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PREFACE

Welcome to the *Proceeding of the 2nd International Symposium Diverticular disease of the colon*.
For those who do not know about this Symposium, it is the second edition of this international meeting on this topic. Diverticulosis of the colon is a very common anatomical condition. In the Western World, it affects more than 70% of over 65rs population, and its prevalence is now increasing even in developing countries. We know that most of patients remain asymptomatic for all their life, but about 25% of them will experience symptoms (the so-called "Diverticular Disease"), and about 5% will develop acute inflammation of the diverticula (the so-called "Acute Diverticulitis"). This means extremely high direct and indirect costs for the National Health Systems. Despite this condition, diverticular disease of the colon, with all its clinical aspects, is still today an ignored and disregarded pathology. However, in the last years there has been some important change both in patho-physiological and therapeutic areas: these news allow to understand more about the causes of the disease and to start new therapeutic courses, even if not always shared by all the experts. This 2nd International Symposium Diverticular disease of the colon represents the perfect place for debate and link between the research and clinic, a chance for the growth of new generations and opportunity of constructive discussion. The event envisaged the participation of 400 national and international experts in order to analyze the state of the art of this important disease, and to share common diagnostic and therapeutic pathways.
We are very grateful to the speakers who, in addition of delivering excellent lectures, kindly accepted to increase their already intense workload by writing a short overview of their speeches.
Also, we would like to thank the team of The Triumph Italy S.r.l. for their excellent work as technical secretariat and dedication to this publication. Any defect in this CD is the editors' responsibility, not theirs.
Once again, welcome to the *Proceeding of the 2nd International Symposium Diverticular disease of the colon*. For those who attended the course they will be an opportunity for virtually going back to the meeting room. For those who did not attend, these *Proceedings* hopefully would be a major reason to apply for future editions.

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GENETICS AND INFLAMMATION – A PARADIGM FOR COMPLEX DISEASES

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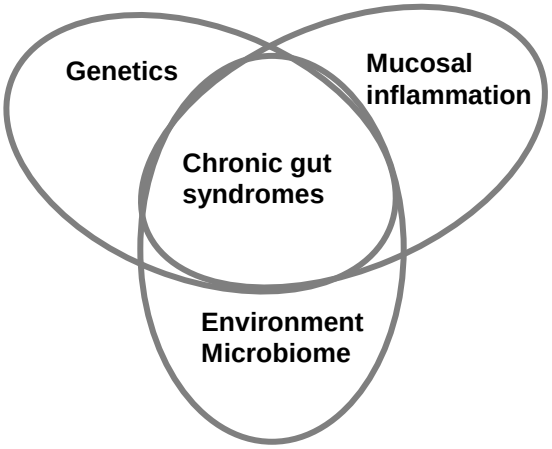
Inflammation is the key component of symptom generation in complex chronic gut syndromes (1), the major example being inflammatory bowel disease (IBD). Inflammation can be triggered by infection, as seen in another chronic gut syndrome - post infectious irritable bowel syndrome (PI-IBS) (2). Patterns of inflammation give rise to the disease phenotype, seen on biopsy.
The sequence of events in these syndromes is likely dependent upon a myriad of host and environmental factors including genetic, environment (diet, early life and stress) in conjunction with an inherent inflammatory response of the gut mucosa to pathogens and



composition of the microbiome.
These conditions may commonly co-exist. In terms of disease phenotype, there are some similarities, with both IBD and IBS patients exhibiting similar inflammatory responses (3). Importantly, the major immune-related genes identified as polymorphisms in PI-IBS patients are also important in IBD. For instance genetic variations in the *TNFSF15* gene have been identified as a risk factor for IBD (4). SNPs in this gene are also associated with a significant risk of IBS, particularly IBS constipation (5) and also diverticulitis (6).
Both IBS and IBD are characterized by dysbiosis. The IBD field has for some time investigated the hypothesis that IBD is initiated by a single enteric pathogen but given the similarities in terms of immune gene risk loci, it is more likely that the loss of immune homeostasis observed in IBD patients is a more complex and severe manifestation of the immunopathology present in PI-IBS patients (7). The inflammation observed in functional gastrointestinal disorders is consistent with low-grade immune activation and may be indicative of loss of homeostasis rather than organic immune activation (8).
Another key player may be the change in the gut microbiome as a result of infection or environment. The complexity of the interaction goes beyond the constituents of the microbiome as it is becoming apparent that the host genome also influences the composition of the microbial milieu. Understanding of how the microbiome orchestrates gut architecture is evolving and it is now

recognized that microbial-derived metabolites are capable of initiating epigenetic changes that influence gut homeostasis (9).

Overlap of chronic gut syndromes also occurs in diverticular disease (DD), as inflammation (diverticulitis) in some patients leads to IBS- like symptoms, referred to as post-diverticulitis-IBS (10). Similarly, in DD environmental factors pose a risk to develop disease and studies of heritability of DD in twins shows conclusive evidence that genetic susceptibility occurs. A challenge is to tease out relative contributions of the host genetic susceptibility, the environment, such as dietary induced changes in microbiota and the host inflammatory response which may underlie the subsequent development of diverticulitis in DD (11).

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NEUROMUSCULAR FUNCTION ABNORMALITIES

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Introduction

Colonic diverticulosis is an age-related disorder of the large bowel featuring outpouching of the colonic wall, is relatively frequent in the general population [1], and represents the fifth most important gastrointestinal disease in terms of health-care costs in Western countries [2]. Although factors such as genetic predisposition, intrinsic anatomic features of the large bowel, colonic wall modifications with aging, and dietary fiber are likely to contribute to the formation of diverticula, it is commonly thought that abnormal colonic motility might play an important pathophysiologic role [3].

Rectosigmoid motor activity in colonic diverticulosis

Most data are relatively old, and carried out with suboptimal techniques in the distal colon (rectum, rectosigmoid junction) with blind or rigid rectoscopy positioning of catheters/electrodes, positioning that actually often did not surpass the rectosigmoid junction. Thus, at least some of such studies may have missed the diverticular area, and account for the discrepancies between different studies (see below). Early radiologic and motility studies data showed that patients with diverticulosis had exaggerated motility, both basally and after eating, and suggested that high pressures in the affected segments might be responsible for the formation of diverticula [4,5]. Subsequent studies, by means of electromyographic [6] or manometric [7] techniques, confirmed the presence of similar abnormalities, abnormalities also documented in right-sided colonic diverticulosis [8]. Other authors, however, were not able to demonstrate significant differences in rectosigmoid motility between controls and patients [9,10]. These discrepancies probably justify the different results obtained by surgical procedures focused on the correction of these dysmotilities, showing no [11] or positive effects [12] in improving abnormal colonic motility.

Colonic motor and sensory activity in colonic diverticulosis

The introduction of research techniques that allow records of colonic motor activity for 24 hours or more in the entire colon [13], and the possibility of evaluating visceral perception in the rectosigmoid area [14] have yielded interesting information on the basic pathophysiologic aspects of the motor abnormalities in patients with colonic diverticulosis. In a study comparing 24-hr recordings of colonic motility between healthy controls and patients with diverticulosis, the latter showed a significant increase of motility in the diverticular segments [15]. The motor response to physiological stimuli (meals) [16] 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 [17]; about 20% of this activity was retropropagated. This suggests that in the sigmoid a local non-dominant pacemaker may take over and initiate oral spreading of contractions along the less active proximal colonic segments [15]. Another 24-hr colonic motility study in patients with symptomatic uncomplicated diverticular disease (SUDD) demonstrated a significant increase of regular contractile patterns in the diverticular segments; more than 80% of this was represented by a 2-3 cycles per minute pattern. In addition, more than two thirds of patients, but none of the controls, reported abdominal pain while occurring a regular contractile pattern; this association was statistically significant according to symptom association probability criteria [18]. Concerning visceral perception, one study is available on colonic sensory activity in patients with colonic diverticula. This study compared data obtained in patients with diverticulosis, SUDD, and controls [19]. Perception of rectal distention was increased in SUDD compared to the other two groups,

whereas rectal compliance was similar between the three groups. Sigmoid perception was increased in SUDD (before and after meals) compared to controls, but not to diverticulosis, and the compliance was similar in the three groups. The colonic response to eating did not show significant differences between groups. Thus, SUDD patients, but not those with diverticulosis, have increased perception of distention not only in the affected (sigmoid) segment, but also in the unaffected rectum, and that this increase of perception is not due to abnormal wall compliance. These results suggest that diverticular patients have colonic motor/perceptive abnormalities, likely responsible for, or related to, some of the symptoms complained by these patients.

Pathophysiology of colonic neuromuscular dysfunction in patients with colonic diverticular disease

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 of the properties of the viscus, acting synergically to cause its malfunction. These abnormalities include the muscular thickening often found in the diverticular areas [20], and probably due to elastosis causing abnormal longitudinal muscle relaxation [21], abnormal myogenic activity *in vitro* [22], and a marked decrease of contractile responses to tachykinins [23]. Moreover, diverticular patients display an altered pattern of factors involved in smooth muscle contractility [24]. In addition, there is recent evidence that patients with diverticular disease may have discrete pathological abnormalities, involving one or more components of the enteric nervous system [25-27]. Another interesting point is the relationship between low-grade mucosal inflammation and enteric neurosignaling; mucosal neurotransmitters may play a role in the dysmotility of these patients [28], as shown by an increased number of serotonin-containing cells [29], the decreased serotonin transporter expression and function in patients with recent acute diverticulitis [30], the increased mucosal neuropeptides in SUDD, expression of a previous resolved inflammation [31], and the increased number of colonic mast cells [32].

Conclusions

The pathogenesis of colonic diverticulosis features several basic mechanisms; however, several evidences suggest an important role played by neuromuscular dysfunction. Of course, more studies are needed in this area, to establish in a firm manner the true role of these abnormalities in diverticulosis.

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ROLE OF MICROBIOTA IN COLONIC DIVERTICULAR DISEASE

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The gastrointestinal (GI) tract represents a dynamic network where several players cross-talk forming a functional unit organized as a semipermeable multi-layer ecosystem. This unit is constituted by two main parts: a superficial physical barrier, which prevents bacterial adhesion and regulates paracellular diffusion to the underlying host tissues, and a deeper functional barrier, which is able to discriminate commensal bacteria from pathogens and is responsible for immunological tolerance to commensal and immune response to pathogen microorganisms [1]. Various gut mucosal cells and their defense molecules, the immune system, food particles, and the resident microbiota are able to allow the absorption of nutrients and macromolecules required for human metabolic processes and, on the other hand, protect the individual from potentially invasive microorganisms [2-4]. This complex habitat harbors around 1kg of commensal microbes that include more than 3 million of genes [5, 6]. They belong to the three domains of life, *Bacteria, Archaea* and *Eukarya* [7-9], as well as to viral particles [10, 11]. Recent advances in metagenomic pyrosequencing on human mucosal biopsies, luminal contents and feces, have found that four major microbial phyla, (*Firmicutes, Bacteroides, Proteobacteria* and *Actinobacteria*), represent 98% of the intestinal microbiota and fall into three main groups of strict extremophile anaerobes: *Bacteroides, Clostridium* cluster *XIVa* (also known as the *Clostridium Coccoides* group), and *Clostridium* cluster *IV* (also known as the Clostridium leptum group) [4, 7, 8, 12-19].
A complex and mutualistic symbiosis regulates the relationship between the host and the gut microbiota [13, 20-22]. The mucosal immune system participates in the maintenance of gut microbial communities by directly monitoring the luminal environment through the constant sampling through M-cells that overlie lymphoid follicles and by dendritic cells that resides within the lamina propria. The interaction of these cellular components sustains the delicate equilibrium to maintain intestinal homeostasis, establishing a state of immunological tolerance towards antigens from food and commensal bacteria. This interplay is constantly challenged with several factors such as rapid turnover of the intestinal epithelium and overlaying mucus, exposure to peristaltic activity, food molecules, gastric, pancreatic and biliary secretions, defense molecules, drugs, pH and redox potential variations, and exposure to transient bacteria from the oral cavity and esophagus, and can lead to the collapse of the microbial community structure [19, 22]. On the other hand, resident microbes perform several useful functions, including maintaining barrier function, synthesis and metabolism of nutrients, drug and toxin metabolism, and behavioral conditioning [1]. Gut microbiota is also involved in the digestion of energy substrates, production of vitamins and hormones [23], protection from pathogenic bacteria by consuming nutrients and producing molecules that inhibit their growth [24-26], production of nutrients for mucosal cells [27-29], augmenting total and pathogen-specific mucosal IgA levels upon infection [30, 31], and in modulating immune system development and immunological tolerance [32].
Unfavorable perturbation of microbiota composition, known as dysbiosis, has been associated to chronic, and perhaps also systemic, immune disorders of the gut, such as in the pathogenesis of inflammatory bowel diseases (IBD), and other gastrointestinal disorders, including gastritis, peptic ulcer, irritable bowel syndrome and even gastric and colon cancer [16, 33-35]. Changes in intestinal microbiota composition may play a role in the development of Diverticular disease (DD) and its complications. This may be due to an uninhibited activation of intestinal immune responses. Interestingly, a chronic low-grade inflammation can be found in patients with asymptomatic diverticulosis. Changed stability control factors or genetic variations could have led to these changes in intestinal microbiota composition. The onset of inflammation in diverticulitis shows similarities to the induction of inflammation in IBD. Deficiencies of host immune defenses and

dysfunction of the barrier effect result in increased mucosal adherence of bacteria and promote translocation. A pathogenic immune response is activated and inflammation induced by the formation and topical release of proinflammatory cytokines. Inflammatory and/ or functional changes lead to abdominal symptoms, such as lower abdominal pain/discomfort, bloating, tenesmus, and diarrhea. Evidence that supports the assumption that microbiota and low-grade inflammation play important roles in DD derives from studies demonstrating the efficacy of rifaximin, 5-aminosalicylic acid, and probiotics in achieving symptom relief and disease remission [36]. In particular, Rifaximin, a poorly absorbable antibiotic, decreases the metabolic activity of the intestinal bacterial flora and the degradation of dietary fiber. Cyclic administration of rifaximin with dietary fiber supplementation is more effective in reducing both symptom and complication frequency than simple dietary fiber supplementation in patients with DD [37]. However, a solitary role for microbiota is not likely. The pathogenesis is more likely multifactorial and the result of complex interactions. There may well be some missing links, yet to be discovered, other than a changed microbiome and subsequent activation of immune responses that are necessary for the development of DD and/or its complications. The pathophysiologic significance of these changes in gut microbiome is still uncertain. Importantly, it needs to be determined whether changes in the gut microbiome indeed are a cause or just a consequence of DD. If the exact role of gut microbiota in DD is determined, this could be of great clinical value in the diagnosis and prevention of disease, treatment options, targeting of treatment, and in measuring the effect of therapy.

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COLONOSCOPY

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Colonic diverticula is one of the most frequent conditions found during the endoscopic examination of the lower digestive tract. Although the absolute prevalence is difficult to quantify, it is possible to determine that in the Western world, after 80 years old more than 70% of patients has diverticula.
Colonscopy is still the most widely used diagnostic tool for the patients with colonic diverticula, for this reason the role of endoscopy in the diagnosis and management of diverticular disease is now evolving.
1) Colonscopy is not indicated in order to confirm acute diverticulitis diagnosed with Abdominal CT *(gold standard)*.
2) Colonoscopy is debated in the following conditions:
- to confirm diverticular disease suspect with clinical examination or other imaging test;
- after the resolution of an episode of acute diverticulitis, in patient without colonscopy in the last 3 years
3) Colonoscopy is instead mandatory in case of persistence of symptoms after 10 days of treatment during diverticulitis, in order to exclude other diseases.
4) Urgent Colonscopy is indicated in case of suspected diverticular bleeding
Regarding the timing of endoscopic procedure, AGA raccomandes colonscopy after at least 6 weeks of resolution of acute diverticulitis episode, neverthless recent data showed that earlier approach (after 7-10 day to clinical resolution) do not increase the percentage of endoscopic-related adverse event.
Endoscopic examination has also the role of ruling out other intestinal diseases that can go in the differential diagnosis of acute diverticulitis, such as colon cancer, ischemic colitis, infective colitis, inflammatory bowel disease in the acute phase, especially when radiologic test (CT Abdomen) are not pathognomonic.
Different pictures can be found during colonscopy in patient with diverticula: non flogistic diverticula, segmental colitis associated to diverticulosis (*SCAD*), diverticulitis with or without complications, bleeding diverticula. 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.
Colonoscopy, in patients with diverticular disease, can take an advanced skill, both in recognizing situations of particular risk (*acute diverticulitis with or without perforation*), or in special situations such as massive diverticulosis with virtual colonic lumen, the presence of narrow angles and rigid fixed lumen, or to passing stenosis. The use of endoscopes with different caliber and stiffness can be useful in some cases, giving further help to endoscopist. The treatment of diverticular bleeding is also a challenge for the endoscopist.
Recently we introduced and validated the DICA score (Diverticular inflamation and Complications Assessment), to establish, with objective and reproducible score, the severity of the disease associated with the diverticula. The DICA score consists of purely endoscopic parameters as the number of diverticula (in the right and left colon), the presence of inflammatory sign (edema/hyperemia, erosions, SCAD) and the presence of complications of stigmata, such as stiffness or the luminal stenosis and the presence of complications such as bleeding and the presence of pus.
The main aim of DICA score is to predict the future development of complications and the global outcome of the disease, deciding whether a medical therapy is needed.

In summary, the role of endoscopy in diverticular disease is of prime importance in the staging of the severity, the complications and to choice appropriate medical therapy.

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ULTRASONOGRAPHY

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Introduction

Diverticulosis, colonic diverticular disease and acute diverticulitis are common clinical conditions, with increasing burden in ambulatory visits and diagnostic procedures, hospital admission and mortality, in particular in industrialised countries, in both elderly and young patients [1,2]. The role of diagnostic imaging has became very important for the diagnosis of these conditions, to differentiate them from other symptomatic diseases and from other inflammatory conditions and to tailor the best treatment, providing information on potential outcome and optimising the follow up of patients with diverticular disease and diverticulitis.
Among diagnostic examinations, ultrasound has several advantages. It is non invasive, of ready and quick use, repeatable and accurate. All these features could make of ultrasound – in specific circumstances – the natural extension of the patients' physical examination, with positive repercussion on heath of patients and social costs.
Thereafter, the main role of ultrasonography in diverticular disease of the colon and acute diverticulitis, in particular in detecting these conditions and their complication, and in optimising the treatment and follow up will be discussed.

Ultrasonography in colonic diverticulosis

The term colonic diverticulosis simply reflects the presence of diverticula, regardless to symptoms. It is a common condition in the West, with a prevalence <5% under age of 40, and >65% over 80 [3], and has a strong predilection for the sigmoid and descending colon where it may be associated the thickening of the muscularis propria, mainly of the circular smooth muscle, a condition that may be well observed by ultrasound.
The diverticula may appear at ultrasound as external hyperechoic pockets with shadows (due to internal coprolites) of the colonic wall. The colonic wall maintains its normal stratification even if frequently associated with thickening of the muscolaris propria (usally >2 mm) (Figure 1). All these features are lacking in the right-sided diverticulosis, more common in Asia, and not easy to observe by ultrasound, unless they are complicated.
Ultrasonographic detection of asymptomatic diverticula, as occurs during screening colonoscopy, may occur in clinical practice, but it does not have a relevant impact on the outcome of the patients and does not necessarily require any treatment or change in dietary habit.

Figure 1
Sonographic feature of diverticulosis (a) and diverculitis (b) of the sigmoid colon. Note the thickening of muscolaris propria and the diverticula that appear as hyperechoic pockets with shadowing (due to internal coprolites) in diverticulosis (a). In acute diverticulitis, note the hypoechoic periintestinal area, associated with thickening of the bowel, irregularity of the external margin and hypertrophy of the mesenteric fat (b).

a

b

Ultrasonography in Symptomatic Uncomplicated Diverticular Disease
The role of ultrasound in chronic uncomplicated symptomatic diverticular disease is debated and largely un-investigated. Abdominal ultrasound is currently used as first exam in patients with chronic abdominal complaints. In this context ultrasound with bowel investigation has been proved to be 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.

Ultrasonography in Acute diverticulitis
Ultrasound is widely considered a front-line imaging test for acute diverticulitis being safe, widely available, and easily accessible within the emergency department. It is a fast, low-cost and non-invasive examination. In particular, ultrasound may be a reasonable consideration in thin patients and in young females, where radiation exposure is best avoided. 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, ecc..).
At ultrasound acute diverticulitis appear as hypoechoic periintestinal area, associated with marked thickening of the bowel, irregularity of the external margin at the level of diverticula and hypertrophy of the mesenteric fat, where maximum is the tenderness complained by the patient, in particular during the compression with the probe (Figure 1b). However, it has to be acknowledged that these features may be difficult to detect if the inflamed diverticulum is deeply seated in the abdomen and in the pelvis, especially in obese patients and may be more difficult to be appreciated by non expert investigators.
When performed by expert examiners, ultrasound can be reasonably effective [4], in particular when used as a preliminary test in a sequential diagnostic strategy that includes CT as a confirmatory test in negative or un-conclusive examinations. Two

meta-analyses have reported that ultrasound and CT have comparable accuracy in the evaluation of acute diverticulitis [5,6] and other studies have shown that contrast-enhanced ultrasound (CEUS) could further increase the detection of acute diverticulitis and well as the diagnosis and differentiation of its complications like fistulas or covered perforations, inflammatory masses and abscesses [7].

