is also associated with changes in the colonic wall resistance, already associated with aging. Minor risk factors, nevertheless important, are consumption of red meat, increased body mass index, obesity, physical inactivity, smoking, nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroid prescriptions.

Heritable factors also contribute to the development of DD [Strate, 2013]: an observational study investigated familial aggregation of DD analyzing data from 142,123 cases from nationwide patient registries, including 10,420 siblings and 923 twins. They calculated the relative risk (RR) of DD as standardized incidence ratios for siblings versus the general population.
and concordance rates for monozygotic versus dizygotic twin pairs. The contribution of genetic factors in the development of DD ranges from 40 to 50%.

Table 1 summarizes risk factors of DD.

### Pathophysiology

#### Role of the Gut Microbiota

Gut microbiota can be reasonably defined as a hidden organ, which influences human biology from many points of view, serving several different functions (Figure 3) [Grenham, 2011]; it is a delicate and still not completely understood structure, whose alteration can lead to more than one pathological condition.

Gut microbiota is a complex habitat which harbors around 1.5 kg of commensal microbes and that includes more than 3 million of genes [Leser, 2009; Neish, 2009]. These microbes belong to the three domains system, Bacteria, Archaea and Eukarya [Eckburg, 2005; Scanlan, 2008], and viral particles are present as well [Zhang, 2006]. Then, the resident microbiota together with the gut mucosa and the mucosal immune system is part of the functional barrier of the GI tract.

![Microbiota-gut Interplay Serves Many Functions](image)

**Figure 3. Gut Microbiota functions.**

### Classification of risk factors

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Table 1. Risks factors of DD.
A complex and mutualistic symbiosis regulates the relationship between the host and the gut microbiota [Backhed, 2005]. The mucosal immune system participates in the maintenance of gut microbial communities and the interaction of these components sustains the delicate equilibrium in maintaining intestinal homeostasis. Gut microbiota carries out several functions: digestion of energy substrates, production of vitamins and hormones [Sekirov, 2010], protection from pathogenic bacteria by consuming nutrients to inhibit their growth on one side while producing nutrients for mucosal cells [Dharmani, 2009] and modulation of immune system development and immunological tolerance [Allen, 2008].

Three main factors guarantee the appropriate functioning of gut microbiota: abundance, diversity and balance. A huge number of microorganisms is present in a healthy microbiota (about 100 trillions) and the higher the number of different species, the better. As in all the big communities, all members need to live in a complex and stable balance; **dysbiosis is a perturbation of microbiota balance due to several environmental variables** (i.e. habits such as smoking and drinking, stress, diet, drugs) and it has been associated to chronic, and perhaps also systemic, immune disorders of the gut. Dysbiosis is associated with the pathogenesis of inflammatory bowel diseases (IBD), and other gastrointestinal disorders, including gastritis, peptic ulcer, irritable bowel syndrome and even gastric and colon cancer [Sartor, 2008]. **Dysbiosis may play a role also in the development of DD.**

Since the techniques to explore fecal microbiota are very recent, only few studies have focused on its characterization in diverticular disease. Some studies have shown the presence of bacterial overgrowth in subgroups of patients with diverticular disease [Tursi, 2005]. The recent development of culture-independent approaches, such as metagenomics, is greatly contributing to the understanding of gut microbiota composition. Gueimonde et al. [Gueimonde, 2007] collected and analyzed biopsy specimens of patients with colorectal cancer (CRC), IBD or diverticulitis and found that strains of the genus *Bifidobacterium* were present in all samples of patients with diverticulitis or IBD, but only in a 76% of CRC patients. *Bifidobacterium longum* and *Bifidobacterium animalis* were significantly higher in patients with diverticulitis compared to the other two groups, while *Bifidobacterium adolescentis* and *Bifidobacterium catenulatum* were absent in patients with diverticulitis. A recent analysis of fecal specimens found an increase of *Proteobacteria* and *Actinobacteria* in patients with SUD compared with healthy controls, where most represented species was *Collinsella Aerofaciens* [Lopetuso, 2014]. Despite these interesting observations, **there is no definite evidence allowing to correlate diverticular disease and its complications to a specific bacterial strain.**

**Neuromuscular Function Abnormalities**

The introduction of techniques that allow to record the colonic motor activity for 24 hours or more, in the whole colon, and the possibility of evaluating visceral perception in the recto sigmoid area, [Bassotti, 1993] have yielded interesting information about the pathophysiological role of colonic motility in the formation of diverticula.

