THE THERAPEUTIC MANAGEMENT IN COLONIC DIVERTICULAR DISEASE - A REVIEW

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ABSTRACT:
INTRODUCTION. THE DIVERTICULAR DISEASE REPRESENTS A COMMON PATHOLOGY IN DEVELOPED OR DEVELOPING COUNTRIES. FOR ABOUT 80% OF PATIENTS THE DISEASE IS ASYMPTOMATIC (DIVERTICULOSIS), 20% DEVELOPING NON-SPECIFIC DIGESTIVE SYMPTOMS (UNCOMPLICATED SYMPTOMATIC DIVERTICULAR DISEASE) OR CMPLICATIONS, SUCH AS ACUTE DIVERTICULITIS.
MATERIAL AND METHOD. THE AIM OF THE RESEARCH IS TO PRESENT THE THERAPEUTICAL APPROACH IN COLONIC DIVERTICULOSIS, UNCOMPLICATED SYMPTOMATIC DIVERTICULAR DISEASE AND ACUTE DIVERTICULITIS, A REVIEW OF THE RECENT MEDICAL LITERATURE BEING MADE TO SUPPORT THE INFORMATION PROVIDED.
RESULTS. THE DATA AVAILABLE FROM THE LAST 10 YEARS REGARDING THE SUBJECT HAVE BEEN ANALYZED. OVER THE PAST 5 YEARS 6 DIFFERENT THERAPEUTIC GUIDELINES FOR THE COLONIC DIVERTICULAR DISEASE HAVE BEEN REGISTERED. THERE ARE NO CLEAR INDICATIONS REGARDING THE MEDICAL TREATMENT IN ASYMPTOMATIC COLONIC DIVERTICULOSIS, THE INDICATIONS BEING ALSO LIMITED IN THE CASE OF LOWERING THE RISK OF DIVERTICULOSIS BY INCREASING THE FIBER INTAKE. THERE IS NOT YET A THERAPEUTIC STANDARD IN ASYMPTOMATIC DIVERTICULAR DISEASE, VARIOUS THERAPEUTIC STRATEGIES WITH FIBERS, PROBIOTICS, RIFAXIMIN OR MESALAZINE BEING TAKEN INTO CONSIDERATION. AN AGREEMENT HAS BEEN REACHED IN THE TREATMENT OF THE ACUTE DIVERTICULITIS, THE LATEST GUIDELINES DEMONSTRATING THE FACT THAT ANTIBIOTICS CAN BE ADMINISTERED ONLY IN CAREFULLY SELECTED CASES, AVOIDING THEIR ROUTINE USE. THE RESULTS OF THE VARIOUS STUDIES REGARDING THE PRIMARY OR SECONDARY PROPHYLAXIS IN ACUTE DIVERTICULITIS AND THE EFFICACY OF RIFAXIMIN OR MESALAZINE ARE HETEROGENOUS.
CONCLUSIONS. THE THERAPEUTIC MANAGEMENT IN COLONIC DIVERTICULOSIS AND IN UNCOMPLICATED SYMPTOMATIC DIVERTICULAR DISEASE, AS WELL AS THE PRIMARY AND SECONDARY PROPHYLAXIS STRATEGIES REPRESENT REAL CHALLENGES OF THE DAILY MEDICAL PRACTICE.

KEY WORDS: ACUTE DIVERTICULITIS, DIVERTICULOSIS, UNCOMPLICATED SYMPTOMATIC DIVERTICULAR DISEASE, THERAPEUTIC MANAGEMENT, SURGERY

INTRODUCTION

The frecquency of the colonic diverticulosis in Western Europe is high, affecting about 50-66% of people ≥ 80 years of age. Thus, diverticulosis represents a common pathology, taking into consideration the increasing life expectancy and the aging of the general population. Recent studies have demonstrated that colonic diverticulosis is the most common non-neoplastic pathology incidentally discovered during screening colonoscopy[11].

Among the patients with colonic diverticulosis, approximately 15-25% develop acute diverticulitis, a recent study reporting a percentage of less than 4%. From a semiological point of view, the symptoms are similar to the irritable bowel syndrome, with the difference that the abdominal pain in diverticular disease persists over 24 hours. For 15% of the patients with acute diverticulitis, complications such as abscess, fistula, perforation, peritonitis, or intestinal obstruction occur. The recurrence of diverticulitis after a first episode was estimated at 15-30%.

[11] Shahedi K, Fuller G, Bolus R, et al. *Longterm risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy*. Clin Gastroenterol Hepatol 2013; 11: 1609–1613

Thus, the colonic diverticular disease represents a challenge in daily medical practice, having an important impact upon the health system[12].

The spectrum of the diverticular pathology is broad, covering various clinical scenarios through symptomatology, severity and prognosis. The pathogenesis of chronic symptomatology associated with uncomplicated disease is not completely known, the chronic inflammation secondary to the bacterial-induced immune response being the possible cause of the symptoms. Recent studies demonstrate the fact that in the etiopathogenicity of the diseasethe intestinal microbiome is involved, an idea that expands the therapeutic options, including selective antibiotics, anti-inflammatory drugs and probiotics[13].