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COMPUTED TOMOGRAPHY

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Acute diverticulitis

The evaluation of patients with acute diverticulitis includes medical history, physical examination, and laboratory testing, but cross-sectional imaging often plays a pivotal role in verifying the diagnosis. In practice, clinical diagnosis without imaging confirmation is unreliable [1-2]. Different radiologic tests can be applied for the diagnosis of acute diverticulitis, including ultrasound, computed tomography (CT), and magnetic resonance (MR) imaging. Both CT colonography (CTC) and the double contrast barium enema (DCBE) are contraindicated in the setting of suspected acute diverticulitis.

In some cases, CT may be deemed necessary to confirm suspected US-guided diagnosis, and to assess for complications. Two meta-analyses have reported that ultrasound and CT have comparable accuracy in the evaluation of acute diverticulitis [3-4], although these data may be somewhat biased.

All the limitations associated with ultrasound can be overcome by conventional abdominal CT, which is generally considered by most as the preferred front-line radiologic test for evaluating patients with suspected acute diverticulitis. Strengths of CT examination include its reproducibility, operator independence, wide availability, and high accuracy for diagnosing acute disease [3-4]. CT allows for comprehensive evaluation, including the grading of severity and detection of complications that affect therapeutic management. Diagnosis can be directly made on the basis of localized bowel wall thickening that is centered on an inflamed diverticulum, with surrounding peridiverticular inflammation of the pericolonic fat. As diverticulitis is primarily an extraluminal disease, cross-sectional imaging holds a distinct advantage over luminal studies. Covered or free perforations can be rapidly and reliably diagnosed by the direct detection of air inclusions outside the intestinal lumen, often associated with mesenteric fasciae thickening and free fluid.

CT evaluation is valuable for its appraisal of disease severity, which impacts therapeutic management. In particular, different severity scores and guidelines [5-9] strive to divide patients into two main categories, namely uncomplicated and complicated acute diverticulitis. In uncomplicated cases, the CT findings are generally limited to phlegmonous reaction of pericolonic fat tissue, whereas complicated features include peridiverticular abscess, significant pneumoperitoneum, and diffuse peritonitis. Moreover, CT grading of acute diverticulitis has prognostic significance in terms of disease recurrence after an initial episode of acute disease [10].

In addition to being highly accurate for acute diverticulitis itself, CT is also the most accurate test for diagnosing alternative conditions [11-12], including acute appendicitis [13].

CTC and DCBE are contraindicated in patients with acute diverticulitis, adding no additional useful information to conventional CT evaluation for acute management. Since both examinations include active colonic distention with either room air or carbon dioxide, there is at least a theoretical concern for extension of the typical microperforation associated with acute diverticulitis to more frank perforation and peritonitis. DCBE in particular is an obsolete test and should be abandoned, regardless of the clinical scenario. This test has a lower accuracy than CTC and optical colonoscopy for colorectal evaluation [14], is associated with higher ionizing radiation exposure [15], and is less acceptable for patients [16]. On occasion, findings of unsuspected mild acute or

subacute diverticulitis may be encountered at CTC in patients with only minimal or no apparent symptoms.
MR imaging currently does not play an important role in the work-up of patients with suspected acute diverticulitis, but can be considered in selected cases, such as pregnant women. Although there are some advantages compared with other radiologic tests (e.g., lack of ionizing radiation exposure and high intrinsic contrast resolution), MR availability in the emergency department is currently limited in most hospital settings. To date, there is relatively little evidence regarding the accuracy of MR for acute diverticulitis, limited to small select patient cohorts [17-18]. However, due to the rapid technological progress in terms of MR imaging speed and resolution, and the increasing availability of MR, its role in the setting of the non-traumatic acute abdomen appears to be rapidly expanding. The imaging findings of MR are analogous to CT, but there may be a learning curve in diagnostic interpretation [19].

Chronic diverticular disease
In contrast to acute diverticulitis, the role of imaging in chronic diverticular disease is in evolution and still subject to debate. Among the radiologic exams, CTC has the potential to play a pivotal role due to the unique 2D/3D combination that allows for comprehensive endoluminal and extraluminal evaluation. In particular, CTC looks promising in evaluating patients who have recently recovered from an episode of acute diverticulitis, representing a natural extension of the imaging performed in during acute phase. One major strength of CTC over DBCE, US, and MR is related to the ability to confirm the diagnosis of diverticular disease or suggesting superimposed CRC. CTC can also explain persistent symptoms due to unknown complications such as peridiverticular abscesses or fistulas, and determine the severity of disease, which may impact therapeutic management decisions. Moreover, a high quality CTC examination can generally be obtained even in cases of severe luminal stenosis [20-21], allowing adequate accuracy in diagnosing proximal colonic polyps and CRC [22-23]. This has particular value in the setting of right-sided advanced neoplasia, which could be ignored for a prolonged period of time due to an incomplete optical colonoscopy.
With CTC, diverticula can be easily recognized as outpouchings of the colonic wall, which can be air-filled, contrast-filled, or impacted with stool. Due to colonic distention, CTC is also able to demonstrate the presence of associated wall thickening and luminal stenosis. Wall thickening can reach 10-15 mm and typically involves a long colonic segment. Short-segment wall thickening should raise concern for CRC in the differential diagnosis, although most cases represent pseudotumoral diverticular masses or less commonly, mucosal prolapse.
To reduce both the risk of perforation risk and of the likelihood of a residual acute inflammatory component, CTC should be carried out at least two or three months after the acute episode of diverticulitis.
In our opinion, it may be advisable to modify the standard CTC protocol slightly in the setting of known complicated diverticular disease. For example, it can be useful to perform the CTC examination with IV contrast. In particular, a contrast-enhanced regimen should be considered in the presence of severe wall thickening and luminal stenosis, when the differential diagnosis between diverticular disease and CRC is more relevant. Another scenario generally requiring IV contrast is when there is potential concern for diverticular complication such as abscesses or fistula [24]. To optimize distention of the entire colon, which is critical for high quality examination, automated carbon dioxide insufflation is preferred [25]. In addition, a spasmolytic agent may help optimize distention as well.
It is unreliable to describe the degree of severity of diverticular disease in a subjective manner. Recently, a diverticular disease severity score (DDSS) based on CTC findings [24] 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). In the case of DDSS grade 4, where marked wall thickening is associated with severe luminal stenosis, surgical options should be considered. In practice, the simultaneous presence of severe stenosis and the inability to exclude

CRC are both potential indications for surgery [26]. Moreover, this validated CTC-based DDSS score seems to have prognostic value in the follow-up of acute diverticulitis [27].
In patients with diverticular disease, it can be challenging to recognize a superimposed colorectal cancer (CRC), but these two entities are both relatively common in elderly patients, and can therefore coexist. This differential diagnosis is particularly tricky in cases of marked wall thickening and severe luminal stenosis from diverticular disease. Some authors [28-29] have described a number of CTC findings as being useful in differentiating these two disease entities. Of these various findings, the absence of diverticula in the affected segment and the presence of a shoulder phenomenon are the two most important findings for CRC. Other CTC signs in favor of cancer include shorter length with straightening of the involved segment, absence of mesenteric fascia thickening, presence of distorted folds, and the presence of prominent local lymph nodes.
The above mentioned criteria are useful in ruling out CRC, but sometimes the CTC findings will overlap. In these selected cases, referral to optical colonoscopy or flexible sigmoidoscopy may be necessary to allow for direct mucosal evaluation and biopsy. In other cases, the surgical option may be indicated regardless of underlying cause. There are a variety of treatment options for patients with chronic diverticular disease, leading to some controversy in the surgical guidelines [26]. In particular, the surgical option takes into account multiple factors, including patient age, number of recurrent episodes of acute diverticulitis, and presence of complications. Before elective surgery, surgeons could benefit from detailed anatomic information regarding the entire colon, and CTC in our opinion represents the test of choice in providing this. In this regard, CTC is clearly superior to both optical colonoscopy and the barium enema. In particular, CTC provides detailed information on colon anatomy, total number and distribution of diverticula, and the degree of wall thickening and luminal stenosis. Surgical treatment is often considered when CTC detects unsuspected complications, such as abscess or fistula. CTC can also guide clinicians and surgeons when the appropriate therapeutic management is uncertain. For example, CTC diagnosis of unsuspected severe luminal stenosis could be a key factor in deciding on a surgical option. The surgical approach is generally laparoscopic, and surgeons could benefit from information about the vascular map derived from CTC [30-31]. Of course, to obtain this level of detail requires a contrast-enhanced CTC protocol, adding an arterial contrast phase to the standard portal venous phase. In general, the initial position (e.g., prone) is obtained prior to IV contrast, allowing for assessment of enhancement.

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DIVERTICULAR DISEASE AND IBS: OVERLAPPING OR MISUNDERSTANDING?

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The Irritable bowel syndrome is characterised by abdominal pain and disturbed bowel habit, often with bloating in a patient in whom other significant diagnoses has been excluded. Since IBS lacks biomarker it cannot be easily distinguished from other disorders which cause similar symptoms.
Current definitions exclude structural or biochemical abnormalities (1) but this lags behind research which shows subgroups of IBS have objective abnormalities, both central and peripheral. Peripheral abnormalities include increased gut permeability (2), immune activation, increased mast cells (3), abnormal serotonin availability (4), altered enteric nerves (5) and abnormal gut microbiota (6). Central abnormalities include elevated anxiety, depression and somatisation (7) and impaired descending inhibitory control mechanisms leading to abnormal pain processing. Central and peripheral factors often interact for example psychological stress can impair gut barrier function. These abnormalities may occur together or separately indicating that IBS patients are heterogenous and in the future are likely to be subdivided according to dominant underlying mechanism.
Diverticular associated disorders can be divided into 2 patterns. Type 1 is characterised by isolated episodes of pain, fever and disturbed bowel habit lasting 1-2 weeks with long symptom-free periods. Type 2 is characterised by recurrent pain often associated with disturbed bowel habit several times per week lasting a few hours to days, a pattern more typical of IBS. Type 1 may evolve into Type 2 in some patients. Some of the mechanisms described in IBS are relevant to patients with symptomatic diverticular disease. Thus immune activation (8), increased serotonin availability and abnormal enteric nerves (9) have all been demonstrated though so far none have been proven to be relevant therapeutic targets. Abnormal central processing of painful stimuli and anxiety, depression and somatisation (10) are also important predictors of symptoms as are social factors like bereavement and social isolation (11).
All these factors should be considered when deciding on the individualised treatment our patients deserve.

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ACCURACY OF BIOMARKERS OF PAST AND PRESENT INFLAMMATION

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Biomarkers may be useful tools in managing diverticular disease (DD). In particular, they may be useful in assessing disease‘s activity, in predicting and preventing clinical relapse of the disease, in predicting and preventing surgery, and finally in evaluating the response to therapy. Unfortunately, biomarkers have not been deeply Investigated in DD, and only in the last years some data have been published.

C-Reactive Protein

As an acute-phase reactant, CRP is increased in acute diverticulitis and it seems to be the best biomarker in that form of disease. The CRP values expressed in diverticulitis may be useful in distinguishing between acute uncomplicated diverticulitis (AUD) and acute complicated diverticulitis (ACD). In fact, the mean values of CRP are 2.50 mg/dl (range 1.0–3.50) and 20.50 mg/dl (range 15.0–33.50) in AUD and ACD, respectively (p=0.005) [1]. On the other hand, values >50 mg/dl are strongly suggestive of acute diverticulitis, especially in association with direct tenderness only in the left lower quadrant, and the absence of vomiting [2].

CRP is also the stronger marker colonic perforation in acute diverticulitis as well. Käser et al. [3] found recently that a CRP below 50 mg/l suggests a perforation to be unlikely in acute sigmoid diverticulitis, whereas a CRP higher than 200 mg/l is a strong indicator of perforation. Finally, CRP seems to be the best marker to assess response to therapy.

Ridgway et al. [4] performed recently a clinical trial assessing the role of intravenous or oral antibiotics in obtaining remission in AUD. They found that intravenous and oral antibiotics are both effective in obtaining resolution of symptoms in those patients. Moreover, they found that serial decrease CRP in both groups was noted, and that CRP strongly correlated with the resolution of left lower quadrant tenderness by day 6 of treatment (r = 0.40).

Other Serological Markers in DD

Assessment of white blood cells (WBCs) has been the mainstay in the diagnosis of DD. Increased WBC count is considered one of the key clinical factors to pose the diagnosis of acute diverticulitis (associated with left lower quadrant pain and abdominal tenderness) [5]. However, it is not a useful marker of disease activity in clinical practice as there are many factors besides disease activity (systemic glucocorticosteroids, immunosuppressants, presence of abscess) that affect it.

As in IBD, WBC count values are related to the severity of the diverticulitis, showing higher values in complicated diverticulitis [1,3] . However, WBC count shows low sensitivity and specificity than CRP both in diagnosis [3,6] and monitoring acute diverticulitis after treatment [4,5,7].

A Promising Fecal Marker in DD: Fecal Calprotectin

FC is a cytoplasmic antimicrobial compound prominent in granulocytes, monocytes, and macrophages. 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 [8,9]. After the first report about a slightly increasing FC levels in diverticulosis than in healthy controls [10], a study assess the role of FC in colonic DD, comparing it with IBS patients and healthy controls. Moreover, FC levels in different degrees of DD were compared, and FC in symptomatic DD before and after treatment was assessed as well [11]. FC was not increased in healthy controls or IBS patients and no difference was found between asymptomatic diverticulosis, healthy controls, and IBS patients. Higher FC values were found in AUD and in SUDD than in healthy controls or in IBS patients.

FC values correlated with inflammatory infiltrate. FC decreased after treatment to normal values both in AUD, and in symptomatic uncomplicated DD (SUDD) after treatment [11]. These results

have been confirmed by another study, which used the same semiquantitative method to assess FC [12].
These results are very interesting for the clinical practice. First of all, FC measuring seems to be related to the severity of the disease. So, detecting of higher values may be synonymous of severity of diverticulitis. The second important point is that we can be able in monitoring the therapeutic response to the treatment only assessing FC, which decreases according to the therapeutic response. But the most important point is that FC seems to be able in discriminating between SUDD and IBS, which shared a lot of symptoms. The is a key point, due to the higher risk of over- or undertreatment in patients suffering from abdominal paint and incorrectly classified.

Other Biomarkers in DD

Other markers may be identified as biomarkers in DD. In particular, we have some immunohistochemical markers or cytokines that represent the stage of the disease. Among other, it is worth of noting the matrix metalloproteinase and their inhibitors, tachykinins and some cytokines.

Conclusions

Although biomarkers have not been completely investigated in DD, we know today that serological marker may be helpful in managing DD [13]. In particular, CRP seems to be the most sensitive marker of disease activity and response to therapy. Unfortunately, CRP, as well as other inflammatory markers, by definition are not increased in SUDD. In this field, FC seems to be a promising tool, in particular in differentiating between IBS and SUDD [14]. Further, larger studies are needed to understand the role of other biomarkers, from tachykinins to cytokines, in the clinical setting of DD.

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What is Segmental Colitis Associated with Diverticulosis?

Diverticular disease of the colon affects the majority of the Western population older than 60 year (1, 2). For many years, the inflammatory symptoms of diverticular disease of the colon have been divided into two main categories:

1. Acute diverticulitis of the colon. This is a form of inflammation which is mainly of diverticular origin. In this type of inflammation, the inflammatory process originates from the diverticula and extends to the colonic mucosa around the diverticula, but usually does not involve the interdiverticular mucosa (3, 4).
2. The so-called "segmental colitis associated with diverticulosis", better known by its acronym "SCAD". This is a chronic inflammatory process localized in the colonic area presenting diverticulosis, and therefore mainly in the sigmoid colon (5). By definition, both the rectum and the right colon are spared from any inflammation both endoscopically and histologically (6).

Recent data have hypothesized that SCAD may be an independent clinical entity within the IBD set of diseases. Several characteristics seem to support this hypothesis:

1. Similar to that occurs in IBD patients, SCAD patient present much higher levels of tumor necrosis factor-alpha (TNF-α) compared with control population (matched patients with irritable bowel syndrome) (7,8);
2. Histopathology study found recently that histological inflammation was surprising similar between UC and SCAD, and cytoarchitectural structure was altered in both diseases as well. However, mucin depletion and increased number of plasma cells, lymphocytes and histioid cells was found in UC than in SCAD (9).
3. In patients with SCAD refractory to conventional treatment, infliximab seems to be a good therapeutic option (10);

How to differentiate beween diverticular disese and SCAD

Both diverticular disease and SCAD affect the same colonic district, having similarities well identified (in example, old ages affected in both diseases and a benign course, since surgery is generally required only for severe form of the diseases) (11,12). However, there are specific differences that help in posing the correct diagnosis (see table 1):

1. The main characteristic is the endoscopic appearance of SCAD, which is quite different from that of DD. In particular, the endoscopic appearance of SCAD always shows inflammatory involvement of the interdiverticular mucosa, with sparing of the peridiverticular mucosa, which may be involved only in cases of severe inflammation (4,13). In almost all patients we can see sparing of peridiverticular mucosa, whilst involvement of this region is typical of diverticular inflammation. On the contrary, inflammation in diverticulitis always affects peridiverticular mucosa, and involvement of interdiverticular mucosa may occur only in case of severe disease. Moreover, the endoscopic appearance of SCAD is often similar to that of IBD. Even if not applicable in all cases, most SCAD patients present an endoscopic picture similar to UC and CD, endoscopically defined as "ulcerative colitis like" and "Crohn's colitis like" (4,13);

2. Histopathology is quite differing between SCAD and diverticular disease. SCAD shows always active inflammatory infiltrate, often resembling UC. On the contrary, diverticular disease often shows unspecific inflammatory infiltrate, sometimes active, but never similar to that of IBD (14,15).

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Table 1. SCAD and diverticular disease: similarities and differences

Similarities

Older ages affected
May affect the same colonic regions (sigmoid, descending colon)
Endoscopic lesions are limited to colonic regions harboring diverticula
Endoscopic and histological sparing in other colonic areas without diverticula

Differences

Endoscopic lesions in SCAD are typical (_crescentic fold disease‘‘ or SCAD type A), or similar to UC (SCAD types B and D) or to CD (SCAD type C); endoscopic lesions of DD are often nonspecific
Inflammatory infiltrate in SCAD resembles IBD in most of cases (active and chronic inflammatory infiltrate, glandular distortion, transmucosal inflammation, cryptic abscesses); inflammatory infiltrate in DD is chronic in most patients, and only in acute diverticulitis can an active, unstructured inflammatory infiltrate be found
TNF-α overexpressed in SCAD, values higher than those detected in DD

SCAD segmental colitis associated with diverticulosis, DD diverticular disease, IBD inflammatory bowel diseases, TNF-α tumor necrosis factoralpha, UC ulcerative colitis, CD Crohn‘s disease

DIVERTICULAR DISEASE AND COLORECTAL CANCER: INCIDENTAL

DIAGNOSIS OR REAL ASSOCIATION?

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INTRODUCTION

Associations between diverticular disease of the colon and the colorectal cancer has been studied for more than 60 years. Theoretically, many options are possible including:

- these two diseases may be associated due to causal relationship
- they may be associated due to common risk factors and similar causes
- these are two separate entities, unrelated to each other
- one may mask the other due to similar localization (in sigmoid colon) and cause diagnostic difficulties.

Below available the most recent studies dealing with this problem are presented.

RESULTS FROM AVAILABLE STUDIES

The earliest studies published in the 80-ties, that were using barium enema as well as old-type endoscopy for diagnosis of the diverticulas suggested that as many as one-third to even half of patients with diverticulas finally had a colorectal cancer. Such studies initiatied the notion that diverticulosis leads to colon cancer. Furthermore, such conclusion was stressed by the similar epidemiology of both diseases; both with increasing frequency with age. Also similar trends were observed concerning populations living the so called western style. The hypothesis of strong relationship was supported by endoscopic, radiologic and autopsy studies proving coexistence of both diseases. However, over time the body of evidence was not so convincing anymore, with more and more studies showing no or a negative association. This was present especially in studies in which the first year after diagnosis of diverticulosis was excluded from analysis. The data from the older studies were gathered by Morini et al. in their extensive review paper (1). The same authors also provided extensive review retrieving older studies showing relationship between diverticulosis and colorectal adenomas, including autopsy studies. Furthermore, studies documenting microscopic and macroscopic findings in the area of diverticulosis were extracted (1).