In a study comparing 24-h recordings of colonic motility between healthy controls and patients with diverticulosis, the latter showed a **significant increase of motility in the diverticular segments** [Bassotti, 2001]. The motor response to physiological stimuli (meals) was also altered in the patients’ group, featuring a sort of spastic activity, especially in the sigmoid colon. In addition, compared to controls, patients displayed a significant increase of high-amplitude propagated contractions, the manometric equivalent of mass movements [Bassotti, 1988]; about 20% of this activity was retro propagated. Another 24-hr colonic motility study in patients with SUD demonstrated a significant increase of regular contractile patterns in the diverticular segments [Bassotti, 2005].

The **motor and perceptive abnormalities** of the large bowel observed in these patients might be reconducted to the presence of subtle anatomic and physiological alterations such as muscular thickening often found in the diverticular areas [Whiteway, 1985]. These finding were probably due to elastosis causing abnormal longitudinal muscle relaxation [Golder, 2007], abnormal myogenic activity in vitro, and a marked decrease of contractile responses to tachykinins [Fornai, 2014].

Moreover, patients with DD display an altered pattern of factors involved in smooth muscle contractility and of components of the enteric nervous system. Alterations in enteric neurosignaling include a decreased serotonin transporter expression and function in patients with recent acute diverticulitis, [Costedio, 2008], an increased mucosal neuropeptides in SUD, expression of a previous resolved inflammation [Simpson, 2009], and an increased number of colonic mast cells [Bassotti, 2013].

**Inflammation**

The onset of inflammation in diverticulitis shows similarities with IBD. Deficiencies of host immune defenses and dysfunction of the barrier effect result in increased mucosal adherence of bacteria activating a pathogenic immune response and
inducing inflammation. Inflammatory and/or functional changes lead to abdominal symptoms, such as lower abdominal pain/discomfort, bloating, tenesmus, and diarrhea (Figure 4).

**Inflammation is able to cause permanent changes in gut microbiota.**

Low-grade inflammation in particular appears to be pivotal in the pathophysiology of symptoms in both AD and SUDD, [Humes, 2012] in the context of bacteria-induced immune activation and consequent inflammation. Changes in the colonic microbiota are clearly critical to the pathogenesis of diverticular complications, such as diverticulitis and peri-diverticular abscesses, and more subtle changes in microbiota composition may be important in the chronic manifestations of SUDD. Altered bacterial flora triggers intestinal inflammation by impairing mucosal barrier function and up-regulating inflammatory cytokine release and this might explain the development of diverticular inflammation [Quigley, 2010].

**Genetic factors**

Inflammation plays a key role in the change in the gut microbiome DNA, as it can cause epigenetic modifications that can influence gut homeostasis and lead to dysbiosis. It is also possible that even transient environmental factors, involved in the development of inflammation, increase the risk to develop a disease, which can leave a permanent mark on DNA, that become hereditable (Figure 5).

![Figure 4. Role of dysbiosis in DD symptom development.](image)
**Prognosis and DICA score**

The first endoscopic classification of DD of the colon, called **DICA - Diverticular Inflammation and Complication Assessment**, has been recently developed. It takes into account few endoscopic findings of the colon with diverticula [Tursi, 2015], consisting of four items (Figure 6):

1. **Diverticulosis extension**: left, right colon. Two points are assigned to diverticulosis located in the left colon because in Western world diverticulosis (and therefore diverticulitis) occurs more frequently in the left than in the right colon.
2. **Number of diverticula** (in each district): up to 15 (grade I), more than 15 (grade II).
3. **Presence of inflammation**: edema/hyperemia, erosions, Segmental Colitis Associated with Diverticulosis. When different degrees of inflammation are detected, the most severe grade of inflammation has to be reported.
4. **Complications**: Rigidity of the colon, Stenosis, Pus, Bleeding.