The most recent studies using large databases were published trying to finally solve the dilemma. The first important study was done in Sweden by Granlund et al (2). This was a huge nation-wide case control study involving 41,037 patients with colorectal cancer identified by Swedish Cancer Registry. Each case was matched with 2 controls without cancer. Cases and controls were then searched for the episode of hospitalizations with the diagnosis of diverticular disease. Odds ratios for receiving the diagnosis of colon cancer was calculated after hospital discharge for diverticular disease. Further, cancer mortality was calculated for those cases with and without diverticular disease. Results are important and meaningful. The odds ratio for receiving the diagnosis of colon cancer was extremely high 31,49 (95% CI 19,00- 52,21) within 6 months following hospitalization for diverticular disease. The risk of diagnosis of colon cancer was, however, not increased 12 month after hospitalization. Among patients with colon cancer the mortality was not different between patients with and without diverticular disease. Authors

additionally gave strong recommendation that patients with diverticular disease should have a high quality diagnostic work-up within first 12 months after initial episode of diverticular disease.

The second large study was performed in Taiwan (3). The methodology was different. Authors, first retrieved a cohort of 41,359 patients with diverticular disease from National Health Research Institute database. Of those patients, 28,909 had diverticulitis and 12, 450 had diverticulosis. These patients were matched with 4 controls comprising 165,436 individuals without diverticular disease. In the initial analysis the risk of colorectal cancer was significantly increased (adjusted HR:4,54, 95%CI 4,19-4.91). However, in the proper analysis performed after excluding the first 12 month of follow up, the adjusted hazard ratio was not increased at all (HR 0,98, 95% CI 0,85-1,13). He risk was also not increased for both sub-cohorts with diverticulosis and diverticulitis. Authors drew similar conclusions as in Swedish study: diverticular disease does not increase the risk of colorectal cancer. The risk is only increased within the first year after diagnosis of diverticular disease which rather suggests the misclassification and misdiagnosis of diverticular disease.

The third large study comes from United States and deals with separate problem of interval cancer following colonoscopy (4). Authors first, using SEER and Medicare databases retrieved 299,260 patients aged 69 years or more with colorectal cancer diagnosed between 1994 and 2005. After exclusions the study sample consisted of 57,839 patients with colorectal cancer who had a colonoscopy documented. Of those, 53,647 underwent colonoscopy within 6 months of cancer diagnosis (most probably it was diagnostic colonoscopy). The remaining 4,192 patient had their colonoscopy within 6-36 month period, which represented the so called interval cancer (presumably missed cancers). The main result was that 23,6% of patients from the first group had the diverticulosis diagnosed earlier, while much more, 51,2% of patients of the second group (interval cancer group) – had the diverticular disease diagnosed earlier. Authors concluded that diverticulosis was strongly associated with interval colorectal cancer in all segments of the large bowel. Because interval colorectal cancer was present in all segments, this suggests that the explanation of this finding does not lay in impaired visualization of lesion during colonoscopy in patients with diverticulosis. In conclusion findings of this large study is a bit puzzling and requires further explanations.

Interestingly, some authors suggested protective role of diverticular disease in populations undergoing screening for colorectal cancer using FOBT- due to the fact that positive result is more frequently expected in those with diverticulas leading to colonoscopy. This special clinical situation and interesting hypothesis needs further exploration and validation.

SUMMARY

Diverticular disease, as most recent large population based studies suggest, does not increase the risk of colon cancer after the first year of diagnosis. Within the first year of diagnosis the association is strong, most probably due to difficulties with differential diagnosis and misclassifications and shared symptoms. All experts also agree that colon cancer has to be excluded using modern techniques after the first episode of suspected diverticulitis.

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EPIDEMIOLOGY OF DIVERTICULOSIS AND DIVERTICULAR DISEASE

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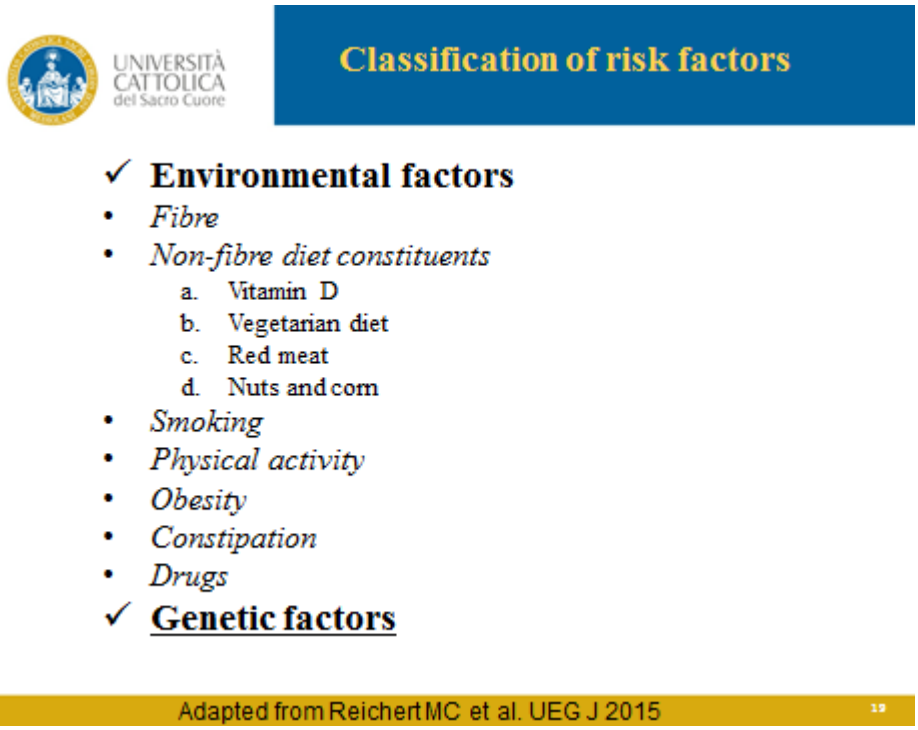
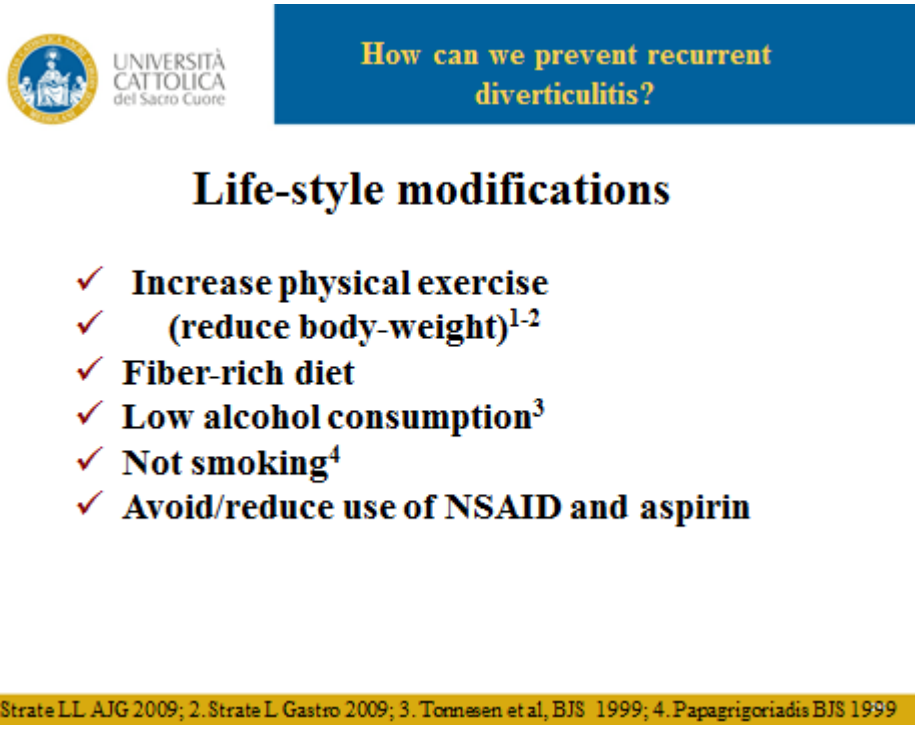
Diverticular disease (DD) and its complications represent a burden for the health systems all over the world. Recent data obtained from the 2010 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey (United States), report that diverticular disease is the 8th most frequent outpatient gastrointestinal diagnosis with 2,7 million of clinic visits (1). In addition, inpatients gastrointestinal, liver and pancreatic discharge diagnoses from 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 (1). 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 (1). Data obtained from the Scottish Morbidity Records confirm that DD is an increasing burden on health service resources, particularly in younger age groups (2). The study cohort included all patients with a hospital admission and a primary diagnosis of diverticular disease (DD). There were 90,990 admissions for DD from 2000 to 2010 with an average annual increase per year of 4.5% (2). Standardized mortality ratio (SMR) among patients having an operative primary management for DD was 4.95 in case of emergency admission route and 2.80 for patients with elective admission route in the group of age $\leq$ 55 years old (2). The worldwide prevalence of diverticulosis differs according to the different geographical areas. In particular, the prevalence was higher in Western Europe, North America, Japan and Australia and lower in Africa and Middle East, reflecting different dietary habits and life-style. The prevalence of asymptomatic diverticulosis increases with age. In a recent study from Taiwan, the prevalence of asymptomatic diverticulosis ranges from 4.7% in subjects with age less than 39 years old to 24.4% in subjects aged more than 70 years old (3). The prevalence rate of diverticulitis in patients with diverticulosis is not as high as it was believed in the past. Indeed, in a cohort of 433 patients with diverticulosis diagnosed with endoscopy (index colonoscopy between 1998 and 2000) and followed for a mean time of 14.1 years 30 cases of diverticulitis (7%) occurred (4). Of these, 19 were mild diverticulitis (medically treated) and 11 were severe diverticulitis (needing surgical intervention). The overall prevalence was of 4.8 cases of diverticulitis per 1000 patient-year (4). Another study performed in the Tokyo area included 1514 patients with endoscopy-confirmed asymptomatic diverticulosis (5). The study end-point was a bleeding event with a median follow-up time of 46 months (5). Bleeding events occurred in 35 patients with an overall incidence of 0.46 per 1000 patient-year; age $\geq$70 and bilateral diverticulosis were significant risk factors for bleeding (5).
In table 1 are reported the most important risk factors involved in the occurrence of diverticulosis and DD.



It should be emphasized that the contribution of genetic factors in the development of DD in twins ranges from 40 to 50% (6). In table 2 are reported some life-style modifications that could reduce the risk of diverticulitis in patients with diverticulosis.



Further studies are needed to better understand the natural history of diverticular disease and its complications and to better define the risk factors involved in the different stages of diverticular disease.

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MYTHS AND EVIDENCES IN DIVERTICULAR DISEASE

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Diverticular disease is a very common entity. At epidemiologic studies, it affects 50% of people at age 50 years, 60% at age 60 years, and almost 70% of people in theirs 70s and 80s. From this high frequency and prevalence and based on a neglected little understood disease, it raised a lot of myths between patients and doctors that managed colonic diverticular disease. Let's talk about some of the myths and some myth-busters that have been provided by the evidence from a series of studies that have come out recently.

Epidemiology

Myth

Diverticulosis Frequently Progresses to Diverticulitis

It is a very frequent concern in medicine practice. The literature says that 10%-25% of patients with diverticulosis will develop diverticulitis. A retrospective epidemiologic study using the Veterans Affairs of Greater Los Angeles database included more than 2200 patients and looked at a period of 11 years. The incidence of diverticulitis wasn't 10%-25% - it was 4.3%. In fact, when they used the diagnosis of established and provocatively ironclad diverticulitis (meaning surgery or CT-established diverticulitis), the incidence rate was even lower, at 1% over 11 years. This number is a lot lower than what we thought, at least according to this database, and whether that extrapolates to and is corroborated by other populations remain to be seen [(1)].

Pathophysiology

Myth

- Fiber Intake Prevents the Development of Diverticulosis
- Constipation Raises the Risk for Diverticulosis
- Nuts and Seeds Increase the Risk of Diverticulitis

On the basis of the pathophysiological considerations, could be argue that a diet rich in fiber and low in meat might prevent the formation of diverticula. In support, one study comparing non-vegetarians and long-term vegetarians (who consumed twice as much fiber) showed an almost three times higher rate of diverticulosis in non-vegetarians [(2)]. In other study that support this concept, immigrants from countries with a low prevalence of diverticular disease reach the same prevalence level as individuals in their new home country after adopting Western eating habits [(3)].

However, Peery *et al*.[(4)] failed to show a preventive effect of fiber intake on the development of diverticulosis but found that a high-fiber diet was associated with increased prevalence of asymptomatic diverticulosis. Furthermore, in patients with diverticulosis, we would think that patients who have less frequent stools would be at higher risk, but in fact, the risk for diverticulosis was reduced compared with the people who had stools daily or more frequently. They also looked at hard stools and straining to have a bowel movement. The odds ratios were 25% lower for diverticulosis in these individuals compared with those who reported having "normal" bowel consistency. Based on this study low fiber intake and constipation are not associated with a higher frequency of diverticulosis

We have data that dietary fiber is useful in the prevention of constipation, and this may be beneficial from a quality-of-life standpoint, but as it relates to the prevention of diverticulosis, we just don't have the evidence to support that. Also, two large prospective cohort studies have shown a protective effect of high fiber when symptomatic diverticular disease was used as an outcome measure. In the Health Professionals Follow-up Study (HPFS), men within the highest quintile of fiber intake had a 42% risk reduction for the development of symptomatic diverticular disease [(5)].

Similarly, the Oxford-based EPIC study of >47,000 participants (of whom 33% were vegetarians), yielded almost identical results with a 41% risk reduction in the group with the highest fiber intake[6].

Traditionally, patients have been advised to avoid foods that leave rough, undigested particles in the stool, such as nuts, corn or popcorn. In the HPFS study, consumption of nuts or corn was associated with a reduced risk of diverticulitis or diverticular bleeding. Those foods don't seem to make any difference in the development of diverticulosis or diverticulitis [7].

Management of diverticular disease

Myth

Diverticulitis Can Not Be Predicted.

There is evidence from a study of a cohort in Boston, in which vitamin D levels were assessed as a possible predictor of diverticulitis in patients with diverticulosis. Patients with low serum hydroxyvitamin D levels had a much higher likelihood of having diverticulitis or complications of diverticulitis. Vitamin D has a role in maintaining colonic homeostasis and mucosal integrity and in modulating inflammation in the gut. It makes sense that lower vitamin D levels might be associated with a lower incidence of diverticulitis. Check the patient's vitamin D levels and replace if necessary, may help for lots of reasons and has lots of good health implications .We don't have any longitudinal prevention data, but certainly the retrospective data are at least suggestive.

Fecal calprotectin (FC) may have a role in predicting recurrence of diverticulitis. A prospective cohort study was performed on 54 patients suffering from acute uncomplicated diverticulitis diagnosed by computerized tomography. After remission, patients underwent to clinical follow-up every 2 months. After remission and during the follow-up, FC was analyzed. The mean follow-up was 20 months (range 12-24 months). Forty-eight patients were available for the final evaluation, and six patients were lost to follow-up. During follow-up, increased FC was detected in 17 (35.4 %) patients and diverticulitis recurred in eight patients (16.7 %). Diverticulitis recurred in eight (16.7 %) patients: seven (87.5 %) patients showed increased FC during the follow-up, and only one (12.5 %) patient with recurrent diverticulitis did not show increased FC. Diverticulitis recurrence was strictly related to the presence of abnormal FC test during follow-up [9] .

A periodic analysis and control of FC levels may be an option for patients with diverticular disease. We recently evaluated the effects of mesalazine and/or probiotics in FC levels in patients with symptomatic uncomplicated diverticular disease (SUDD).[10] 163 patients with SUDD and > FC 150microg / gr were selected. Patients received mesalazine 800mg b.i.d. for 60 days and made new FC dosage. 115 patients (71%) presented FC <150microgr / g (normal range). 48 (29%) patients presented CF> 150 microgr / g and were divided into 3 groups: 1) MP group: 16 patients using mesalazine 800mg bid and a mix of probiotics (L. acidophilus, L. casei, L. lactis, B. lactis, B. bifidum) bid for 8 days; 2) Group P: 16 patients using mix of probiotics (L. acidophilus, L. casei, L. lactis, B. lactis, B. bifidum) b.i.d. for eight days; and 3) M3 group: 16 patients with mesalazine 800 mg tid for 8 days. There was a statistically significant decrease (51.8%) in FC levels after combined treatment (MP group), $p<0.002$. Statistically significant reduction was also seen in FC levels (42.2%) after treatment with higher doses of mesalamine (M3 group), $p<0.01$. No significant reduction in FC levels were seen in probiotic group (Group P).

Myth

Recurrent Diverticulitis Is Inevitable. The patient with diverticulosis and a history of diverticulitis, nothing can be done to prevent the recurrence of diverticulitis.

A recent published study[11] looked at 210 patients who had recurrent diverticulitis. They were randomly assigned to 1 of 4 groups:

- Placebo;
- Mesalamine 1.6 g/day;

• Lactobacillus DG 24 billion units daily; or
• Mesalamine 1.6 g/day and lactobacillus DG 24 billion units daily.

At 1 year, the recurrence rate was 46% in the placebo group (unusually high), approximately 14% in each of the mesalamine and lactobacillus DG groups, and 0% in the combination group. We know from other trials that 5-aminosalicylic acid (5-ASA) drugs may have a preventive benefit, but now it seems to be apparent that the combination with a probiotic could be better. We know that recurrent diverticulitis is associated with exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), so avoidance of NSAIDs and the use of a 5-ASA drug combined with a probiotic may make some sense in patients with relapsing disease.

Treatment

Myth

In Diverticulitis Recurrence Surgery is Indicated

Diverticulitis Must be Treated with Antibiotics

Until a decade ago, two episodes of recurrence—especially in combination with elevated markers of inflammation indicative of type 3b diverticular disease—prompted the recommendation of elective sigmoid resection[12] to prevent severe complications. Studies from the past decade have suggested that the risk of severe complicated disease is highest during the first attack of acute diverticulitis and decreases with subsequent bouts [13,14] Moreover, a considerable proportion of patients (6–30%) report persistence of symptoms after elective sigmoid resection [15,16,17,18,19,20,21]. The general recommendation of elective sigmoid resection after two attacks of diverticulitis has, therefore, been abandoned in favour of a more individual approach based on the patient's risk level and medical conditions.

There are several recent studies that have prompted a re-evaluation of using antibiotics for acute diverticulitis. There were two prospective trials to support this paradigm shift [22,23].

One recently published trial included approximately 670 patients from Sweden and Iceland who were allocated on an inpatient basis to receive 7 days of antibiotics or intravenous fluids only. The trial found no significant difference in the time to resolution of symptoms, complications, duration of hospital stay, or the risk for recurrence.

A second trial included approximately 530 patients from The Netherlands who had a first occurrence of imaging-confirmed acute uncomplicated diverticulitis.[10] Patients, now inpatients, were allocated to receive either 10 days of antibiotics or observation. Similarly, this trial found no significant difference in time to resolution of symptoms, complications, duration of hospital stay, or risk for recurrence.

There are four countries in Europe (Dutch, Danish, German, and Italian society consensus reports) that have already changed their national guideline recommendations regarding the use of antibiotics. Now say that antibiotics can be omitted in patients without risk factors who have uncomplicated disease, but these patients should be monitored closely.

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PROGNOSTIC ROLE OF THE ENDOSCOPIC CLASSIFICATION "DICA"

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Introduction

Diverticulosis of the colon is the most frequent structural alteration of the colon diagnosed at colonoscopy (1). However, an endoscopic classification of diverticulosis and DD was absent until now. This is surprising if we consider the high number of colonoscopies performed worldwide, that diverticulosis is the most frequently recognized alteration at colonoscopy (1), and that endoscopic signs of diverticular inflammation are found in 0.48-1.7% of patients undergoing colonoscopy (2,3). Furthermore, some characteristic of the colon harbouring diverticula has been already identified as predictor of the outcome of the disease. In example, radiology found diverticulosis extension as one of the strongest predictors of recurrence of diverticulitis (4). However, it is poorly known whether specific endoscopic findings are able to influence the outcome of DD, and patients may differ from each other. For example, having scattered sigmoid diverticula may be different from having diffuse diverticulosis and rigidity of the colon at inflation, but whether this difference has a prognostic significance, is poorly known.

The first endoscopic classification for diverticular disease: the DICA classification

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 (5), consisting of 4 endoscopic items (figure 1):

a. 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.

b. Number of diverticula (in each district): up to 15 (grade I), more than 15 (grade II).

c. Presence of inflammation: Edema/Hyperemia; Erosions; Segmental Colitis Associated with Diverticulosis. When different degrees of inflammation were detected, the most severe grade of inflammation had to be reported.

d. Complications:

- Rigidity of the colon: poor distension of the diverticular district to inflation, also including a mild stenosis allowing a standard colonoscope to pass through the narrowed lumen;
- Stenosis: a stenosis not allowing a standard colonoscope to pass or narrowed lumen with elevated risk of perforation due to presence of some anatomical characteristics (e.g. a several diverticula at the splenic flexure);
- Pus: purulent material passing from the diverticular opening.
- Bleeding.

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

Predictive value of the DICA endoscopic classification: results from an international study

This was a multicenter, international retrospective cohort study. In order to have results coming from real life, patients with DD were identified from tertiary, secondary and primary clinical centers. Twenty-one centers were from Italy, 2 from Brazil, 1 from Venezuela and 1 from Norway. From December 31, 2014, patients with endoscopic diagnosis of DD were selected if they met the following criteria: (1) cases were at the first endoscopic diagnosis of diverticulosis/diverticular disease; 2) properly recorded on electronic database; (2) complete clinical and endoscopic data available. If clinical follow-up data were incomplete, they could be completed by telephone interview.

The following information was recorded from each patient: age at the time of diagnosis of DD, DICA score at diagnosis, presence of abdominal pain, months of follow-up, C-reactive protein >5mg/L and fecal calprotectin test positivity at diagnosis (if available), therapy (if any) during follow-up to maintain remission, time to occurrence/recurrence of diverticulitis; need for colonic surgery.

The study enrolled 1651 patient. According to DICA score, patients were distributed as follows: 939 (56.9%) patients in DICA 1, 501 (30.3%) patients in DICA 2 and 211 (12.8) patients in DICA 3. However, in the subgroup of 68 coming from Brazil and Venezuela 52 (76.5%) patients were DICA 1, 13 (19.1%) were DICA 2 and 3 (4.4%) were DICA 3. A significant difference was present in this subgroup compared with the entire study group (p=0.005).

Mean age did not differ between the three groups, while males were significantly lesser in DICA 3 (p=0.003). Either presence of abdominal pain, C-reactive protein positivity and fecal calprotectin positivity were significantly related to the DICA score. In particular, abdominal pain ranged from less than 40% of DICA 1 to more than 85% of DICA 3, CRP positivity ranged from about 18% of DICA 1 to about 90% of DICA 3, fecal calprotectin positivity ranged from less than 49% of DICA 1 to more than 93% of DICA 3 ($p<0.0001$ for each parameter).

Primary endpoints

The median (interquartile range) follow-up was 24 (9-138) months. Acute diverticulitis (AD) occurred/recurred in 263 (15.9%) patients. At each level of DICA classification a significant increase of AD occurrence/recurrence was detected. In particular, AD occurred in 34 (3.8%) patients in DICA 1, and recurred in 110 (21.9%) patients in DICA 2, and in 119 (56.4%) patients in DICA 3. Acute complicated diverticulitis occurred in 23 (1.4%) patients, and was significantly more frequent in DICA 3: it occurred in one DICA 1 patient group, in 7 DICA 2 patients group, and in 15 DICA 3 patients group (p=0.038).

Surgery was necessary in 57 (3.5%) of those cases. At each level of DICA classification a significant increase of surgery were detected. In particular, it was necessary in 3 (0.3%) patients in DICA 1, in 21 (4.2%) patients in DICA 2, and in 33 (15.6%) patients in DICA 3. The reason for surgery differ but not significantly between the 3 groups. In particular, urgent surgery occurred in 32 (1.9%) of cases, and it was necessary in 1 (33.3%) patient in DICA 1, in 11 (52.4%) patients in DICA 2, and in 20 (60.6%) patients in DICA 3 (p=0.333).

DICA was the only factor significantly associated to the occurrence/recurrence of AD and surgery either at univariate or multivariate analysis.

Secondary endopoint

Therapy with various regimens was taken by 883 (53.5%) patients during the follow-up. In particular rifaximin based therapy was taken by 337 (38.1%) subjects, mesalazine based therapy by 298 (33.7%), rifaximin combined with mesalazine by 111 (12.6%) and other therapies by 137 (15.5%). Being on therapy was effective to prevent occurrence/recurrence of AD in DICA 2 ones with a HR (95% CI) of 0.598 (0.391 to 0.914) (p=0.006, log rank test). No significant effect was

detected either in DICA 1 patients (p=0.109, log rank test) or in DICA 3 ones (p=0.437, log rank test). Therapeutic regimens including mesalazine were the only effective therapies to reduce diverticulitis occurrence/recurrence compared to no therapy.

How endoscopic classification DICA impacts on our clinical practice

Since diverticulosis is the most common finding at colonoscopy (1), and since endoscopic signs of inflammation may be frequently detected in those patients (2,3), 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 fulfil the following end-points: to use a common language in describing the colon harbouring diverticula and to identify endoscopic findings predictive of disease outcome. While the first end-point has been already reached (5), the second end-point has been reached in this study.

The first finding of this large, retrospective, multicentre, international study is that clinical characteristics of the people harbouring diverticula are linked to DICA score. In particular, we found that severity of abdominal pain, CRP and fecal calprotectin expression were significantly expressed according to DICA score. Moreover, we found that DICA classification is the only predictor for occurrence/recurrence of AD. Thus, patients with simple diverticulosis, and without signs of active or past inflammation, namely DICA 1 patients, are at lower risk of developing inflammatory complications, while patients having diverticulosis with signs of active or past inflammation, namely DICA 3, are at higher risk. The same seems to occur when we consider surgery for those patients: DICA 1 patients are at lower, while DICA 3 ones are at higher risk of surgery.

The second finding of this study is that we identified for the first time a specific subgroup of patients having diverticulosis, who require scheduled treatment in order to prevent occurrence/recurrence of complications. Outcomes were not influenced by scheduled treatment in DICA 1 and 3 patients. Hence, to advice or not scheduled therapy in those patients does not influence the risk to develop occurrence/recurrence of AD or need of surgery: DICA 1 patients persist being at lower, while DICA 3 patient persist being at higher risk. On the contrary, DICA 2 is the only subgroup in which treatment influences the outcome of the disease. These patients showed lower occurrence/recurrence of AD or need of surgery under scheduled treatment than patients under simple clinical observation without therapy.

The third finding of this study is that mesalazine-based therapies were identified as the best treatments to reach these outcomes. The beneficial effect of mesalazine occurs in those patients with signs of mild inflammation (i.e., edema or hyperemia), that can be easily managed with an anti-inflammatory drug (6-8). It is hypothesized that those patients are on DICA 2 score. On the contrary, mesalazine is completely ineffective in patients with recurrent attack of acute uncomplicated diverticulitis, patients that are more likely to be on DICA 3 score. We can speculate on this different mesalazine behaviour in these subgroups. In DICA 2, inflammation may be confined in colonic mucosa, where mesalazine is able to work (9). On the contrary, in DICA 3 we have finding of past (rigidity/stenosis) or active (pus) inflammation involving the entire colonic wall, where mesalazine, a drug working only in the mucosa, is probably no more effective (9).

Of course, the retrospective design of this study has some limitations on the interpretation of these finding. Results of the prospective study currently are therefore particularly welcomed to confirm these results.

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Items	Points
Diverticulosis extension	
Left colon	2
Right colon	1
Number of diverticula (in each district)	
Up to 15: grade I	0
>15: grade II	1
Presence of inflammatory signs	
Edema/hyperemia	1
Erosions	2
SCAD	3
Presence of complications	
Rigidity of the colon	4
Stenosis	4
Pus	4
Bleeding	4

DICA classification	Numerical value
DICA 1	From 1 to 3 points
DICA 2	From 4 to 7 points
DICA 3	>7 points

SCAD, segmental colitis associated with diverticulosis

Figure 1. Diverticular Inflammation and Complication Assessment (DICA) Classification.

ANTIBIOTICS

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Introduction:

Diverticular disease of the colon 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. It is uncommon in subjects under 40 years of age increase up to 65% in those aged 65 years or more whereas 80% of patients who present with diverticulitis are 50 or older. Diverticula can present in number from solitary to hundreds, they are typically 5-10 mm in diameter. Diverticulosis occurs primarily in the sigmoid and descending colon in more than 90% of patients, but may be prevalent in varying degrees in the rest of the colon [1]. Eighty percent of patients with diverticular disease will remain asymptomatic for their lifespam, but 15-20% will develop symptoms, and approximately 1/4 of them will eventually have an episode of symptomatic painful diverticular disease without inflammation; up to 10-25% if patients with diverticula will have an episode of acute diverticulitis, 1-2% will require hospitalization and 0.5% will require surgery. Diverticula are also responsible for the majority of episodes of lower gastrointestinal bleeding [2].

In this summary the presence of diverticula in the colon in the absence of overt inflammation will be called diverticulosis or uncomplicated diverticular disease (UDD). It may be symptomatic or asymptomatic. The term –acute colonic diverticulitis" (ACD) is used to describe inflammation of the diverticula, wich may or may not progress to complications (complicated ACD). There is also chronic diverticulitis, because of recurrent diverticulitis or because of the development of a segmental colitis associated with the diverticula [3]. Figure 1. Summary, the clinical spectrum of diverticular disease is wide.

Management of uncomplicated diverticular disease (UDD)

In patients with **asymptomatic UDD** [2] , a high fiber diet may be recommended because its possible prophylactic benefit in preventing symptomatic UDD and complications. There is no evidence that other drugs are useful in these patients. The rationale for the use of antibiotics in **symptomatic UDD** is not clearly established. Recent studies suggest that changes in gut microbiota (intestinal bacterial overgrowth) could contribute to symptoms development due to excessive production of bowel gas through carbohydrate fermentation. In order to avoid systematic effects, poorly absorbed antimicrobials act against enteric pathogens but have minimal risk of systematic toxicity or side effects. Rifaximin may decrease metabolic activity of bowel flora, increasing fecal mass, and may also eradicate bacterial overgrowth. Three open and two double blind RCT [4-8] have examined the effectiveness of cyclic administration of rifaximn and fiber in reducing symptoms compared with fiber alone. A systematic review and two meta-analysis have analyzed theses trials [9-10]. They concluded that combined treatment is effective in obtaining symptom relief at 1 year in patients with UDD; 35% of patients treated with fiber alone were asymptomatic compared with 64% in group of combined treatment. The number needed to treat was three for rifaximin vs placebo to relieve symptom and nine to avoid complications. Summary, the best results

have been obtained using a combination of soluble fiber, such as glucomannan, and rifaximin 1 week every month.

Treatment of acute colonic diverticulitis (ACD)

In patients with mild symptoms and without signs of complicated ACD, the combination of pain in lower left abdomen, the absence of vomiting and a C reative protein > 50mg/l, may be sufficient for the diagnosis. If imaging is indicated, a conditional strategy with ultrasound as first line technique and followed by computerized tomography (CT), if ultrasound is inconclusive may represent the most effective approach. Hinchey et al. proposed a classification of ACD, which distinguishes five stages; stage 0: clinically mild diverticulitis, stage Ia: pericolic inflammation; Ib: abscess < 5 cm in the proximity of the primary inflammation, stage II: intra-abdominal, pelvic or retroperitoneal abscess or abscess distant from the primary inflammation; stage III: generalized purulent peritonitis and stage IV: fecal peritonitis.

HINCHEY stage 0 or Ia: The majority of uncomplicated ACD with this Hinchey stage can be safely treated conservatively with success rate between 70-100% [11]. In cases of uncomplicated ACD, criteria for inpatient management are significant inflammation (include presence of fever or peritonitis), intolerance to oral fluids, age over 80-85 years, immune-suppression, or severe comorbidities. In most cases, a short hospital stay will be sufficient. There is not evidence that dietary restrictions influenced treatment outcomes, although most physicians usually recommend clear liquid diet. A recent Cochrane review found that the best available data do no support the routine use of antibiotics [12]. Antibiotics neither accelerate recovery nor prevent complications or recurrence. Therefore, the use of antibiotics in this case is questionable. Probably, they would be appropriate in selected patients (generalized infection and in immunocompromised patients). Various antibiotics may be used, ranging from ampicillin to third generation cephalosporins, as long as it is effective against gram positive, gram negative and anaerobic bacteria. **The combination of ciprofloxacin and metronidazole is probably the most prescribed oral treatment**. Recent data have shown that there are no advantages of intravenous over oral antibiotics and of intravenous 4 days treatment over 7 days treatment [13-15] .Usually, clinical improvement is observed within 3-4 days of treatment.

ACD HINCHEY Ib or II with Abscess: Approximately 15% of patients with ACD will develop an abscess. Hospitalization is indicated. Small abscesses (< 4 cm), need conservative treatment with broad spectrum antibiotics, which is successful in up to 70% [16]. When conservative treatment fails or in larger abscesses, percutaneous drainage should be performed, which is successful in up to 80%. Surgery will be a rescue treatment when previously mentioned treatments fail.

ACD HINCHEY III or IV and purulent or faecal peritonitis: Peritonitis is the most serious complication, with a mortality of 14%. Although there is no evidence, early surgery is considered standard therapy for these patients. In critical ill patients with hemodynamic instability, Hartmann´s procedure is recommended. However, in hemodynamically stable patients, primary anastomosis with or without proximal faecal diversion has to be considered a preferable choice.

Prevention of recurrent ACD

The evidence to define the optimal treatment following an ACD episode in order to prevent a new episode is scarce. There are three recent systematic reviews that assessed the role of cyclic rifaximin in preventing recurrence of ACD, but did not show a clear benefit [10, 17,18]. From a pathophysiologic point of view, a plausible explanation of ineffectiveness of rifaximin in preventing

recurrences could be that a cyclic treatment may not control the colonic bacterial population during full month, because colonic bacterial population recovers within 7-14 days after the end of rifaximin. However, a recent Spanish open RCT has shown that cyclic rifaximin can improve symptoms and maintain periods of remission following ACD [19]. Recurrences occurred in 10, 4% of patients given rifaximin plus fiber vs 19, 3% of fiber alone. Moreover, patients first diagnosed since ≥ 1 year had a higher risk of exacerbation (OR 3, 34, 95% CI: 0.01-12.18). But, further studies are needed since- at present time- no recommendations can be made. There is not evidence to support the use of other antibiotics in this setting.

Summary

In symptomatic UDD, the aims of treatment are to prevent complications and reduce symptoms. According to current evidence, fiber plus cyclic seems to be an effective therapy. In the ACD, antibiotics seem to remain the mainstay of treatment and an outpatient management is considered the optimal approach in the vast majority of patients with uncomplicated ACD. However, inpatient management and intravenous antibiotics are necessary in complicated ACD. Currently, the role of emergency surgery is changing. Most diverticulitis-associated abscesses can be treated with intravenous antibiotics and/or percutaneous drainage and emergency surgery will be considered standard treatment only in patients with peritonitis. Finally, elective surgery after recovery from ACD should be made on a case-by-case basis

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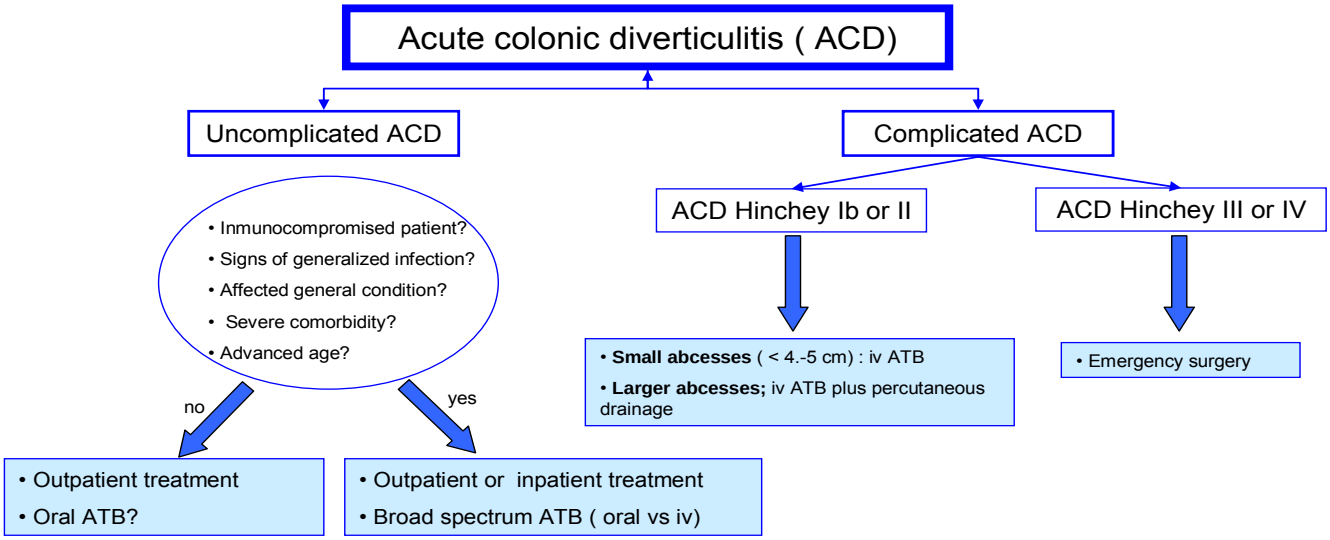
Figure 1: Algorithm for management of acute colonic diverticulitis. Taken from reference 1. Figure 4:



Nota: ATB: Antibiotics, iv; intravenous

AMINOSALICYLATES

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Colonic diverticulosis is common in Western industrialized countries, increases with age and occurs in up to 65% of people over the age of 60 years. Although in most cases colonic diverticula do not generate troubles during lifetime, 10-25% of subjects, develop symptoms, such as abdominal pain and changes in bowel habit, a condition termed symptomatic uncomplicated diverticular disease (SUDD). Diverticulitis is the most common complication, affecting 10-25% of patients, of which 15% develop further complications including bleeding, abscesses, fistulae, stenosis or peritonitis. The related morbidity and mortality, the use of imaging techniques, the requirement of expensive medical and surgical treatments account for a substantial social and economic burden.[1, 2]
Little is known about the natural history of diverticular disease. However, one study suggests that the risk of recurrent attacks of diverticulitis after a first episode is estimated between 7% and 45%.[3] Although prophylactic surgery has been recommended after 2 attacks of diverticulitis, this view has changed in recent years and has given more space to the conservative approach.[4] This has created a large population of post-diverticulitis patients at potential risk for subsequent attacks, raising the important clinical question as to whether any medical therapy can alter their natural history.
Although no disease modifying therapies are as yet approved to manage SUUD symptoms or prevent acute diverticulitis several dietary and pharmacological approaches have been proposed although their efficacy has not always been tested in controlled trials. These approaches include, among others, a high fiber diet, avoidance of seeds and popcorn, the use of anti-spasmodics, for the management of pain, non-absorbable antibiotics and probiotics based on the dogma that bacterial overgrowth in the diverticulum is the initiatior of a pathogenetic cascade of events eventually culminating in diverticulitis and complications. The rational for the use of aminosalicylates, such as mesalazine or balsazide, is based on the evidence that inflammation may underlie symptoms and diverticulitis in patients with diverticular disease.[5, 6]

AMYNOSALICYLATES

5-Aminosalicylic acid (mesalazine) is an anti-inflammatory agent widely used in the treatment of ulcerative colitis. After oral or rectal administration, mesalazine, is absorbed by colonic epithelial cells and its efficacy is related to its mucosal concentration.[7] The anti-inflammatory mechanism of mesalazine is not completely understood, but believed to be dependent on: 1) reduction in the synthesis of prostaglandins and pro-inflammatory cytokines, including interleukin-1 and tumor necrosis factor-alpha; 2) inhibition of the chemiotaxis of neurophils; 3) inhibition of the activation of nuclear factor Kappa-B transcription factor family; 4) the activation of nuclear receptors (i.e. the gamma form of peroxisome proliferator-activated receptors), which downregulate inflammation and reduce inflammatory cytokine release; 5) promotion of mucosal barrier effect; 6) change in colonic luminal pH which would favor the growth of beneficial bacteria such as *Bifidobacteria* and Lactobacilli; 6) antibacterial activity with inhibition of expression of bacterial genes involved in invasiveness, epithelial adherence proliferation, antibiotic resistance.[7-10] Some of these effects need to be confirmed in further studies.

MESALAZINE IN DIVERTICULAR DISEASE

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. There are some limitations related to the currently available Literature. These drawbacks are related to the heterogeneity of study design, the frequently use of an open

label design, the use of combinations of therapies in the same trial, the sometimes small sample size and insufficient details in the reported data. These limitations reduce the overall quality of the results and the level of recommendation in clinical practice.[11] Given these limitations, the conclusion of a systematic review of the Literature was that medical treatment showed some evidence of improvement in symptoms in patients with SUDD, but its role in the prevention of acute diverticulitis remains to be defined.[11] Two recent large controlled studies on the efficacy of mesalazine have been published and helped only in part the numerous questions that the clinician faces when approaching the patient with diverticular disease. The first study addressed the effect of mesalazine in the control of symptoms in patients with SUDD[12] and the second evaluated the therapeutic role of mesalazine in the prevention of recurrent diverticulitis and will be briefly mentioned below.[13]

Symptomatic uncomplicated diverticular disease.