Therefore, DICA is classified as DICA 1, up to 3 points; DICA 2, 4 to 7 points; DICA 3, more than 7 points.

Since diverticulosis is the most common finding at colonoscopy, and endoscopic signs of inflammation may be frequently detected in those patients [Tursi, 2011], it is hypothesized that endoscopic characteristics may be predictive of the outcome of the disease.

**DICA classification has been developed and validated in order to use a common language in describing the colon harboring diverticula and to identify endoscopic findings predictive of disease outcome.**

Results of a multicenter, international, retrospective cohort study have been presented at The 2nd International Symposium: Diverticular Disease of the colon, held in Rome in April 2016. Aim of the study was to understand how DICA score could affect clinical practice. The study involved 21 centers and enrolled 1651 patients with a diagnosis of DD. At enrollment DICA score was evaluated together with diagnostic parameters such as CRP and fecal calprotectin. Among patients, different therapies were taken: mesalazine or rifaximin alone, rifaximin together with mesalazine and other therapies.

Firstly, this large study shown that clinical characteristics of the people harboring diverticula are linked to DICA score. In particular, severity of abdominal pain, CRP and fecal calprotectin expression were significantly expressed, according to DICA score, which was also found to be the only predictor for occurrence/recurrence of AD.

DICA 1 patients are at lower risk of developing inflammatory complications, while patients having diverticulosis, with past or active inflammation, namely DICA 3, are at higher risk.

Furthermore, a subgroup of patients having diverticulosis, who require scheduled treatment in order to prevent occurrence/recurrence of complications, has been identified for the first time. DICA 2 is the only subgroup in which treatment influences the outcome of the disease.

In conclusion, DICA classification has shown to be a new and practical instrument that can be used by clinicians for the objective description of the colon harboring diverticula.
FOCUS ON SUDD

While the clinical symptoms of complicated DD are well known by all physicians, the more prevalent SUDD is often misdiagnosed and these patients are usually mistreated, leading to sub-optimal clinical benefit.

Recently, low-grade inflammation, altered intestinal microbiota, visceral hypersensitivity, and abnormal colonic motility have been identified as factors leading to symptom development, thus changing and improving the therapeutic approach. The pathogenesis of SUDD seems to be related to an interaction between colonic microbiota alterations, and immune, enteric nerve, and muscular system dysfunction [Cuomo, 2014].

The main symptom of SUDD is abdominal pain (colicky or steady, typically exacerbated by eating and relieved by flatus or bowel movements, usually located in the left lower quadrant) that may be associated with other symptoms such as disturbances of bowel habits (constipation and diarrhea), flatulence, heartburn, nausea and vomiting, palpable abdominal mass and abdominal distension [Colecchia, 2003].

These unspecific symptoms could make the diagnosis of SUDD an issue; in particular, Irritable Bowel Syndrome (IBS) and SUDD share several symptoms, such as bloating, loose/hard stool urgency, straining, mucus per rectum, bleeding, incontinence [Simpson, 2003]. The main symptomatic difference that might initially drive the physician towards the right diagnosis is that in IBS the pain is usually vague and located in the center of the abdomen, while in SUDD, pain is frequently lateralized and localized in the left iliac fossa (Figure 7). Moreover, in IBS, pain presents a median duration of 3 hours (range 0.1-12h, IQR 1.5-4 h) whereas in SUDD, pain has significantly longer duration (median duration 3 days, range 1-60 days, IQR 2-5 days) [Spiller, 2010; Simpson, 2003]. Moreover, in IBS, individual features linked to anxiety problems usually play an important role in the evaluation of the patient.

Diagnosis

Diagnosis usually relies on instrumental tools as SUDD is characterized by nonspecific symptoms, which overlap with those of other conditions, such as, among others, appendicitis, cholecystis, constipation, IBS, infective colitis or urinary tract infection.