The effect of mesalazine in SUUD has been investigated in numerous open label studies as well as in three double-blind, placebo-controlled studies. One of these controlled studies showed that lower abdominal pain was significantly ameliorated in patients treated with mesalazine over patients treated with placebo. However, a statistical significance was reached only in the per-protocol analysis (P=0.05) but not in the intention to treat evaluation (P=0.374).[14] Several factors contributed to this inconsistency, including an unbalanced distribution of patients, particularly for the use of medications in the placebo and active drug arms. Interestingly, in ad hoc analyses, the authors found that the presence of diverticula in the descending colon represented a confounding factor, indeed after normalization of this and other factors the statistical analysis almost reached significance. Another confounder may be represented by the heterogeneity of the population under study and in particular the possible inclusion of patients with irritable bowel syndrome. Unfortunately, all these studies did not include patients according to the presence of low-grade intestinal inflammation that have been indicated to underlie symptom development in at least subgroups of patients with SUDD.[5, 15, 16]

Another multicenter double-blind, placebo-controlled study assessed the efficacy of pulse treatment with mesalazine with or without probiotics (10 days per month for 12 months) on the recurrence of abdominal pain in SUUD patients. The results showed that the combination of mesalazine with *Lactobacillus casei* was superior to placebo in the maintenance of remission in SUDD. While these studies are promising, there is a need for very large studies powered enough to identify predictors of response and biomarkers useful to identify patients who merit one over another type of treatment. In the recent mesalazine trial in patients with irritable bowel syndrome there was clearly a subgroup of patients that showed a sustained marked response to mesalazine, further suggesting the need to identify the phenotype and predictors of the responders[17].

Prevention of diverticulitis.

A double-blind placebo controlled study assessed the prevention of acute diverticulitis in patients receiving mesalazine (1.6 g/day for 10 days/month), a probiotic (L. casei subgroup DG, 24 billion/day for 10 days/month), mesalazine plus probiotic or placebo. The results showed that mesalazine was better than placebo in preventing acute diverticulitis.[6] In line with these results Gaman et al., randomized patients to receive either mesalazine (n=68) or placebo (n=52). Patients on mesalazine were significantly less likely to experience a flare over a mean follow-up of 40.5 months.[18] These studies are highly demanding as diverticulitis is a relatively uncommon complication and long follow-up studies are needed to detect recurrences. However, in contrast with these promising data are the results on the efficacy and safety of multimatrix mesalazine vs placebo in the prevention of recurrent diverticulitis. This outcome was assessed in two large identically designed studies: PREVENT1 conducted in 590 patients and PREVENT2 in 592 patients. Adult patients with ≥ 1 episodes of acute diverticulitis in the previous 24 months that resolved without surgery were randomized to receive mesalazine 1.2 g, 2.4 g, or 4.8 g or placebo, once daily for two

years. The results showed that mesalazine did not reduce the rate of recurrence or time to recurrence. The authors concluded that mesalazine is not recommended for this indication.

Conclusions

In conclusion, evidence suggests some efficacy of mesalazine in the control of symptoms in patients with uncomplicated disease. The largest study so far published on the efficacy of mesalazine in the prevention of diverticulitis showed that mesalazine was not superior than placebo. However, some argue that this is not the last word as many issues remain open and unresolved.

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PROBIOTICS

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In an era when inflammatory bowel disease (IBD) represents a fertile ground for research, enjoying the fruits of innovative therapeutic approaches, and irritable bowel sindrome (IBS) witnesses increasing interest by both basic scientists and clinicians, colonic diverticela and their complications remain relatively forgotten. Diverticulosis however is common and, as our populations age, its prevalence is steadily increasing [1].
Despite the pathogenesis of chronic symptoms in the aftermath of acute diverticulitis as well as the link between uncomplicated diverticulosis and symptoms (leading to the so-called symptomatic uncomplicated diverticular disease, SUDD) are complex and still not fully understood [2], low-grade inflammation appears to be pivotal in the pathophysiology of symptoms in both clinical settings [3]. This intriguing hypothesis must be viewed in the context of bacteria-induced immune activation and consequent inflammation. Indeed, while changes in the colonic microbiota are clearly critical to the pathogenesis of diverticular complications, such as diverticulitis and peri-diverticular abscesses, more subtle changes in microbiota composition may well be important to the more chronic manifestations of diverticulosis [4].
Alteration in bacterial flora in diverticular disease occurs primarily as a result of fecal stasis, which Is a result of slow colonic transit and stagnation of fecal material in the diverticula themselves. The ~~–b~~lind-pouch" theory, which implicates fecal stasis and bacterial overgrowth in the pathogenesis of clinical conditions such as appendicitis and pouchitis, has been similarly used to explain the development of diverticular inflammation [5]. Altered bacterial flora in these regions trigger intestinal inflammation by impairing mucosal barrier function and up-regulating inflammatory cytokine release [4].
However, only few studies have focused on the microbiological characterization of the microbiota in diverticular disease. Some studies have shown the presence of bacterial overgrowth in subgroups of patients with diverticular disease [6,7]. However, traditional methods of investigation are nowadays inadequate, since a large portion of the resident bacterial flora is not cultivable and few data are available to date. The most commonly isolated organisms are anaerobes (Bacteroides, Peptostreptococcus, Clostridium, and Fusobacterium), while the most often cultivated ones are Gram-negatives, particularly Escherichia coli, and facultative Gram-positives, such as Streptococci. The recent development of culture-independent approaches, such as metagenomics, is greatly contributing to the understanding of gut microbiota composition. Gueimonde *et al.* [8] collected and analysed 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 found in significantly higher proportions 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 SUDD compared with healthy controls, with most represented species being *Collinsella Aerofacien* [9]. Despite these interesting observations, there is no definite evidence allowing correlating diverticular disease and its complications to a *specific* bacterial strain.
While both systemic and poorly absorbed antibiotics are often prescribed to patients with colonic diverticular disease [5,10], relatively few studies have attempted the manipulation of gut microbiota as a therapeutic target. Compared with antimicrobial therapy, less invasive and more physiologic approaches to modulate intestinal microecology are represented by probiotics, prebiotics and symbiotics.

According to the original FAO/WHO definition [11], probiotics are ~~"li~~ve microorganisms, which – when administered in adequate amounts – confer a health benefit on the host". The rationale for the use of probiotics for the treatment of gut microbiota-related diseases is the restoration of intestinal homeostasis by beneficial microbes. Most probiotics consist of Lactobacilli and Bifidobacteria, but also yeasts such as *Saccharomyces boulardii* have been used with good clinical outcomes. Probiotics have the ability to restore balance to enteric flora, primarily by decreasing numbers of pathogenic gram-negative bacteria [12]. By competitively inhibiting pathogenic bacterial overgrowth at the mucosal level, probiotics improve mucosal defense by enhancing tight junction integrity [13] decreasing bacterial translocation, and down-regulating pro-inflammatory cytokines such as tumor necrosis factor (TNF) [14].

A significant proportion of patients with DD complain of symptoms resembling or overlapping those of IBS, making a clear differentiation between these two clinical conditions challenging [15-17]. Despite the considerable debate regarding whether trials of different probiotics should be pooled into a meta-analysis [18], several systematic reviews and meta-analyses [19-24] have consistently shown the efficacy of (single or multi-strain) probiotic treatment on IBS symptom cluster. Some early [25, 26] and one, very recent and comprehensive [27], systematic reviews have also tried to summarize the available literature concerning the use of probiotics, alone or as *add-on* medication, for the treatment of SUDD.

Although several investigations evaluating the clinical efficacy of probiotics have been performed, no definitive results have yet been achieved, mainly due to the heterogeneity of the available studies. Most of the studies have used probiotics in combination with poorly absorbed antimicrobials (dichlorchinolinol or rifaximin) or anti-inflammatory drugs (mesalazine or balsalazide). In only three studies [28-30] there was a arm using probiotics alone (namely *Lactobacillus casei* DG), but only one was a placebo-controlled, double blind trial [30]. Additional two studies [31,32] employed probiotics (*Lactobacillus paracasei* F19 and *Lactobacillus paracasei* B21060) in addition to high-fiber diet while one [33] investigated the efficacy of a probiotic mixture (*Lactobacillus acidophilus* 145, *Lactobacillus helveticus* ATC 15009, *Bifidobacterium* spp. 420 in a phytoextracts-enriched medium). This last investigation 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. Indeed genomic analysis confirmed the significant survivability of ingested *L.acidophilus* and *Bifidobacterium* contained in the symbiotic mixture [33].

The analysis of the available evidence reveals however a poor quality of the published studies, whose design was heterogeneous, with only 2 out of 11 trials being double-blind and randomized. While some studies investigated the symptom improvement, other evaluated the maintenance of remission from abdominal symptoms. In addition, the trial sample size was generally small and the follow-up never exceeded 12 months. The inclusion criteria were variable so that the patient populations recruited in the different studies were different as it was the specific probiotic (single or multi-strain) employed. All these variables make comparison of the results from different studies difficult and prevent any precise estimate of the treatment effect. In the absence of a quantitative estimation, the qualitative analysis of the available data can only suggest a benefit of probiotics in SUDD, but does not allow any evidence-based definite conclusion [27]. As a consequence, the recent Italian Consensus Conference on Diverticular Disease [34] concluded – with the agreement of 84% of the experts – that there is insufficient evidence that probiotics are effective in reducing symptoms of patients with diverticular disease, a statement reiterated by the guidelines of the Italian Society of Colon and Rectal Surgery [35].

Recent pharmacological approaches targeting enteric bacteria (with poorly absorbed antibiotics, like rifaximin, or probiotics) and/or intestinal inflammation (with 5-ASA derivatives) have shown to be capable of controlling symptoms and preventing complications. However, the respective role of these drugs (alone, in combination or sequentially) in the management of symptomatic diverticular disease needs to better defined. Well-designed RCTs, including homogeneous populations of

patients (classified according to the recent DICA criteria [36]), are therefore needed to establish the optimal regimen (daily dose and duration)
of therapy.

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OPEN OR LAPAROSCOPIC TREATMENT: DIFFERENCES AND OUTCOMES

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In the early 20th century, surgical treatment of diverticular disease was made by three stage laparotomy in more than 50% of emergency cases (1). Mortality rate for three-stage resection was around 6% while resection had 17% of mortality (2, 3). Three-stage surgery was indicated only to complications for diverticular disease: perforation with abscess or peritonitis, obstruction, hemorrhage and fistula. The idea of safety for the three-stage resection lasted for many decades (4).
Two facts pushed surgeons on to look for new strategies to treat diverticular disease: the prolonged morbidity of three-stage resection and the high rate of emergency surgery in symptomatic patients (5). Rodkey & Welch (1984) reported the increase use and safety of one-stage resection but not for peritonitis (Table 1).
Surgical treatment evolved and changed mainly in the past two decades. Three-stage was followed by two-stage and one-stage procedures with development of antibiotics, intensive care support, parenteral nutritional supplementation and improved image diagnostic.
Laparoscopy colectomy appeared in the 1990s a few years after the first laparoscopy procedure (6). The laparoscopic colon surgery improved dramatically in the last decade from laparoscopic-assisted colectomy to one port laparoscopic surgery. Laparoscopy gained more acceptance among colorectal surgeons nowadays and represent the first option to elective colonic surgery. Open surgery and hand assisted laparoscopic still remain indicated in more complexes cases (7).
Advantages of laparoscopy include faster recovery, shorter hospital stay, decreased postoperative pain, earlier return to work and resumption of normal daily activity besides cosmetic benefits. Laparoscopy is commonly used for elective surgery, but for emergency surgery is still considered too challenging and is not usually recommended.
Some authors reported superiority of laparoscopic sigmoidectomy compared to open sigmoidectomy for perforated diverticulitis with regard to postoperative morbidity and hospital stay (Table 2) (8, 9). But the superiority of peritoneal laparoscopic lavage compared to open surgery still remain controversial (10, 11). Kaushik et al. (2016) (11) reviewing literature conclude that colon resection with primary anastomosis with purulent peritonitis is acceptable and peritoneal lavage may play a role in peritonitis without perforation. Schultz et al. (2016) (10) did not find advantages in the use of laparoscopic lavage vs primary resection and also laparoscopic lavage showed worse outcomes in secondary end points.
Venix et al (2015) (9) reported that laparoscopic sigmoidectomy showed less postoperative morbidity and hospital stay compared to open sigmoidectomy. Angenete et al. (2016) (12) in a randomized controlled multicenter trial, demonstrated the feasibility and safety of laparoscopic lavage as treatment for patients with perforated diverticulitis Hinchey III in the short-term (Table 3). They reported a mortality rate of 7.7% for laparoscopic lavage and 11.4% for open Hartmann‘ s procedure. Single port laparoscopic surgery for diverticulitis has been used but some times a small incision like a Pfannenstiel may facilitate the approach to the pelvis with the same outcomes (13).
Surgical approach to diverticulitis Hinchey III or IV may be done initially by laparoscopy with all benefits of laparoscopic surgery. Laparoscopy may be used only in hemodynamically stable septic peritonitis. Many studies have demonstrated that is feasible and safe. Conversions may be necessary and are related to the inflammatory process with a severe adhesion syndrome. Visible perforations in open surgery may be related to the handling of the inflamed colon rather than a more advanced disease.

Advantages of laparoscopy include faster recovery, shorter hospital stay, decreased postoperative pain, earlier return to work and resumption of normal daily activity as well as cosmetic benefits. All these factors may have done general population to accept more easily minimally invasive surgical treatment to diverticulitis. But this growing rate of elective colectomy was not followed by a decrease in emergency surgery for diverticulitis (Figure 1) (14).
Laparoscopy seems to offer a less invasive alternative that is peritoneal lavage without resection to Hinchey III cases. Efforts of many investigators trying to avoid colon resection and stoma creation in patients with peritonitis need to be confirmed by long-term randomized trials.

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Table 1 - Comparison of one-stage resections and anastomoses in a single institution in two decades (1)

	1964–1973			1974–1983		
	Total Cases	One-stage Cases	Resection and Anastomosis (%)	Total Cases	One-stage Cases	Resection and Anastomosis (%)
Pericolic abscess	47	28	59.6	38	35	92.1
Pelvic abscess, local peritonitis	85	9	10.6	113	53	46.9
General peritonitis	17	1	5.9	51	0	0
Obstruction	15	5	30.0	38	27	71.1
Bleeding	36	30	83.3	29	22	75.9
Fistula	28	3	10.7	34	12	35.3
Pain	110	82	74.5	47	46	97.9
Totals	338	158	46.7	350	195	55.7

Table 2 - Surgical and short term postoperative outcomes in the propensity-matched cohort (8).

	Laparoscopic sigmoidectomy $N = 39$	Open sigmoidectomy $N = 78$	P value
Duration of surgery, minutes	127 (105–159)	96.5 (87–120)	0.003
Hartmann's procedure	26 (66.7)	51 (65.4)	0.890
Primary anastomosis	13 (33.3)	27 (34.6)	
Ileostomy rate	8/13 (61.5)	12/27 (44.4)	0.597
Postoperative ICU admission	11 (36.7)	28 (50.0)	0.305
In-hospital mortality	1 (2.6)	3 (3.9)	0.685
In-hospital overall morbidity	17 (43.6)	51 (66.2)	0.016
In-hospital severe morbidity (>IIIB)	5 (12.8)	15 (19.5)	0.253
Reinterventions	5 (12.8)	15 (19.5)	0.739
Surgical reinterventions	2 (5.1)	7 (9.1)	0.485
Percutaneous reinterventions	3 (7.7)	10 (13.0)	0.419
Postoperative hospital stay, days	7 (5–13)	9 (7–14)	0.016

Data are mean (SD), number (%), or median (interquartile range). *ICU* intensive care unit. Severe morbidity defined as Clavien–Dindo ≥IIIB

Table 3 - Results from the randomized controlled trial DILALA. Short-term outcome data (11).

	Laparoscopic Lavage (n = 39)	Hartmann's Procedure (n = 36)	*P*	Missing Data
Time in recovery unit, h	4 (1–12)	6 (2–44)	0.045	5 (12.8%)/4 (11.1%)
Required intensive care, n	5/39 (12.8%)	4/36 (11.1%)	0.802	
Number of days with drainage	3 (0–21)	2 (0–17)	0.021	1 (2.6%)/7 (19.4%)
Blood transfusion, n	4/39 (10.3%)	2/36 (5.6%)	0.453	
Postoperative hospital stay, d	6 (2–27)	9 (4–36)	0.037	1 (2.6%)/2 (5.6%)
Stoma related problems, n				
Skin irritation around the ostomy	N/A	5/36(13.9%)		
Difficulties learning to care for the stoma	N/A	11/36 (30.6%)		
Reoperation within 30 days, n	5/38 (13.2%)	6/35 (17.1%)	0.634	1 (2.6%)/1 (2.8%)
Mortality within 30 days, n	3/39 (7.7%)	0/36 (0%)	0.094	
Mortality within 90 days, n	3/39 (7.7%)	4/36 (11.4%)	0.583	
Readmission within 30 days, n	0/38	2/35 (5.7%)	0.135	1 (2.6%)/1 (2.8%)
More than 1 readmission within 30 days, n	0/38	1/35 (5.7%)	0.294	1 (2.6%)/1 (2.8%)

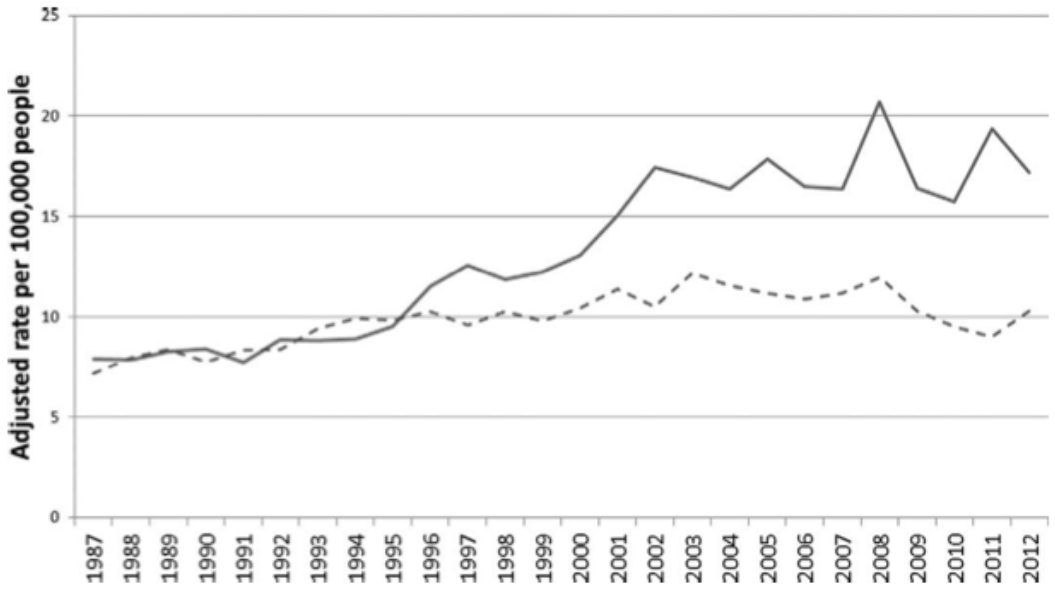

Figure 1- Rates of elective and nonelective colectomy 1987–2012. Age- and sex-adjusted rates (to the 2000 state census population) of elective colectomy (solid line) and nonelective colectomy (dashed line) over 26 years in Washington State (14).

LONG-TERM OUTCOME OF ELECTIVE SURGERY

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Background and Indications

The indication for elective surgery after an acute episode of diverticulitis is currently under revision. Nowadays a consensus on the indications for elective sigmoid resection in patients with acute diverticulitis and concomitant abscess initially managed with a non–operative way has not been reached yet, unlike the surgical management of perforation, fistulae and stricture. Before 2006 elective surgery was considered the best choice after two episodes of diverticulitis (1), while in 2006, the American Society of Colon and Rectal Surgeons (ASCRS) declared that the decision of elective sigmoid resection should be taken by a case-by-case evaluation (2).
Recent data about the natural history of diverticulitis has shown that only 5.5% of patients with recurrent episodes of diverticulitis require emergency surgery, while the remaining part of patients has a good prognosis without urgent surgical treatment (3). Moreover, the majority of patients with complicated diverticulitis show such event at the first episode. (4-6). The number of previous episodes of diverticulitis can't be considered an indication for elective surgical treatment because the risk of perforation seems to be reduced in recurrent diverticulitis, possibly due to adhesion formation by inflammation (4-7).
There are some characteristics that should be considered to select patients who might benefit from elective sigmoid resection; surgical treatment is probably the best approach in a selected group of patients who suffer greatly from their disease.
Many studies have demonstrated that 40-80% of patients show symptoms after conservative treatment, with reduced health-related quality of life (HRQoL) and increased costs for multiple specialist consultations, pain medication and productivity losses. Obviously this is the same situation of patients with recurrent diverticulitis, which often present symptoms also between the recurrence (8).

Surgery

Patients with complicated diverticulosis can be treated either with an open or a laparoscopic sigmoid resection. There are two randomized trials which show the advantages of laparoscopic surgery compared to open surgery. In fact both in the –Sigma trial" (9) and in the study by Gervaz et al (10) patients underwent to open surgery are characterized by more complications, higher pain scores and longer hospital stay compared to patients with laparoscopic treatment. Operating time is significantly longer in the laparoscopic group. Patients treated with open sigmoid resection have anastomotic leaks more frequently than patients treated by laparoscopic sigmoid resection, and even if patients subjected to open surgery have more comorbidities, the rate of anastomotic leaks remains higher in this group even when these differences are accounted for (11).

Proximal and distal margin resection, vascular approach and splenic flexure are the main surgical steps to consider: the current recommendation about resection margins is to make the proximal part of the anastomosis in soft pliable colon and to include the colorectal junction in the distal resection; as regards vascular approach, there are a lot of studies which show that preservation of inferior mesenteric artery (IMA) could improve the quality of bowel function and could limit the risk of anastomotic leakage (12); finally the mobilization of splenic flexure is necessary to obtain tension- free anastomosis (13).

Long- term Outcome

Patients with persistent or recurrent symptoms after an episode of diverticulitis show an improvement of general QoL with elective sigmoid resection, because of a reduction of discomfort caused by abdominal pain and by abnormal defecation and fatigue. Open and laparoscopic sigmoid resection are both characterized by excellent long-term results in terms of gastrointestinal function, quality of life, and patient satisfaction. Laparoscopic surgery has significant benefits only in terms of cosmetic effects (14), while prospective randomized trials are necessary to demonstrate additional long-term benefits, such as reduction in incisional hernias, adhesions ad small bowel obstruction.

Conclusions

Patients with persisting abdominal pains after an episode of diverticulitis and/or recurrent episodes of diverticulitis can be treated with either a conservative and operative management. However a randomised controlled trial is necessary to define if the morbidity and mortality associated with surgery is superior than the risk of complicated recurrence after conservative management.

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PERITONITIS IN DIVERTICULAR DISEASE. FROM HARTMANN TO PERITONEAL LAVAGE

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Diverticular disease is not a new concept and the presence of diverticula wthin the colon has been documented as early as 1700 by the French surgeon Alexis Litre. He believed that a diverticulum may be formed when part only of the wall of the intestine enters the hernial sac and not the whole diameter, so that only one side of the intestine is pulled out and finally becomes a longer and longer canal.
In 1896 William Mayo operated on his first case of internal fecal fistula into the bladder, a
and later had resected the colon in cases thought to be cancer which were found to be diverticulitis. He did the first report of surgical treatment for diverticulitis in 1907.
At the review of the literature, we found that two years before Humphry Rolleton, an English surgeon, published at Lancet an interesting report. He described a case with an intraperitoneal abscess circumscribed around the sigmoid. In that time he called *Pericolitis Sinistra* with Abscess formation. Now, we can understand that it was a Perforated Diverticulitis. More than one century ago, Rolleston ~~–e~~vacuated the pus, washed out the cavity and a large drainage tube was inserted".
The first surgical technique, known as the ~~–t~~hree-stage procedure", was developed at Mayo Clinic and the first experience of classic three-stage operation was reported on 1924. The technique consist in a colostomy at the level of the transverse colon and the positioning of drainage; the resection of the diseased colon after a period of 3–6 months; and stoma closure after a further 3–6 months. This technique had a high rate of mortality.
Surgeons didn't have antibiotics. Three stage procedure was mainly used in perforation, obstruction and fistula formation.
The second method, the ~~–t~~wo-stage" or Hartmann's procedure, was used for the first time by Henry Hartmann in 1921 in order to perform sigmoid resection for the treatment of neoplastic disease. It consists of a segmental resection of the diseased colon without a primary anastomosis but with an end colostomy; intestinal continuity can be restored during a second operation. Widely used since the 1950s, Hartmann procedure became the standard of care in the 1980s, but has a significant complication rate and mortality rates range from 5% to 14%. The continuity restoration was not possible around 25-50% of cases. During many years many papers reported a controversy between three and two stage procedure. In 2000, American Society of Colon and Rectal Surgeons (ASCRS) pointed ~~–T~~hree-stage operative approach strategy (non resectional surgery) was no longer recommended for most patients". Then, Hartmann's procedure was considered a gold standard for complicated acute diverticulitis.
A ~~–o~~ne-stage" procedure [primary resection with anastomosis (PRA)] has been proposed since 1990. The most feared complication of this technique is anastomotic leakage, however, the risk of anastomotic dehiscence can be reduced by performing a proximal loop ileostomy to be closed during a second procedure. The performance of a diverting loop ileostomy has been reported to decrease the rate of symptomatic anastomotic leakage in patients operated for rectal cancer. The same is found in case of diverticular peritonitis. Improvements in surgical and radiological intervention techniques and progress in the antibiotics management of peritoneal sepsis led to an increasing interest in colonic resection with primary anastomosis.
A new controversy appeared. Advantages and disadvantages between Hartman procedure and resection with primary anastomosis with or without ileostomy. Many papers was done but no significant differences were found between primary resection with anastomosis and Hartmann's procedure with respect to mortality, morbidity, sepsis, wound complications and duration of procedure. The key has been in cost.

In a bid to reduce the mortality and morbidity associated with emergency surgery, two methods have been used: percutaneous drainage by ultrasound or computed tomography and peritoneal lavage with drainage.

The progress of antibiotic development and interventional radiographic techniques has changed the management of perforated diverticulitis. The high specificity of CT scan has allowed this modality to become a surrogate to the perioperative assessment made by the Hinchey classification . Furthermore, CT scan has become an important therapeutic modality. It is now recognized that patients with small, contained perforations, who are not systemically ill, can be treated initially with antibiotics alone or by CT-guided percutaneous drainage. It‘s usually done through the anterior or lateral abdominal wall in order to avoid damaging the inferior epigastric artery and deep circumflex iliac vessels, although transgluteal, transperineal, transvaginal and transanal approaches can also be used. The size of the drain used is very important because complete evacuation of the abscess must be obtained. Percutaneous drainage of abdominal abscesses is the preferred treatment strategy in contained diverticular perforations.

In 1996, Faranda first described a nonresectional laparoscopic procedure that seemed to be a more promising alternative. In patients with peritonitis without gross fecal contamination, laparoscopic peritoneal lavage, inspection of the colon, and the placement of abdominal drains appear to diminish morbidity and improve outcome. In a series of 100 patients with PPD, Myers showed excellent results after laparoscopic lavage and drainage of the peritoneal cavity, with morbidity and mortality rates <5%. This technique is a back to the future, with best technical tools, better medical support and broad spectrum antibiotics we are doing a similar surgery that Rolleston did more than 100 years ago.

Since 2012 to 2014, we included 17 cases Hinchey III for peritoneal lavage and drainage. None of them had co morbidities. 12 males and 5 females with an average age of 56.8 years. Main complications were respiratory. No mortality. Discharged at 4.2 days.

Recently the World Health Organization accepted the laparoscopic peritoneal lavage and drainage as a secure alternative in patients with Hinchey III.

Probably in a short future the management of Complicated Acute Diverticulitis will be more of decisions than incisions.

DIVERTICULAR DISEASE – HOW TO MAKE THE DIAGNOSIS IN PRIMARY CARE

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Background

General Practitioners are in the front line of symptoms and problems being presented by patients. Patients often present with undifferentiated symptoms, with no obvious pointers towards a specific diagnosis and indeed, there may be no diagnosis possible. Symptoms and clusters of clinical issues may point towards a likely problem but immediately available investigations may not be of much value. Against this backdrop of uncertainty GPs find themselves having to reach a probable diagnosis for conditions that are not clear cut and often co-exist with other medical conditions.
Gastroenterology comprises around 10% of a GPs workload, of which lower gastrointestinal problems constitute around 50%. The commonest lower GI problems presenting often have no clear-cut underlying diagnosis: diarrhoea (often due to short duration infections), constipation (frequently associated with increasing age or drug therapies), functional problems (IBS) and of course, abdominal pain of differing durations and intensity. Relatively few patients undergo extensive investigations unless the symptoms are severe, progressive or associated with alarm symptoms. For example, in a recent study the prevalence of episodic diarrhoea in the community, in the absence of a pre-existing diagnosis, across eleven countries, was reported as high as 23% (1). Taking into account other lower GI disorders such as IBS the overall community prevalence of lower GI problems is likely to be 30% or more.

The diagnostic challenge

Diverticula and diverticular disease commonly affects the left colon, and the prevalence increases with age. There are global differences as in Asian populations where the condition more often affects younger patients and the right colon. Approximately 50% of people have diverticula by the age of 50 years and 70% by the age of 70 years. Around 75% of people with diverticula have asymptomatic diverticulosis (2).
Therefore, the diagnosis of diverticular disease and diverticulitis in primary care can be challenging. There are no clear diagnostic symptoms, signs or first line blood tests. There is overlap with other conditions such as IBS, biliary or other GI conditions and urological and gynecological problems. Prior knowledge of the presence of diverticula is not always available and the presenting picture can vary from a non-specific pain and tenderness to acute signs with a mass, requiring urgent attention.

Making the diagnosis

Diverticular disease is characterized by intermittent lower abdominal pain, fever and change in bowel habit. These may be associated with dysuria, increased urinary frequency and more significant symptoms such as rectal bleeding, abscess formation and peritonitis. The essential basis of the diagnosis is the exclusion of other causes and the confirmation of the presence of diverticula. Where there is no confirmed presence of diverticula urgent action, including hospital admission may be needed (2).
Positive action is necessary when active diverticular disease or diverticulitis is suspected. In addition to a history and full examination, particularly to assess the possible acute nature of the problem, the patient should have a full blood count and if available, the CRP level. There is also evidence that fecal calprotectin levels are raised in patients with uncomplicated diverticulitis (as compared with controls and in IBS). Rectal bleeding can result from diverticula, and this finding requires appropriate investigations. The definitive diagnosis of the presence of diverticula relies on colonoscopy or CT scanning, sometimes available directly to the primary care physician but this is not usually an option in the acute situation.

An important aspect of the diagnostic process is to assess the severity of the acute condition, as mild and uncomplicated diverticulitis usually can be managed at home, while in more severe disease, or with any suspicion of perforation, abscess or fistula, admission to hospital is needed.
The GP needs to be aware of the possibility of diverticular hemorrhage, usually abrupt, painless and large which occurs in 1% of people with diverticulitis. Other diagnostic but complicating factors include dysuria and frequency when the inflamed bowel is in contact with the bladder, perforation and peritonitis, abscess and fistula formation and intestinal obstruction due to recurrent inflammatory episodes.
Ruling out other diagnoses can be an issue for primary care, and appropriate investigations should be performed for a satisfactory clarification of the condition.

Differential diagnoses
In patients with lower abdominal pain differential diagnoses include: irritable bowel syndrome, appendicitis, and colitis and bowel cancer. Gynaecological causes include pelvic inflammatory disease, ovarian cyst or torsion and ectopic pregnancy. Urological conditions to be excluded include urinary tract infection or urinary tract obstruction, including ureteric stone. For obvious reasons patients with rectal bleeding or alteration of bowel habit should be considered for bowel cancer or colitis (2).

Summary
In summary, the primary care physician should maintain a high index of suspicion for diverticular problems in people with abdominal pain, especially over the age of 50 years, and in particular, where a prior investigation may have indicated the presence of diverticula. Whilst the majority of people with diverticular disease are symptom-free there is the possibility of significant problems, characteristically lower abdominal pain and fever, and complications such as bleeding, fistula and abscess formation. These require urgent management and admission to hospital if there is no prior recorded history of diverticulae. In managing the patient it is important for the GP to assess the severity of the condition, the probability of diverticular disease being the cause of the patient‘s symptoms and an evaluation for differential diagnoses, some of which can be life threatening.

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MANAGEMENT AND REFERRAL OF PATIENTS WITH SYMPTOMATIC DIVERTICULAR DISEASE IN PRIMARY CARE

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Background
Diverticular disease of the colon, in its various forms, is one of the most common diseases of the large intestine. Although its diagnosis and treatment primarily involves the General Practitioner (GP), current guidelines are quite conflicting (1,2). These differences can be detected not only between European countries (1,2), but also between gastroenterologist and surgeons (3). In this way, we investigate the current opinion of Italian GP on treatment strategies for patients with diverticulosis and diverticular disease.

Italian Survey on Diverticular Disease
A web-based survey was conducted among Italian GP. After recalling about the definitions of diverticulosis, Symptomatic Uncomplicated Diverticular Disease (SUDD) and Acute Diverticulitis of the colon, thirteen questions were aimed at the management options for diverticulosis and diverticular disease in primary care.
Two-hundred and fifty-five survey were analysed, and 245 surveys were filled out. After reviewing data supplied, the most important finding were:
a) Diagnosis. Colonoscopy was the most prescribed instrumental tool to pose diagnosis of diverticulosis and diverticular disease and, when required, in the follow up of SUDD and diverticulitis; either in SUDD and diverticulitis, follow-up laboratory analysis were frequently required.
b) Treatment. Fiber supplement was strongly advised in SUDD, more than in diverticulosis; 30% of the Italian GPs still recommends a no-seeds diet; Rifaximin was the most prescribed drug (in about three-quarters of patients), followed by probiotics (in about 40% of patients) in managing each form of the disease. In particular, one forth of patients with simple diverticulosis receive treatment with rifaximin and/or probiotics, and rifaximin was also the most prescribed drug in the treatment of SUDD, in the SUDD follow-up, and even in the diverticulitis follow-up.
Question and results are reported in table I.

Conclusions
Review of the surveys supplied by the Italian GPs, clearly emerges that current management of diverticular disease in primary care still conflict with literature and more recent guidelines.

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QUESTIONS	ANSWERS	Percentage distribution of the answers

What is the most frequent symptom complained by your patients with Symptomatic Uncomplicated Diverticular Disease?	a. Abdominal pain in the left lower quadrant; b. Diffuse abdominal pain; c. Diarrhea; d. Constipation; e. Alternate alvus; f. Meteorism	a. 26 % b. 23 % c. 8 % d. 9 % e. 18 % f. 16 %
How the diagnosis of Symptomatic Uncomplicated Diverticular Disease was made?	a. Rx barium enema b. Colonoscopy c. Abdomen CT; d. Abdomen Ultrasonography ; e. Virtual colonoscopy.	a. 19 % b .77 % c. 1 % d. 1 % e. 2 %
Do you prescribe dietary advice in patients with diverticulosis?	a. Low fiber diet; b. High fiber diet; c. Diet without seeds; d. I do not prescribe any specific dietary advice	a. 9 % b. 44 % c. 30 % d. 17 %
Do you prescribe dietary advice in patients with SUDD	a. Low fiber diet; b. High fiber diet; c. Diet without seeds; d. I do not prescribe any specific dietary advice	a. 15 % b. 41 % c. 30 % d. 14 %
Do you usually prescribe drugs in patients with asymptomatic diverticulosis?	a. Rifaximin; b. Mesalamine; c. Probiotics; d. Ciprofloxacin; e. Metronidazole; f. Co-trimoxazole; g. I do not prescribe any medication in these patients	a. 26 % b. 6 % c. 25 % d. 2 % f. 1 % g. 40 %
What medications do you usually prescribe for symptomatic patients?	a. Rifaximin; b. Mesalamine; c. Probiotics d. Ciprofloxacin; e. Metronidazole; f. Co-trimoxazole g. Spasmolithics; h. Fiber supplement	a. 82.8 % b. 36.3 % c. 59.5 % d. 27.3 % e. 13.6 % f. 4.8 % g. 0 % h. 10.6 %
Do you usually prescribe drugs in the follow-up of these patients to prevent recurrence of Symptomatic Uncomplicated Diverticular Disease?	a. Rifaximin; b. Mesalamine; c. Probiotics d. Ciprofloxacin; e. Metronidazole; f. Co-trimoxazole; g. Fiber supplement; h. I do not prescribe any medication in the follow-up of these patients	a. 66 % b. 17.1 % c. 44.4 % d. 0.2 % e. 0.2 % f. 0.0 % g. 15.5 % h. 18.7 %

Do you generally prescribe instrumental examinations in the follow-up of Symptomatic Uncomplicated Diverticular Disease?	a. Rx barium enema; b. Colonoscopy c. Abdomen CT; d. Abdomen Ultrasonography; e. Virtual colonoscopy; f. I do not prescribe any instrumental examination in the follow-up of these patients	a. 5 % b. 21 % c. 1 % d. 4 % e. 2 % f. 67 %
Do you generally prescribe laboratory analysis in the follow-up of patients who have had an episode of Symptomatic Uncomplicated Diverticular Disease?	a. Haemochrome; b. ESR; c. CRP d. Faecal calprotectin; e. FOBT; f. I do not prescribe any laboratory check in these patients	a. 24 % b.16 % c. 16 % d.14 % e. 7 % f. 23 %
75-year-old patient in good general condition, known for colon diverticulosis, blames fever, constipation and pain to the left hemi abdomen; the abdomen is negotiable on palpation and peristalsis is present. Do you send the patient to the Hospital or you manage it at home?:	a. I send the patient to the Hospita;l b. I manage him at home	a. 17 % b. 83 %
Do you generally prescribe medications in the patient follow-up, to prevent recurrence of diverticulitis?	a. Rifaximin; b. Mesalamine; c. Probiotics; d. Ciprofloxacin; e. Metronidazole; f. Co-trimoxazole; g. I do not prescribe any medication in the follow-up of these patients	a. 42.5 % b. 12.4 % c. 28.2 % d. 3.5 % e. 2.1 % f. 1.1 % g. 9.8 %
Do you think that a patient with two previous episodes of acute diverticulitis, treated with conservative medical therapy, should undergo surgery?:	a. YES b. NO	a. 14 % b. 86 %
Do you generally prescribe laboratory analysis in the follow-up of patients who have had diverticulitis?	a. Haemochrome; b. ESR; c. CRP; d. Faecal calprotectin; e. FOBT; f. I do not prescribe any laboratory check in these patients	a. 25 % b. 20 % c. 20 % d. 14 % e. 8 % f. 13 %

STATISTIC DANCE ON DIVERTICULAR DISEASE

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Diverticular disease of the colon is the fifth most important gastrointestinal disease in terms of direct and indirect healthcare costs in western countries.
The main topics on treatment of diverticular disease are:

- Use of Rifaximine
- Use of Mesalazine
- Use of Antibiotics in Diverticulitis.

Rifaximin: This poorly absorbable antibiotic has been successfully used in recent years in the treatment of SUDD, and also seems to be effective in maintaining SUDD remission. A recent meta-analysis examined four prospective randomized trials (only one conducted in double-blind placebo-controlled fashion) including 1660 patients. The pooled rate of difference for symptom relief was 29.0% in favor of rifaximin (rifaximin vs. control; 95% CI 24.5-33.6; P<0.0001) with a clinically significant Number Needed to Treat (NNT=3)[1]. The use of rifaximine in prevention of diverticulitis, data from three open randomized trials (comprising a total of 1492 patients) and four comparing rifaximin plus glucomannan or fiber supplementation vs. glucomannan or fiber alone, reported that rifaximin led to a slight benefit in preventing acute diverticulitis, but only the largest study showed significant results. Cumulative data from placebo controlled and unblinded trials showed that the rate of acute diverticulitis was significantly less frequent in patients treated with rifaximin plus fiber supplementation than with fiber alone (11/970 (1.1%) vs. 20/690 (2.9%; P=0.012)[2-5]. According to these results, the number needed to be treated to prevent an attack of acute diverticulitis in 1 year with the rifaximin plus fiber supplementation regimen reached is 57 (NNT: 57).

Mesalazine: 5-ASA is another option for the treatment of SUDD. Although limited by the open-label design, the favorable effect of mesalazine on SUDD has been demonstrated by several open-label studies[6,7]. Three double-blind, placebo-controlled studies have also recently assessed the role of mesalazine in treating those patients[8-10]. Data on the role of mesalazine, five randomized open trials (comprising more than 400 patients) in preventing acute diverticulitis, did not show any significant effects, however, there were only seven episodes of acute diverticulitis per year (yearly incidence rate of 2%). More recently, a double-blind, double dummy placebo-controlled trial assessed the prevention of acute diverticulitis occurrence as secondary endpoint, found mesalazine significantly better than placebo in preventing acute diverticulitis[9].

Antibiotics in Diverticulitis: Conservative treatment of uncomplicated or mild diverticulitis usually includes antibiotic therapy. It is, however, uncertain whether patients with acute diverticulitis indeed benefit from antibiotics. In most guidelines issued by professional organizations antibiotics are considered mandatory in the treatment of mild diverticulitis. The treatment of acute diverticulitis by intravenous fluid replacement, limiting oral intake, and broadspectrum antibiotics is common practice but is not supported by a strong evidence base. People with mild symptoms and no evidence of generalised sepsis can be managed at home with oral antibiotics. People with CT-proven mild uncomplicated diverticulitis may not benefit from having intravenous antibiotics. This is in keeping with current thoughts on disease pathophysiology; however, the evidence for this approach is based on one RCT. People with severe pain or signs of compromise should be admitted for analgesia, bowel rest, intravenous fluid replacement, and intravenous antibiotics.

Despite these results, further studies are needed as most published trials were uncontrolled, often small, and lacking of strict enrolment criteria. For these reasons different pharmacological and non-pharmacological approaches are currently approved in North America or Europe to prevent acute attacks of diverticulitis or to treat patients with symptomatic disease.
Selecting patients according to the colonic characteristics may be an option to increase therapeutic efficacy. To this end, an endoscopic classification of DD has been recently developed and validated[11]. This classification, called DICA is able to predict the outcome of the disease according to the severity of the score. In other words, simple and/or asymptomatic diverticulosis does not appear to need any maintenance treatment to prevent occurrence of complications, while a colon with signs of recurrent inflammatory attack may be unresponsive to maintenance treatment to prevent recurrence of complications.
In conclusion, the DICA Classification may be a useful guide for the treatment of patients.