Ultrasonography

Scientists are looking at ultrasound with renewed interest as this technique might be able more than others to promptly detect a considerable portion of patients affected by SUDD, which once diagnosed could promptly start a treatment avoiding the development of complications.

Among diagnostic examinations, ultrasound has several advantages being noninvasive, of ready and quick use, repeatable and accurate. All these features make ultrasound an useful tool in the patients’ physical examination, with an evident positive repercussion on the health of patients, and social costs as well. Abdominal ultrasound is currently used as first exam in patients with chronic abdominal complaints.

Another advantage of ultrasound is the ability to correlate imaging findings with the region of greatest tenderness in real time, providing in such instances useful information for the differential diagnosis (e.g. ovarian cysts, stones in the urinary tract, epiploic appendagitis) [Maconi, 2016].

Two meta-analyses have reported that ultrasound and CT have comparable accuracy in the evaluation of acute
diverticulitis [Lameris, 2008; Liljegren, 2007] and other studies have shown that contrast-enhanced ultrasound (CEUS) could further increase the detection of acute diverticulitis as well as the diagnosis and differentiation of its complications like fistulas or covered perforations, inflammatory masses and abscesses [Girlich, 2010]. In this context, ultrasound with bowel investigation has been proved very useful in detecting inflammatory disorders, like Crohn’s disease and ulcerative colitis and acute abdominal conditions, like epiploic appendagitis. However, the usefulness of ultrasound to distinguish these conditions from diverticular disease and other functional disorders such as irritable bowel syndrome has not been still fully investigated. Anyway, in patients that for several reasons do not require or necessitate a prompt invasive investigation of the colon, ultrasound could be a useful preliminary investigation.

Endoscopy
According to gold standard, colonoscopy is not indicated to confirm acute diverticulitis diagnosed with abdominal CT. Moreover, its utility in confirming diverticular disease suspect is still debated, after the resolution of an episode of acute diverticulitis too. The American Gastroenterological Association recommends colonoscopy after at least 6 weeks of resolution of acute diverticulitis episode [Tursi, 2015]. Colonoscopy is instead mandatory in case of persistence of symptoms after 10 days of treatment during diverticulitis, in order to exclude other diseases, and urgent colonoscopy is indicated in case of suspected diverticular bleeding. Endoscopic examination has also the role of carrying out differential diagnosis ruling out pathologies such as colon cancer, ischemic colitis, infective colitis, inflammatory bowel disease in the acute phase. In addition, colonoscopy may reveal indirect signs of previous acute diverticulitis, as the rigidity of the colonic wall and the sub-stenosis or stenosis of the intestinal lumen [Daniels, 2014].

Computed Tomography Colonography (CTC)
Reproducibility, operator independence, wide availability, and high accuracy for diagnosing acute disease are the strengths of CTC examination [Lameris, 2008; Liljegren, 2007]. Furthermore, CTC allows for comprehensive evaluation, including the grading of severity and detection of complications that affect therapeutic management. Recently, a diverticular disease severity score (DDSS) based on CTC findings [Flor, 2013] has been proposed. The score is based on the varying degrees of two CTC findings, wall thickening and lumen stenosis, and consists of four grades (DDSS 1–4). This validated CTC-based DDSS score seems to have prognostic value in the follow-up of acute diverticulitis [Flor, 2015]. Surgeons could benefit from detailed anatomic information regarding the entire colon, and CTC represents the test of choice in case of elective surgery, as it is clearly superior to both optical colonoscopy and the barium enema: CTC provides detailed information on colon anatomy, total number and distribution of diverticula, and the degree of wall thickening and luminal stenosis [Flor, 2015].

Markers
Biomarkers may be useful tools in managing diverticular disease as to assessing disease’s activity, predicting and preventing clinical relapse of the disease, surgery, and finally, in evaluating the response to therapy. Despite being a key clinical factor for the diagnosis of acute diverticulitis, a simple white blood cell count has low specificity [Tursi, 2010]; more specific markers should be used.