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ITALIAN GUIDELINES ON DIVERTICULAR DISEASE OF THE COLON

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The primary aim was to provide clinical guidelines for appropriate definition, diagnosis and management of diverticular disease (DD). The promoter of this initiative was the Italian Study Group of Diverticular Disease (Gruppo Italiano Malattia Diverticolare - GRIMAD). GRIMAD identified a Scientific Board of Experts), which defined the methodology and targets, and acted as developer and reviewer.

Topics such as epidemiology, risk factors, diagnosis, medical and surgical treatment of DD in patients with uncomplicated and complicated DD were reviewed by a scientific board of experts who proposed 76 statements graded according to level of evidence and strength of recommendation, and 55 were approved by an independent jury. Each topic was explored focusing on the more relevant clinical questions. Comparison and discussion of expert opinions, pertinent statements, and replies to specific questions, were presented and approved based on a systematic literature search of the available evidence.

The methodology to process guidelines involved six steps:

1) The scientific board selected four main areas of interest in DD : (i) definition and epidemiology, (ii) pathophysiology, (iii) diagnosis, and (iv) medical and surgical therapy. 2) For each topic, a working party was created, which included a coordinator and at least two experts. The latter were chosen on the basis of their recognized scientific expertise in DD . The working party selected, together with the scientific board, a number of clinically relevant, clear, answerable questions, focusing on current practice and areas of controversy. The questions were circulated among the working parties to share relevance, improve clarity, and avoid duplication. A preliminary meeting of the working parties was held in Bologna (June 2011) in order to share methods, aims, timelines, and the entire guideline processing. 3) The working parties independently carried out a systematic search for, and analysis of, the literature relevant to their topics by October 2012, using Medline/PubMed and the Cochrane data base. Each recommendation was graded according to the Oxford Centre for Evidence-Based Medicine, according to the level of evidence (EL) (1). 4) By November 2012 the working parties issued initial statements and attributed to them a grade (strength) of recommendation (RG), from A to D, consistent with the level of evidence. Each coordinator drafted provisional statements that were circulated within his/her group. 5) Subsequently, each four area coordinator evaluated the preliminary statements produced and the related grades of evidence. A redrafted document containing the statements was then prepared and submitted to the all participants for an online session for a first round of votes and comments, using a simplified scale (agreement/disagreement); they voted using a modified Delphi procedure until a minimum agreement level of at least 67% was achieved for each statement. Statements were then submitted to the scientific board, which wrote an advanced version, and fed back the new statements to the working parties. 6) On the 19th and 20th of February, 2013 a Consensus Meeting was held in Bologna. The consensus group consisted of 33 participants, selected taking into account diverse expertise in various aspects of DD, and geographical distribution. The consensus group was led by a non-voting chairman and the four non-voting members of the scientific board , and included experts of working parties and multi-disciplinary professionals/experts such as gastroenterologists, GI endoscopists, surgeons, radiologists, pathologists, and general practitioners. Overall, 76 statements were submitted to the global consensus group. Following a plenary discussion held before voting, twenty-one statements were deleted, and 45 were partially rephrased. The final 55 statements were then submitted to the global consensus group for anonymous keypad

voting (Delphi process) without any explanation or justification. The Delphi process brought to a change of view from a position previously held, avoiding any uneasiness among participants or influence on individual votes. The agreement/disagreement level was scored on a six-point Likert scale as follows: A+: strongly agree; A: agree with minor reservations; A−: agree with major reservations; D−: disagree with major reservations; D: disagree with minor reservations; D+: strongly disagree. Level of agreement was expressed as percentage of each point of the scale. Immediate feedback was given to participants on a screen, who were prompted by the non-voting chairman and the non-voting members of the scientific board to discuss the statements, and suggest changes in case of controversy (<67% agreement). The entire work and discussions were tape-recorded.

The format of the following recommendations comprises the question, statement, its level of evidence and strength of recommendation, and the percent agreement of the global consensus group with the final version (2).

The document comprises statements that are accompanied by comments made by each working party and reviewed by the scientific board taking into account relevant observations and suggestions made during the plenary discussion. In some areas the evidence level is low, reflecting the lack of randomized trials and good quality studies. For some topics only the expert opinion was considered, where appropriate.

These guidelines represent a consensus of best practice based on the available evidence at the time they were issued. They may not apply to all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify some aspects of these statements, and revision may be necessary as new data become available. These guidelines are intended to be an educational tool to provide information that may assist gastroenterologist and surgeons in providing care to patients. They are not rules and should not be constructed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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SCANDINAVIAN GUIDELINES ON DIVERTICULAR DISEASE

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In Scandinavia official guidelines for the management of diverticular disease exist only in Denmark [1]. However, my impression from several local guidelines, Scandinavian publications and surgical meetings is that the treatment policy is quite similar in the Scandinavian countries. In my talk I will concentrate on imaging, treatment options and follow up of acute diverticulitis (complicated and uncomplicated) and I will discuss indications for elective sigmoid resection in patients with diverticular disease.

Imaging
In most Scandinavian hospitals computed tomography (CT) is the investigation of choice to diagnose acute diverticulitis. This is also what is recommended in the Danish guidelines [1]. Also in several Scandinavian publications CT is used as a standard investigation [2-5]. There is no tradition in Scandinavia for the use of ultrasound as diagnostic tool for these patients. The main reason for this seems to be that ultrasound is much more operator dependent than CT.

Acute uncomplicated diverticulitis
Antibiotics

After that results from the AVOD trial [2] have been published, many hospitals in Sweden and Norway have implemented new treatment policies for acute uncomplicated diverticulitis. In many hospitals antibiotics are now reserved for high risk patients and patients with complicated diverticulitis. This is also the recommendation in the Danish guidelines [1].
Follow up after uncomplicated diverticulits

Many hospitals in Scandinavia still practice a routine colon examination after acute uncomplicated diverticulitis, either as colonoscopy or as CT colonography. This routine has been supported by the findings of a large population based Swedish study that showed an increased risk of colorectal cancer within the first 12 month after primary diagnosis of diverticular disease [6]. The Danish guidelines recommend a colon investigation approximately 6 weeks after an acute attack of uncomplicated diverticulitis [1]. The recent review articles to this topic [7, 8] have encouraged a few hospitals to abandoned this practice in patients with CT verified uncomplicated diverticulitis. Routine colon examination is however standard for all patients with complicated diverticulits.
Perforated diverticulitis with or without abscess formation
Perforated diverticulitis is often diagnosed by extra luminal air or fluid on an abdominal CT which has become a standard tool in Scandinavia when evaluating patients with an acute abdomen. The Danish guidelines recommend diagnostic laparoscopy in case of radiological findings suggesting free perforation. Some hospitals do however reserve operative treatment to patients with clinical findings of diffuse peritonitis and hemodynamically unstable patients. Many surgeons in Scandinavia prefer to treat stable patients without clinical sings of peritonitis with antibiotics only. This practice is supported by recently published cohort studies [9, 10]. Abscesses over the size of 2 cm are drained if possible. For abscesses larger than 5 cm operative drainage is considered if percutaneous drainage is not feasible.

Operative treatment for patients with perforated diverticulitis
For purulent peritonitis there is currently no consensus among Scandinavian surgeons on which procedure to perform. Many colleagues agree that primary resection and anastomosis is safe for many patients but the general condition of the patient should be considered. Two Scandinavian trials have investigated laparoscopic lavage as an option. The results were somewhat contrary [5,

11]. The Danish guidelines were written before publication of the results form the randomized trials and recommend laparoscopic lavage for patients with purulent diverticulits. In case of feculent peritonitis (Hinchey grade 4) primary resection with terminal colostomy (Hartmann‘s procedure) is the treatment of choice for most surgeons in Scandinavia [5, 11]. The Danish guidelines recommend resection in patients with feculent peritonitis, they make however no recommendation as to whether or not a primary anastomosis should be performed [1].

Elective sigmoidectomy

After the publication by Haglund in 1979 most of the Scandinavian surgeons have been quite reluctant to the international trend of extended indications for elective sigmoid resection in patients with diverticular disease [12]. Haglund showed that elective surgery could not prevent serious attacks of diverticulitis, as complications are most likely to occur at the first attack. Most hospitals have reserved elective sigmoid resection for patients with frequent recurrences of diverticulitis and patients with complications such as stenosis, fistula or persisting abscesses which is also the recommendation in the Danish guidelines[1]. This practice has now been supported by the latest international publications and guidelines [13-15].

Symptomatic uncomplicated diverticular disease

Symptomatic uncomplicated diverticular disease (SUDD) is addressed in the Danish guidelines which make some suggestions for the treatment of this condition[1]. My impression from meetings and conversations with colleagues is however, that most surgeons consider this condition as a coincidence of diverticulosis and irritable bowel syndrome. Traditionally Scandinavian surgeons are reluctant to operate on patients without a history of acute diverticulitis, especially if there is no morphologic explanation for their symptoms other than the mere existence of diverticulosis.

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AUSTRALIAN GUIDELINES ON DIVERTICULAR DISEASE

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In Australia (2008) the proportion of all deaths from digestive disease which did not include cancer, was 3.4%, and diverticular disease (DD) accounted 0.2% of all deaths (female predominant) (1), and it is one of the five most costly gastrointestinal disorders affecting the US population. (2)
In a survey conducted in Brisbane, (3), 48% of all comers had diverticular disease found at post mortem.
For this very common and costly condition, which guidelines are available specifically in Australia?
For physicians and GPs, guidelines most used are: Diverticular Disease and Diverticulitis [revised 2011 Feb]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2015 Jul. (4)
For surgeons, the paper by Ooi et al (5) is commonly used which quotes Guidelines issued by the American Society of Colon and Rectal Surgeons
Consumer information on diverticular disease is available from the Gastroenterological Society of Australia at their website (6) and dietary advice is available from the Dieticians Association of Australia (7).
There is a need for a robust epidemiological study in Australia and up to date medical/surgical guidelines that take the most recent global literature into account.

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ORAL PRESENTATIONS

SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE: EVALUATION OF MESALAMINE AND/OR PROBIOTICS TREATMENT IN FECAL CALPROTECTIN

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Keywords – Diverticular disease, mesalamine, probiotics

Background - Recent observations suggest that symptomatic uncomplicated diverticular disease (SUDD) is related to changes in colonc microflora and mild inflammation. Fecal calprotectin (FC) is a protein related to intestinal inflammation. The use of mesalamine can improve symptoms and reduce the FC levels to normal levels in many patients but in some cases, these levels remain high. The persistence of FC in altered levels is related to complications of the diverticular disease. The management of these patients is still unknown.

Aims - To evaluate the effects of mesalamine and / or probiotics in FC levels in patients with SUDD. Methods -163 patients with SUDD and FC >150microg/gr were selected after colonoscopy and CT . Were excluded patients younger than 18 years, with cancer, inflammatory bowel disease, gastroenteritis, previous intestinal surgery, and use of anti-inflammatory drugs. Patients received mesalazine 800mg b.i.d. for 60 days and made new dosage FC. 48 patients presented CF >150 microgr g and were divided into 3 groups: 1) MP group: 16 patients using mesalazine 800mg bid and a mix of probiotics (*L. acidophilus, L.casei, L. lactis, B. lactis, B. bifidum*) bid for 8 days; 2) Group P: 16 patients using mix of probiotics (*L. acidophilus, L.casei, L. lactis, B. lactis, B. bifidum*) bid for eight days; and 3) M3 group: 16 patients with mesalazine 800 mg tid for 8 days. After treatment, all of them made new dosage FC.

Results - After 60 days of treatment with mesalazine 800 mg bid, 115 patients (71%) presented FC <150microgr/g and 48 (29%) FC >150microgr / g. There was a statistically significant decrease (51.8%) in FC levels after combined treatment: MP group (309.70 ± 121.80 x150.80 ± 104.23, p <0.002). Statistically significant reduction was also seen in FC levels (42.2%) after treatment with higher doses of mesalamine : M3 Group (x 455.40±264.17 261.50±209.16, p <0.01). No significant reduction in FC levels were seen in Group P (537± 360, 82 x 284 196.69±50, p=0.08). There was a greater reduction in levels of CF MP Group (51.8%) than in M3 (42.2%), but there was no statistically significant difference.

Conclusion - FC levels reduced to baseline in most patients after treatment with mesalazine 1.6g. The combined use of mesalazine and probiotics or increasing the dose of mesalazine can contribute to reducing FC levels in SUDD.

ROLE OF CT COLONOGRAPHY IN EARLY FOLLOW-UP OF ACUTE COMPLICATED DIVERTICULITIS

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Keywords: Diverticulitis, CECT, CTC, Hinchey , Outcome.

Introduction: Patient evaluation after an episode of acute complicated diverticulitis (ACD) is mandatory, and contrast-enhancement CT (CECT) still remains the "gold-standard" [1]. However the diagnostic follow-up of those patients is still controversial [2, 3] especially because the indications of a surgical treatment are changing [4, 5], so the re-evaluation after an episode of ACD represent a possible new indication for other diagnostic techniques [6, 7]. Considering diverticular disease, CT colonography (CTC) today represents a robust and safe technique that allows a complete low dose evaluation of the extention of the disease with a precise definition of lenght/wall thickness of the interested segment, providing a detailed map of colonic/extracolonic findings [8, 9]. Considering ACD early follow-up, we evaluate value of CTC in order to set a correct treatment strategy.

Material and Methods: From April 2009 to August 2014, 66 patients underwent unenhanced low-dose CTC follow-up (28 males, 38 females, aged 38-91 yo) 6-8 weeks after ACD, conservatively treated.

All patients previously performed CECT and were classified using modified Hinchey classification.

CTC exam evaluated colonic/extracolonic findings, assessing short-term course and staging of diverticular disease. No CTC complications occured.

Results: CTC quality was good in 59/66 patients (89%); in 7 cases we obtain suboptimal distension due to diverticular disease or colonic stenosis.

At baseline CECT we found: Hinchey I (n=30, 46%), II (n=22, 33%); III (n=14, 21%); IV (n=0, 0%) stages.

CTC findings follow-up allowed to keep conservative treatment in all cases of Hinchey I (100%), in 8/22 cases of Hinchey II (36%) and in 8/14 cases of Hinchey III (57%).

Twenty patients not understaged (14/22 Hinchey II, 64%, and 6/14 Hinchey III, 43%) underwent laparoscopic/open surgery. CTC also revealed 4 unknown polyps >6 mm and 28 extracolonic findings, 4 with major clinical relevance that changed treatment strategy.

Conclusion: CTC is a safe and accurate method to evaluate severity of ACD, especially in short-term follow-up, allowing an overview of colonic/extracolonic findings and guiding correct therapeutic planning.

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EFFECT OF HIGH PERIOPERATIVE OXYGEN FRACTION ON SURGICAL SITE INFECTION FOLLOWING SURGERY FOR ACUTE SIGMOID DIVERTICULITIS. A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, CONTROLLED, MONOCENTRIC TRIAL

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Key words: controlled trial, hyperoxia, surgical site infection, outcomes.

Background: The clinical role of hyperoxia for preventing surgical site infection (SSI) remains uncertain because randomized controlled trials on this topic have reported disparate results. One of the principal reasons for such mixed results may be that prior trials have entered a heterogeneous population of patients and procedures. The aim of our study was to assess the influence of hyperoxigenation on SSI by using the most homogeneous study population.

Materials and methods: From January 2009 to December 2015, we studied, in a prospective randomized study, 85 patients who underwent open intraperitoneal anastomosis for acute sigmoid diverticulitis. Patients were assigned randomly to an oxygen/air mixture with a fraction of inspired oxygen (FiO_2) of 30% (n=43) or 80% (n=42). Administration was commenced after induction of anesthesia and maintained for 6 hours after surgery.

Results: The overall wound infection rate was 24.7% (21 out of 85): 14 patients (32.5%) had a wound infection in the 30% FiO_2 group and 7 (16.6%) in the 80% FiO_2 group ($p< 0.05$). the risk of SSI was 43% lower in the 80% FiO_2 group (RR, 0.68; 95% confidence interval, 0.35-0.88) vs 30% FiO_2.

Conclusions: Supplemental 80% FiO_2 during and for 6 hours after open surgery for acute sigmoid diverticulitis, reducing post-operative SSI, should be considered part of ongoing quality improvement activities releted to surgical care, with few risk to the patients and little associates cost.

ASSESSMENT OF FECAL MICROBIOTA AND FECAL METABOLOME IN SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE OF THE COLON

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Key words: fecal metabolome; fecal microbiota; symptomatic uncomplicated diverticular disease.

Background: Pathogenesis of Symptomatic Uncomplicated Diverticular Disease (SUDD) is not completely understood. Imbalance of colonic microbiota is considered a milestone in occurrence of symptoms (1), but whether intestinal microbiota is really altered in those patients is unknown. Metabolic profiling is a powerful exploratory tool for understanding interactions between nutrients, the intestinal metabolism and the microbiota composition in health and disease, and metabolomics technologies have been applied for the screening of different pathological conditions that are linked with a metabolic imbalance (2).

Aims: We performed a prospective study assessing fecal microbiota and metabolome in symptomatic uncomplicated diverticular disease (SUDD).

Methods: Stool samples from 52 consecutive female patients (17 with SUDD, 16 with asymptomatic diverticulosis (AD), and 19 healthy), born and living in the same geographic area, were analysed. Real-time PCR was used to quantify targeted microorganisms. High-resolution proton nuclear magnetic resonance spectroscopy in combination with Multivariate Analysisl were assessed in determining fecal metabolome.

Results: The total amount of bacteria in fecal samples of the three groups was not significantly different. In AD group a reduction in the percentage of bifidobacteria and enterobacteria and an increase of Clostridia and lactobacilli compared to total bacteria was observed. In both AD and SUDD groups an increase of *Akkermansia muciniphila* was also observed in comparison to healthy group. These differences were however not significant. NMR-based metabolomics of fecal waters did not show any significant change between healthy and SUDD subjects. However, significant differences in N-Acetyl-compounds were found between AD and SUDD patients. Partial Least Square Analysis showed that SUDD patients, with higher N-Acetyl-compound levels as compared to AD patients, showed higher levels in bifidobacteria and enterobacteria, and lower levels in clostridia and lactobacillus spp.

Conclusions: SUDD does not show any significant quantitative and qualitative alteration of the analysed fecal microbiota. However, increasing expression of some metabolites as expression of different SUDD metabolic activity was found.

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THE EFFECT OF A LIQUID MULTI-STRAIN PROBIOTIC IN SYMPTOMATIC DIVERTICULAR DISEASE – A RANDOMISED DOUBLE-BLIND CONTROLLED-TRIAL

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Background
Diverticular disease is a significant burden on healthcare systems without standardized treatment. While some patients may benefit from elective surgery, other patients have less acute complaints and/or are poor surgical candidates. Probiotics are a plausible treatment option, as they may alter intestinal bacterial composition and have other local metabolic effects. We hypothesized that a probiotic would reduce abdominal pain in patients with symptomatic diverticular disease.
Methods
We conducted a single-center, randomized, double-blind, placebo-controlled trial of probiotic treatment in adult patients with symptomatic diverticular disease. We randomly assigned 143 patients to receive 1 mL/kg/day of probiotic liquid (72 patients) or placebo (71 patients) daily for 3 months. The primary endpoint was a decrease in abdominal pain. Secondary endpoints included a decrease in the frequency of 9 abdominal symptoms.
Results
143 patients were enrolled and 120 patients completed the trial. Overall, patients initiated treatment with a mean pain score 8.5 +/- 7.4, with a reduction to 6.0 +/- 6.6 following treatment. There was no difference between patients on probiotic and on placebo (P=0.12).
The odds of experiencing constipation at least a few times per week was significantly less for patients on Symprove™ (OR=0.25 [95% CI 0.08-0.79], P=0.02). The odds of reporting frequent diarrhea were also significantly less for patients on Symprove™ (OR 0.33 [95% CI 0.13-0.84], P=0.02).
Conclusions
Multi-strain liquid probiotic did not improve abdominal pain scores, but did significantly decrease the frequency of constipation and diarrhea. Patients with altered bowel habits and diverticular disease may benefit from probiotic treatment.

POSTERS

ASSOCIATION BETWEEN COLONIC DIVERTICULA AND COLORECTAL POLYPS AND CANCER

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Keywords: Diverticula, Colorectal cancer, Polyps, Adenoma, Dysplasia.

Introduction: colonic diverticula and neoplastic colorectal lesions are found in similar ranges of age and populations, but it is unclear whether there is a shared pathway in their development. Their frequency increases with age and seems to be associated with a lack of dietary fibres, increased dietary saturated fats, obesity and a slow colonic transit time. The association of diverticula and colorectal polyps and cancer has been previously evaluated, reporting conflicting results. Despite common epidemiologic predisposing factors, the association between colonic diverticula and colorectal polyps and cancer remains unclear and needs to be better defined, as it could have important implications for the screening of colorectal cancer.

The aim of this study is to evaluate the association between colonic diverticula and colorectal polyps and cancer.