Fecal Calprotectin: FC is considered a very promising marker. It is a cytoplasmic antimicrobial compound prominent in granulocytes, monocytes, and macrophages and it accounts for approximately 60% of the total cytosolic protein. It is released from cells during cell activation or death, and it is stable in feces for several days after excretion [Costa, 2003]. Several studies have been carried out to assess the role of FC in colonic DD, comparing DD patients with IBS patients and healthy controls. Moreover, FC levels in different degrees of DD were evaluated, and FC in symptomatic DD, before and after treatment, was assessed as well [Tursi, 2009]. No difference in FC level was found between asymptomatic diverticulosis, IBS patients and healthy control. Higher FC values were found in AD and in SUDD compared to healthy controls or IBS patients. FC values correlated with inflammatory infiltrate and it decreased after treatment to normal values in both AUD and SUDD [Tursi, 2009]. These results are very interesting for the clinical practice, as FC plasma level seems to be related to the severity of the disease. Moreover, FC seems to be able to discriminate between SUDD and IBS.

C Reactive Protein: CRP is increased in acute diverticulitis and it seems to be the main biomarker in this disease. The CRP value, in diverticulitis, may be useful in distinguishing between acute uncomplicated diverticulitis (AUD) and acute compli-
cated diverticulitis (ACD). CRP is also the strongest marker for colonic perforation in acute diverticulitis [Käser, 2010] and it seems to be the key to assess response to therapy [Ridgway, 2009].

Unfortunately, CRP value is not increased in SUDD.

**Issues in primary care diagnosis of SUDD**

Gastroenterology comprises around 10% of a GPs workload, of which lower gastrointestinal problems constitute around 50%. In patients with lower abdominal pain, differential diagnoses include irritable bowel syndrome, appendicitis, colitis and bowel cancer. Gynecological causes include pelvic inflammatory disease, ovarian cyst or torsion and ectopic pregnancy. Urological conditions include urinary tract infection or urinary tract obstruction, including ureteric stone. Patients with rectal bleeding or alteration of bowel habit should be considered for cancer or colitis [Nice Guidelines Diverticular Disease].

The diagnosis of SUDD in primary care can be challenging as there is overlap with other conditions and there are no clear diagnostic symptoms, signs or first line blood tests. Patients often present with ambiguous symptoms and GPs find themselves having to reach a probable diagnosis for conditions that are not straightforward and often co-exist with other clinical aspects. Indeed, the commonest GI problems have no clear-cut underlying diagnosis: diarrhea (often due to transient infections), constipation (frequently associated with increasing age or drug therapies), functional problems (IBS) and in general, abdominal pain of varying extents and intensity. Relatively few patients undergo extensive investigations, except if symptoms became severe, progressive or associated with warning signs [Hungin, 2016].

The crucial point of the diagnosis of SUDD is the evidence of diverticula and the exclusion of other diseases [Nice Guidelines Diverticular Disease, http://www.evidence.nhs.uk]. In addition to a patient’s history and complete examination, particularly to assess the possible acute nature of the problem, the patient should have a detailed blood count and if available, the CRP and FC level, which is raised in patients with uncomplicated diverticulitis.

**Therapy**

**Surgery versus conservative approach**

The role of surgery in the treatment of DD is radically changing and emergency surgery is more and more considered standard treatment mainly in patients with peritonitis. Although prophylactic surgery has been recommended after two attacks of diverticulitis, this view has changed in recent years and more space has been given to a conservative approach [Cuomo, 2014]. This line, in the non-complicated forms of DD, include a high fiber diet, the use of anti-spasmodic, non-absorbable antibiotics and probiotics, based on the dogma that bacterial overgrowth in the diverticulum is the first stage of a pathogenic cascade of events, eventually culminating in diverticulitis and complications.

This new trend in patient management has created a large population of post-diverticulitis subjects at potential risk for subsequent attacks, raising the important clinical question as to whether any medical therapy can alter their natural history.