Materials and methods: A one-year prospective study including all consecutive patients undergoing to routine colonoscopy at our GI Unit from September 2014 to September 2015. The presence and location of diverticula, polyps, and cancers was recorded using colonoscopy reports. Types of colorectal neoplastic lesions were defined by histopathological examination. Polyps were classified into adenoma (with low or high dysplasia), hyperplastic or inflammatory polyps. A multiple logistic regression analysis was done to evaluate the association between diverticular disease and colonic lesions.

Results: During the study period 1490 colonoscopies were performed. 447 patients were included (245 M, 202 F, mean age 66 years): 166 (37.1%) patients presented only diverticula, 155 (34.7%) patients presented only polyps, and 126 (28.2%) patients presented both the diseases associated. 14 patients presented colorectal cancer, 5 of which had also diverticula.

There was no significant association between colonic diverticula and adenoma, as well as between diverticula and colorectal cancer. On the other hand, colorectal inflammatory polyps showed a significant association with colonic diverticula.

Conclusions: The results of the study show no association between colonic diverticula and colorectal adenoma nor between diverticula and cancer. Therefore, patients with colonic diverticula do not require a different follow-up for the prevention of colorectal cancer than the general population. Inflammatory polyps are frequently associated to colonic diverticular disease probably due to the same pathogenic factors.

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COMPLICATED DIVERTICULAR DISEASE: OUR EXPERIENCE AND CURRENT MANAGEMENT

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Key words: complicated diverticular disease, Hartmann procedure, outcomes, surgery.
Background: On Literature there is no agreement about treatment of complicated diverticular disease. We analyzed our experience and we compared our results with data from Literature.
Materials and methods: From January 2009 to December 2015 we observed 72 patients (40 male, 32 female) with complicated diverticular disease. Mean age was 72 years (range 51-86). All patients presented bowel perforation. We evaluated patients using Hinchey criteria: 15 patients stage 0, 8 patients stage I, 20 patients stage II, 17 patients stage III and 12 patients stage IV. We performed at stage 0 resection and anastomosis; at stage I resection and anastomosis in 6 cases and resection and anastomosis with ~~"p~~rotection" ileostomy in 2 cases; at stage II resection and anastomosis in 15 cases, resection and anastomosis with ~~"p~~rotection" ileostomy in 4 cases and Hartmann intervention in one case; at stage III resection and anastomosis in 3 cases, resection and anastomosis with ~~"p~~rotection" ileostomy in 6 cases and Hartmann intervention in 8 cases. At stage IV we performed in all cases Hartmann intervention.
Results: 8/72 patients have some complications. After Hartmann intervention we observed complications on 5/21 patients; 3 of them were surgical complications: hernia of stoma in 2 cases, fistula of stoma in one case. Medical complications were respiratory distress and renal failure. After resection and primary anastomosis we observed complication on 3/51 patients (anastomotic dehiscence). Review of Literature didn't shown gold standard on treatment of complicated diverticular disease. In our experience we observed more complications in patients treated with Hartmann intervention.
Conclusion: Correct staging of complicated diverticular disease can determine correct treatment.

PREVALENCE OF COLONIC DIVERTICULOSIS IN PATIENTS AFFECTED BY ULCERATIVE COLITIS: A PROSPECTIVE STUDY

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Key words: colonoscopy, diverticulosis, epidemiology, ulcerative colitis.

Background: Diverticulosis of the colon is an acquired condition that results from herniation of the mucosa and submucosa through defects in the muscular layer [1]. The true prevalence of colonic diverticulosis is difficult to measure because most individuals are asymptomatic. In particularly, in literature, there are few study about the prevalence of colonic diverticulosis in patients affected by ulcerative colitis (UC)[2-4].

Aims: To investigate the prevalence of colonic diverticulosis in UC in an adult population referred to a single centre.

Methods: Computerized data of consecutive patients, referred to our Institution to undergo a colonoscopy for colorectal cancer screening and/or for UC assessment, between January 1, 2009 and December 31, 2009, were retrospectively studied.

Results: Six hundred and five consecutive patients were retrospectively studied. Of these patients, 438 (72.4%) underwent colonoscopy for colorectal cancer screening (Group A) and 167 (27.6%) for UC assessment (Group B). In group A 224 patients (51.1%) were male (average age of 62.7 ± 14.2 SD years, range 35-86 years), in group B 102 (61.1%) were male (average age of 57.6 ± 12.1 SD years, range 25-84 years). Prevalence of colonic diverticulosis was significantly higher in group A (122 patients, 27.8%) than group B (18 patients, 10.8%) ($p<0.0001$, Fisher's exact test). Female gender in patients with colonic diverticulosis was significantly higher in group A than group B (68 patients, 55.7% versus 4 patients, 22.2%, $p=0.0106$, Fisher's exact test). In group A sigma and left colon was involved in 119 (97.6%) patients versus 12 (66.7%) of Group B, with a statistically significant difference ($p=0.0001$, Fisher's exact test), in Group B the right colon was involved in 4 (22.2%) patients versus 1 (0.8%) of Group A, a statistically significant difference ($p=0.0009$, Fisher's exact test).

Conclusions: Results of our study demonstrated that prevalence of colonic diverticulosis was significantly lower in patients with UC than in adult population, emphasizing the relevance of the coexistence of UC and colonic diverticulosis because could make very difficult the clinical management of these patients.

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REDUCING ABDOMINAL SYMPTOMS AND INFLAMMATORY BIOMARKERS IN ACUTE UNCOMPLICATED DIVERTICULITIS

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Key words: Acute Uncomplicated Diverticulitis, probiotics, lactibiane iki, antibiotic, abdominal pain, C-Reactive Protein

INTRODUCTION: Diverticular Disease (DD) is the most frequent abnormality in the digestive tract mainly in developed countries.Most of people suffering from DD are asymptomatic, while 20% experience abdominal symptoms and eventually complications, episodes of diverticulitis or bleeding.
Acute Uncomplicated Diverticulitis (AUD) is defined as the inflammation of a colon diverticulum. Conventional treatment of AUD includes antibiotic therapy, usually Ciprofloxacin and Metronidazole, fasting and fluid therapy.
Although several studies have been performed aimed at evaluating the clinical efficacy of probiotics in AUD, no definitive results have been achieved yet.
Aim of our pilot study is to test the efficacy of *Bifidobacterium Lactis LA 304, Lactobacillus Salivarius LA 302, Lactobacillus Acidophilus LA 201* (Lactibiane IKI®, Biocure), in association with conventional antibiotics in treating AUD compared to conventional antibiotic therapy.
PATIENTS AND METHODS: We enrolled 20 (7M/13F mean age 61,5 +- 11,5 years) consecutive patients who came to the Emergency Department of Foundation Policlinico A. Gemelli Hospital with a diagnosis of AUD. All patients performed routine blood test, dosage of C-Reactive Protein value and they were then randomly divided into two groups:
Group A (10 patients, 2M/8F mean age 59,7 +- 10,3 years) was treated with ciprofloxacin 400mg twice a day and metronidazole 500mg three times a day for one week, with a supplementation of Lactibiane IKI® twice a day for 10 days; Group B (10 patients, 5M/5F mean age 62,6 +- 10,4 years) was treated with ciprofloxacin 400mg twice a day and metronidazole 500mg three times a day for one week.
All patients filled a daily Visual Analog Scale (VAS) for abdominal pain, with a range value from 0 (asymptomatic) to 10, and C-RP value was determined on admission and at discharge. Primary outcome of the study is the reduction of abdominal pain and inflammatory markers (C-RP) in the group treated with Lactibiane IKI® supplementation.
RESULTS: All patients completed the study. No side effect were observed.
As regards the VAS values, we have found that the improvement between day 1 and day 10 for group A has an average of -7.8, compared to -7.0 observed in group B (p=0.45) (-97% vs -86%). The VAS difference between days 1 and 5, is of -6.9 for group A, compared to -5. for group B, with a statistical significance (p = 0.004) (-87% vs -63%). Finally, the difference between days 1 and 3 is also significant (p = 0.011), with a reduction of pain of -4.5 in Group A, against -2.8 in group B (-56% vs -35%).
Regarding C-RP value, the difference between the admittance value and the demission value was -56.1 in patients treated with lactibiane iki compared to -15.5 in the control group, (p = 0.0086).
CONCLUSION: Our pilot study showed that the supplementation with Lactibiane IKI® in the standard AUD therapy significantly reduce abdominal pain and inflammatory markers compared to control group. These interesting results could be due to its anti-inflammatory activity, already well documented in the IBD therapy. Larger studies are needed to validate its use in the clinical practice.

AGE, BMI AND SEVERITY OF ACUTE DIVERTICULITIS: MYTHS OR FACTS?

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KEY WORDS: Modified Hinchey's classification, complicated acute diverticulitis, BMI, retrospective study.

INTRODUCTION: Although it is commonly believed that patients presenting with severe acute diverticulitis are more often obese and elderly, only few evidences are reported in literature about these clinical observations[1,2]. In this study, we tried to determine if body mass index (BMI) and old age are associated with a higher incidence of complicated acute diverticulitis.
MATERIAL AND METHODS: A retrospective review of patients hospitalized with acute diverticulitis between 2013 and 2015 was conducted. Severity of Acute Diverticulitis was graded in according to modified Hinchey's classification[3]. The mean BMI and mean age for each group of patients were calculated. Statistical analysis was performed by one way anova test with significance set at $p < 0.05$.
RESULTS: Charts of 90 patients hospitalized with acute diverticulitis were reviewed. Five groups were identified: 32 patients (36%) were admitted with Hinchey's stage Ia; 21 (23%) with stage Ib; 20 (22%) with stage II; 12 (13%) with stage III and 5 (6%) with stage IV. Mean BMI and mean age were respectively: 25,45 Kg/m^2 (range 40,40-19,10) and 58ys (range 35-87) in group 1; 26,78 Kg/m^2 (range 3,33-20,23) and 58ys (range 34-83) in group 2; 26,14 Kg/m^2 (range 30,48-22,73) and 63ys (range 49-83) in group 3; 26,68 Kg/m^2 (range 34,28-21,25) and 58ys (range 38-87) in group 4; 24,44 Kg/m^2 (range 28,3-18,13) and 66ys (range 26-90) in group 5. There was no significant difference among these groups by either age ($p = 0.762$) or BMI ($p = 0.334$).
DISCUSSION: Numerous studies have shown a correlation between acute diverticulitis and obesity, particularly in people of advanced age[4]. This retrospective study was undertaken to identify a possible link between BMI, age and complicated acute diverticulitis. No significant differences were recognized, among the groups with different grades of acute diverticulitis, in terms of BMI and age. Despite this result, the aetiological relationship between obesity, old age and diverticular complications still remain unclear.

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EVALUATION OF NUTRITIONAL STATUS IN PATIENTS WITH SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE VERSUS

PATIENTS WITH IRRITABLE BOWEL SYNDROME

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KEYWORDS: nutritional status, diverticulosis,uncomplicated diverticular disease, irritable bowel syndrome.

INTRODUCTION: Symptomatic uncomplicated diverticular disease (SUDD) and Irritable Bowel Syndrome (IBS) can lead to different food habits, which could produce different nutritional conditions.[1-2] IBS With Diarrhea (IBS-D) patients are reported to self restrict their diet more than the other subgroups, maybe because usually these patients are more symptomatic.[3] Our aim was to study the nutritional status of patients affected by IBS versus SUDD patients' one.
MATERIALS AND METHODS: Between November 2015 and January 2016, 46 outpatients were enrolled. Nineteen of them (4 males, 15 females), aged between 37 and 84 (mean age 64.6), were diagnosed with Symptomatic Uncomplicated Diverticular Disease (SUDD) (17 DICA I, 2 DICA II)[4,5]. The other 27 patients (5 males, 22 females) aged between 18 and 61 (mean age 37), were diagnosed with IBS according to the Rome III criteria[6] (IBS-D 12, IBS-C 4, IBS- U 2, IBS-M 9). For each patient anthropometric indices (height, weight, BMI, waist circumference) were measured, plus abdominal pain and bloating grade were evaluated via visual analogic scale (VAS).
RESULTS: Mean BMI and waist circumference of patients affected by SUDD are higher than the IBS patients' ones (25,34 vs 22,29 p=0,009; 94,55 cm vs 73,5 cm, p=0,0000001). Differently, mean VAS pain of IBS patients is higher than the SUDD patients' one (7,8 mm vs 1,5 mm, p=0,00000000001). We found no significant difference between mean VAS bloating scores of the two groups. Comparing IBS-D to SUDD patients, we found that mean BMI and waist circumference of SUDD patients are higher than IBS-D ones (25,34 vs 21,97, p=0,01; 94,55 cm vs 76,04 cm, p=0,00004), mean VAS pain of IBS D patients is higher the SUDD patients' one (7,58 mm vs 1,5 mm, p=0,0000007) and the difference between the VAS bloating scores of the two groups is not significative. All data analysis was performed with T Student Test.
CONCLUSION: Patients with SUDD appear to have higher BMI and waist circumference, maybe because of a low-symptomatic disease, or because they tend to exclude only fiber from their diet. The IBS-D vs SUDD analysis related results are less significant than the IBS vs SUDD ones, contrarily to what we expected. Probably this result is due to the low number of the examined group. It would be advisable to extend and continue this study, in order to elaborate some criteria to provide these patients some proper diet suggestions.

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DIVERTICULITIS (HINCHEY III). RESULTS OF 9 YEARS OF EXPERIENCE

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Key words: complicated diverticulitis, laparoscopy, outcomes, surgery.

Introduction: surgical treatment of acute diverticulitis complicated (ADC) is debated. In a recent study (1) of 1046 patients admitted with ADC with a median folow-up of 10 years, 23 % underwent emergency surgery; 27% of whom underwent a colostomy with or without resection, 33% had surgical complications, 4.5% mortality. Another study suggests that the minimally invasive procedure (peritoneal lavage and drainage of the abdominal cavity) has good results in short and long term (2).

Materials and methods : in the present study we considered 200 patients hospitalized in the surgical Department of the hospital in Legnago (Verona, Italy) from 2007 to 2015 with diagnosis of acute diverticulitis. 140 patients (70%) were treated conservatively and 60 (30%) underwent surgery. All cases were approached with laparoscopy. In 48 cases (80%) with Hinchey III we performed a laparoscopic peritoneal lavage, 12 (20%) with a Hinchey IV had an open Hartmann resection. The patients were followed-up.

Results: of 48 patients subjected to laparoscopic peritoneal lavage in 2 procedure (4%) was necessary a re-intervention (Hartmann resection) for fluid collections with peritonitis respecttively after 10 and 15 days since the first procedure.

The mean hospital stay after laparoscopic peritoneal lavage was 6 days (range 4-9) and, in the case of resection 20 days.

Patients undergoing laparoscopic peritoneal lavage were followed in follow up with mean of 60 months (range 2-90): 6 cases (12%) underwent an elective resection: 3 for recurrent episodes of acute diverticulitis not responsive to medical therapy and 3 for stenosis of the sigma. Laparoscopic peritoneal lavage in ADC with Hinchey III was successful in 96% of cases.

Conclusions : Laparoscopic peritoneal lavage in ADC is a valid, safe procedure with a good out-come in the short term, solving cases with Hinchey III in 96% of cases, decreasing postoperative complications. This procedure was failure in only in 4% of cases and was neccessary a reintervention.

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BUDESONIDE FOR THE TREATMENT OF SEGMENTAL COLITIS ASSOCIATED WITH DIVERTICULOSIS (SCAD): PRELIMINARY EXPERIENCE.

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Key Words: budesonide; follow-up; segmental colitis associated with diverticulosis; treatment

Background: Drugs currently used in the treatment of complicated diverticular disease do not always have specific indication for those patients, and are therefore used as "off label". The endoscopic classification DICA (Diverticular Inflammation and Complication Assessment) has recently developed for patients suffering from diverticulosis and diverticular disease [1]. This classification seems to be useful to identify subclass of patients to treat with specific treatments [2].
Aims: To define whether budesonide may be effective in treating segmental colitis associated with diverticulosis (SCAD) with DICA 3 score.
Material and Methods: We enrolled 20 patients (12 F, 8M, mean age 68.5 yrs, range 55-70 yrs) suffering from SCAD. Patients took mesalazine 2.4 g/day plus rifaximin 1.2 g/day or ciprofloxacin 1 g/day for 7 days/month. They suffered from abdominal pain with bloody diarrhea, and showed leukocytosis and significant increasing of ESR, CRP and fecal calprotectin. Diagnosis was posed according to endoscopic [1,3] and histological [3] criteria. All patients were treated with budesonide 9 mg/day for 1 month, followed by 6 mg/day for 7 days/month for 1 year.
Results: All symptoms disappeared except for diarrhea withn 7 days, diarrhea disappeared with 2 weeks; leukocytosis was normal within 2 weeks, and ESR, CRP and fecal calprotectin fell normal within 40 days. During the follow-up, only 2 patients (10%) showed recurrence of symptoms, and were successfully retreated with the same therapeutic regimen of the induction. No significant adverse events were recorded during the follow-up.
Conclusions: SCAD may be considered as a IBD-like inflammation occurring in the colon harbouring diverticula [4]. This permits to use successfully also drugs specifically designed for the treatment of IBD. In this way, this preliminary experience confirms that the treatment of budesonide may be a therapeutic option for the treatment of SCAD too.

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MESALAZINE FOR TREATMENT OF SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE OF THE COLON AND FOR PRIMARY PREVENTION OF DIVERTICULITIS: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS

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Key words: Controlled trials - Diverticular disease – Diverticulitis – Mesalazine -Systematic review

Background: Symptomatic Uncomplicated Diverticular disease (SUDD) is a common gastrointestinal disease, since it affects about one fourth of patient harboring colonic diverticula. Mesalazine has been proposed for the treatment of this disease, but no clear data are currently available.

Aims: To assess the effectiveness of mesalazine in improving symptoms (namely abdominal pain) and in preventing diverticulitis occurrence in patients with SUDD.

Methods: Only randomized clinical trials (RCTs) (irrespective of language, blinding, or publication status), which compared mesalazine with placebo or any other therapy in SUDD, were evaluated. The selected end points were symptom relief and diverticulitis occurrence at maximal follow-up. Absolute Risk Reduction (ARR, with 95% CIs) and the Number Needed to Treat (NNT) were used as measure of the therapeutic effect.

Results: Six RCTs enrolled 1021 patients: 526 patients were treated with mesalazine and 495 with placebo or other therapies. Symptom relief (evaluated in all the studies) with mesalazine was always larger compared to placebo and other therapies. However, ARR was significant only when mesalazine was compared with placebo (30.4, C.I.s 19.4-41.3), high-fiber diet (18.5 %, C.I.s 7.23-29.76) and low-dose rifaximin (23.4 %, C.I.s 14.9-31.8). The incidence of diverticulitis (reported by 4 trials) with mesalazine was lower than that observed with placebo and other treatments, being significant only when compared with placebo (ARR 12 %, C.I.s 2.9-21.0).

Conclusions: Mesalazine is effective in achieving symptom relief and primary prevention of diverticulitis in patients with SUDD.

NUTRITIONAL RISK SCREENING (NRS2002) SYSTEM IN HOSPITALIZED PATIENTS WITH ACUTE DIVERTICULAR DISEASE IN A MEDICINE DEPARTMENT: IMPLEMENTATION OF A LARGE SCALE

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Key Words: Nutritional Risk Security (NRS2002) System; acute diverticular disease; nutritional treatment; hospitalization.

Background: The Nutritional Risk Security (NRS2002) System [1] is recommended for hospitalized patients in order to assess their nutritional status. However, studies assessing large scale systematic screening policies are lacking.
Aims: The aim of this study, which was endorsed by Italian Ministry of Health, was to assess the feasibility of implementing a screening strategy concerning all admissions for diverticular disease of the colon in the Department of Medicine of a Tertiary Hospital.
Material and Methods: All patients suffering from diverticular disease, and admitted to the Medicine Department from 1 January to 31 December 2015, were pre-screened by NRS2002 System by the nursing staff of the Nutritional team at the day of the admission. If the pre-screening was positive, the patients were referred to a supplementary assessment performed by a dietician.
Results: The global number of admission in our Institution was 18,377 patients: 4,667 patients were admitted to the Medicine Department, and 133 suffered from acute diverticular disease. The NRS2002 was applied to all of them. A positive pre-screening test was recorded in 97 (72,9%) patients, and all of those patients underwent to a dietician and nutrition team assessment. A NRS>3 score, describing a severe impaired nutritional status, was found in 61 patients (62,9%). All 97 patients with a NRS2002 positive screening received initial nutritional support by oral supplements (17 patients, 17,52%) or enteral nutrition (22 patients, 22,68%) or Total Parenteral Nutrition (58 patients, 59,8%).
The mean lenght in hospital stay for all 133 patients usually was 6,9 day. However, the lenght in hospital stay was significantly longer for patients with a positive NRS2002, with a mean of 18 days (p=0.01)
Conclusions: A large number of hospitalized patients due to acute diverticular disease are at nutritional risk and have a significant longer stay. Although systematic screening by the nursing staff seems feasible, dietitian complementary evaluation and management is still advised.

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