**Dietary fiber**

Fiber supplementation is generally recommended for the treatment of SUDD. By definition, fiber is incompletely or slowly fermented by microflora in the large intestine promoting normal bowel movements, relief from constipation and ultimately preventing the development of SUDD and diverticulitis by accelerating the fecal transit time and reducing the intraluminal pressure [Cuomo, 2014]. By the way, an excessive intake of fiber in some SUDD patients may lead to worsening of symptoms due to intestinal gas production, so there are no recommendations in the guidelines, every patient should be viewed as a case in itself.

**Non-absorbable antibiotics: Rifaximin-α**

Locally acting, non-absorbable antibiotics seem to improve symptoms relief in patients with SUDD. Thanks to their action on gut microflora, antibiotics may induce a decrease in gas production and in bacterial degradation of fiber, with consequential decrease in abdominal pain and increase in fecal weight, especially at some key-stages of DD such as SUDD. The antibiotic which most of all seems to show this eubiotic capabilities is rifaximin-α, a semi-synthetic product derived from rifamycin, and a structural analogue of rifampin (Figure 8). Rifaximin-α specifically inhibits the binding of the β subunit of RNA polymerase, preventing RNA synthesis, and it is effec-
Rifaximin-α is highly effective against most gram-positive, gram-negative bacteria both aerobes and anaerobes. Rifaximin-α has interesting pharmacokinetic and pharmacodynamic features: due to minimal intestinal permeability and low systemic absorption following oral dose, 80% to 90% of orally administered rifaximin is concentrated in the gut, with less than 0.2% in the liver and kidney, and less than 0.01% in other tissues. Rifaximin-α is hardly metabolized at all, and, due to its extremely limited systemic absorption, drug interactions are uncommon, making it a safe and well-tolerated drug [Koo, 2010].

Emerging preclinical and clinical data suggest that the effect of rifaximin-α is not restricted to a direct antibacterial action in the gastrointestinal region. Indeed, rifaximin-α presents a multifaceted and wider impact: rifaximin-α can be considered as a gut microenvironment modulator, with eubiotic, cytoprotective and bacterial colonization resistance properties.

Three open and two double blind RCT [Colecchia, 2007] have examined the effectiveness of cyclic administration of rifaximin-α and fiber in reducing symptoms, compared with fiber alone, and a systematic review and two meta-analysis have analyzed the results [Latella, 2009; Bianchi, 2011]. Aggregate data, from placebo controlled and unblinded trials, showed that the rate of acute diverticulitis was significantly less frequent in patients treated with rifaximin-α plus fiber supplementation than with fiber alone. It was then concluded that combined treatment (rifaximin-α plus fiber) is effective in obtaining symptom relief at 1 year in patients with SUDD; 64% of patients treated with combined therapy were asymptomatic compared with 35% in fiber alone group.

Cyclic treatment with fiber and rifaximin-α provides a greater prevalence of symptom-free patients and prevents acute diverticulitis more than dietary fiber alone, improving the quality of life [Cuomo, 2014; Pietrzak, 2015]. The number needed to treat to relieve symptom was three for rifaximin-α.

The use of rifaximin-α in patients affected by SUDD seems to be effective in maintaining SUDD remission and it might have a preventive effect on acute and complicated episodes of the disease (Figure 9).

Aminosalicylates

5-Aminosalicylic acid (mesalazine) is an anti-inflammatory agent widely used in the treatment of ulcerative colitis. The clinical scenarios in which the efficacy and safety of mesalazine alone or in combination with probiotics have been studied include SUDD, the prevention of diverticulitis and the prevention of recurrent diverticulitis.

Among some of the most recent studies, PREVENT1 and PREVENT2 evaluated the efficacy and safety of multimatrix mesalamine vs placebo in the prevention of recurrent diverticulitis in 590 (PREVENT1) and 592 (PREVENT2) adult patients with ≥1 episodes of acute diverticulitis in the previous 24 months that resolved without surgery. Patients received mesalamine (1.2 g, 2.4 g, or 4.8 g) or placebo once daily for 104 weeks. The primary endpoint was the proportion of recurrence-free patients at week 104. At the end of the observation, mesalamine did not reduce the rate of diverticulitis recurrence at week 104. Among patients in PREVENT1, 53%-63% did not have disease recurrence, compared with 65% of those given placebo. Among patients
in PREVENT2, 59%-69% of patients did not have disease recurrence, compared with 68% of those given placebo. Mesalamine did not reduce time to recurrence, and the proportions of patients requiring surgery were comparable among treatment groups. Therefore, mesalamine was not superior to placebo in preventing recurrent diverticulitis. [Raskin, 2014]

Moreover, conclusion of a systematic review of the literature was that medical treatment showed some evidence of improvement of symptoms in patients with SUDD, but its role in the prevention of acute diverticulitis remains to be defined [Barbara, 2007].

**Probiotics**

Although several analyses evaluating the clinical efficacy of probiotics have been performed, no definitive results have yet been achieved, mainly due to the heterogeneity of the available results. Most of the studies have used probiotics in combination with poorly absorbed antimicrobials (such as rifaximin-α) or anti-inflammatory drugs (mesalazine or balsalazide). Two studies [Annibale, 2011; Lahner, 2012] employed probiotics (Lactobacillus paracasei F19 and Lactobacillus paracasei B21060) in addition to high-fiber diet while another one [Lamiki, 2010] investigated the efficacy of a probiotic mixture (Lactobacillus acidophilus 145, Lactobacillus helveticus ATC 15009, Bifidobacterium spp. 420 in a phytoextracts-enriched medium). The latter is particularly interesting since – in addition to confirming the efficacy of probiotics on the symptom cluster (constipation, diarrhea and abdominal pain) of SUDD – showed a persistent colonization with the ingested microorganisms [Lamiki, 2010].

**Figure 10** summarizes the possible algorithms for the treatment of SUDD.

The group of Dr De Bastiani of the Italian Group of Gastroenterology Primary Care (GIGA-CP) recently presented an interesting web-based survey, conducted among Italian GPs. After recalling about the definitions of diverticulosis, SUDD and AD, thirteen questions about diagnosis and management options were queried to GPs. About diagnosis, colonoscopy was the most prescribed instrumental test used for diverticulosis and diverticular disease and in the follow up of SUDD and diverticulitis. As to treatment, fiber supplement was strongly advised in SUDD; Italian GPs still recommends a no-seeds diet (30%); rifaximin-α results the most prescribed treatment (in about 75% of patients), followed by probiotics (about 40%) for the managing of every type of disease. In particular, one fourth of patients with simple diverticulosis receive treatment with rifaximin and/or probiotics. Rifaximin-α was also the most prescribed drug in the treatment of SUDD, during the SUDD follow-up, and even in the diverticulitis follow-up [De Bastiani R, 2016]. Despite so, the survey reveals that current management of diverticular disease in primary care is often in conflict with recent literature and guidelines.
Guidelines

When taking into consideration the frequency of DD and the number of GPs and specialists who in their practice are daily committed in its diagnosis and management, the lack of common European and International guidelines really seems to be a paradox. This issue will definitely be discussed in the occasion of the next DICA Congress which will be held in Brazil in 2017 and hopefully sorted out in the occasion of a first world congress which has been long solicited by the most of the scientific community. In the meantime, this issue has been widely debated during the 2nd International Symposium: Diverticular Disease of the Colon, where guidelines from different countries were presented, in detail: Italy, Scandinavian countries, Germany, Eastern Europe, Australia and South America.

Conclusions

DD is not only one of the most prevalent gastrointestinal diseases, but also one of the most complex to diagnose and treat. However, physicians are still divided as to some aspects of this disease: from its classification and pathogenesis, to its diagnosis and treatment. The present evaluation between the experts and their good cooperation will surely lead to useful guidelines to recognize and resolve the different clinical conditions linked to this pathology. Although the scientific debate is still ongoing, some largely agreed key concepts are arising, such as the importance of an early diagnosis, a timely treatment, and the perceived need to overcome the stage of uncertainty that has been characterizing DD for too long.

Experts’ attention is focusing on SUDD, which is statistically the most common form of DD and yet the least diagnosed. Researchers have realized that SUDD is a serious problem, especially for GPs, who, as the first actors in diagnostics, play a pivotal role, often find themselves tangled in a real dilemma, when it comes to differentiate this disease from others, such as IBS and cancer. SUDD represents the most frequent clinical form of DD, but since its symptoms such as abdominal pain, alteration of bowel habits and nausea are rather unspecific, differential diagnosis of this condition can be difficult. SUDD and IBS, however, can be differentiated on the base of pain localization and duration, as well as a careful psychological anamnesis of the subject. Moreover, patients affected by SUDD present neurological alterations of gut motility. A delay in diagnosis, which can lead to the onset of more complex clinical patterns, involves the management of patients in a hospital environment with obvious effects on health care costs. Compared to colonoscopy, (invasive and sometimes traumatic and risky) and

Symptomatic Uncomplicated Diverticular Disease
(left lower quadrant pain > 24 h; altered bowel habits; fecal calprotectin overexpression)

Treatment with:
- Fiber
- Spasmolytics
- rifaximin-α
- Mesalazine

Persistent activity

The same out/in-patient treatment for acute uncomplicated diverticulitis

Treatment for at least 1 year with:
- rifaximin-α and Mesalazine
  (in order to maintain remission)
  or
- rifaximin-α
  (in order to maintain remission and to prevent acute diverticulitis occurrence)

Remission

Figure 10. SUDD therapeutic algorithm.
methodologies such as CT and MRI, (too expensive and often dependent on long waiting lists), which however remain the first choice in complicated cases of DD, ultrasounds seems to be a valuable tool because they allow a quick, painless and unequivocal differential diagnosis between SUDD and others diseases. Ultrasound is gaining popularity, as diagnostic tool for SUDD, due to its undeniable advantages for both the patient and the physician, being easily, safely and quickly performed and repeated with very accurate results. The possibility of the use of such a diagnostic mean not only by specialists, but also by primary care physicians, adequately trained to recognize the main ultrasound features of SUDD, would allow an important initial screening and a timely treatment, and, in the long run, a simplification of diagnostic procedures and lower health costs. Biomarkers (namely CRP and FC) are increasing approval to assess disease severity and response to therapy. DICA classification is a valid prognostic tool based on endoscopic findings in order to predict the course of the disease. Early identification and treatment of DICA 2 patients can likely prevent progression of the disease. Patients affected by SUDD show microbiota alterations, which can cause a harmful degree of gut inflammation, potentially leading to epigenetic modifications. Clinical studies reveal that a pharmacological intervention with Rifaximin-α - with or without the adjuvant treatment of probiotics - on patients affected by SUDD can allow control, stabilization and remission of symptoms, avoiding the worsening of the disease. The recent validation of rifaximin-α as the most suitable treatment for SUDD is due to its action not only as a simple antibiotic, but also as a eubiotic chemical drug. It is now clear that an imbalanced intestinal microbiota contribute to the development of SUDD. Environmental factors may result in a prolonged impairment of intestinal microbiota, which lead to an alteration of the intestinal structure itself and consequently SUDD. Studies reveal that a prompt intervention to restore gut eubiosis in early-detected SUDD patients by means of the protective effect of rifaximin-α, may prevent disease progression and provide an early improvement in patients’ quality of life. Rifaximin-α is a well-tolerated, large-spectrum, non-absorbable antibiotic which acts on gut microbiota, reducing its proliferation and improving symptoms in SUDD. Due to the lack of internationally recognized guidelines, GPs are facing a tough task when it comes not only to DD diagnosis but also to its treatment. An adequate training as to the most recent breakthroughs in DD aimed at GPs, in order to help them to differentiate SUDD from other conditions and to choose the most suitable treatment will lead to a better prognosis of the disease. Further evidence will be necessary to understand the extent, outcomes and limitations of these data, which really seem to be a breakthrough in DD state of the art.

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