The diagnostic protocol for the colonic diverticular disease is well established, but, there are no randomized clinical trials capable to elaborate a standardized therapeutic algorithm, in daily medical practice the treatment usually relying on dogma and less on evidence-based medical principles. The existing therapeutic guidelines are relatively old and based mainly on expert opinions in the field. The scientific community paid attention to the research on the management of acute diverticulitis, diverticulosis and uncomplicated symptomatic diverticular disease being less studied (Table I).

Table I. A comparison between the european and the american approach[14].

	Colonic diverticulosis	Uncomplicated symptomatic diverticular disease	Acute diverticulitis
Andersen et al. (Denmark)	Definition only	Definition only	√
Andeweg et al. (Netherlands)	Definition only		√
Kruis et al. (Germany)	Definition only	Treatment only	√
Pietrzak et al. (Poland)	√	√	√
Cuomo et al. (Italy)	√	√	√
Binda et al. (Italy)	√	√	√
Stollman et al. (USA)	√		√

The purpose of this article is to realize a review of the clinical aspects in diverticular disease, discuss the role of intestinal dysbiosis in the etiopathogenesis of the disease and define the

[12] Strate LL, Modi R, Cohen E, et al. *Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights.* Am J Gastroenterol 2012; 107: 1486–1493. 4

[13] Cianci R, Iacopini F, Petruzziello L, et al. *Involvement of central immunity in uncomplicated diverticular disease.* Scand J Gastroenterol 2009; 44: 108–115; Spiller RC and Sloan TJ. *Do diverticula provide a unique niche for microbiota which can lead to activation of the innate immune system?* Gut 2017; 66: 1175–1176; Barbara G, Scaioli E, Barbaro MR, et al. *Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease.* Gut 2017; 66: 1252–1261; Latella G and Scarpignato C. *Rifaximin in the management of colonic diverticular disease.* Expert Rev Gastroenterol Hepatol 2009; 3: 585–598; Scarpignato C, Bertelé A and Tursi A. *Probiotics for the treatment of symptomatic uncomplicated diverticular disease: rationale and current evidence.* J Clin Gastroenterol 2016; 50(Suppl. 1): S70–S73; Maconi G, Barbara G, Bosetti C, et al. *Treatment of diverticular disease of the colon and prevention of acute diverticulitis: a systematic review.* Dis Colon Rectum 2011; 54: 1326–1338

[14] Carabotti M, Annibale B. Drugs in Context 2018; 7: 212526. DOI: 10.7573/dic.212526

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optimal treatment, analyzing the efficacy and mechanism of action of the currently used therapeutic methods.

MAIN TEXT

MATERIAL AND METHOD

This review is based on recent studies in the field of the diverticular disease. Thomson Reuters Core Collection, Pubmed and Scopus databases were used to search for data published in English this year on the treatment of diverticulosis, uncomplicated asymptomatic diverticular disease or acute diverticulitis and the primary prophylaxis of the latter, including the surgical treatment.

RESULTS

1. Colonic diverticulosis

The colonic diverticulosis represents an incidental finding in asymptomatic patients during routine gastrointestinal evaluations or for another indication. Above 50 years of age, colonic diverticulosis is commonly diagnosed during screening colonoscopy for colorectal cancer (2).

The indication of treatment in asymptomatic patients with colonic diverticulosis represents a medical dilemma, recent studies on pharmacological or surgical treatment suggesting that there is no reason to initiate treatment or monitor asymptomatic patients with colonic diverticulosis[15]. Regarding the special diet, there are not enough indications to support increased fiber intake in order to reduce the risk of colonic diverticulosis[16].

2. Uncomplicated symptomatic diverticular disease

The uncomplicated symptomatic diverticular disease representsa clinical condition of „gray zone"characterized by chronic digestive symptoms as recurrent abdominal pain, abdominal distension and altered bowel transit secondary to the presence of the diverticula. The clinical picture is similar to that of the irritable bowel syndrome, the semiological features that differentiate the uncomplicated symptomatic diverticular colonic disease being represented by:

- Pain located predominantly in the left iliac fossa;
- Abdominal pain persisting over 24 hours;
- Frequent diarrhea;
- No remission of the symptoms after flatulence or defecation.

The main objective in the management of uncomplicated symptomatic diverticular disease is represented by the control of the abdominal symptomatology. No therapeutic standard was established, however, optimal pharmacological and nutritional strategies for the management of the uncomplicated symptomatic diverticular disease were described.

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[15] Pietrzak A, Bartnik W, Szczepkowski M, Krokowicz P, Dziki A, Reguła J, Wallner G. *Polish interdisciplinary consensus on diagnostics and treatment of colonic diverticulosis.* Pol Przegl Chir. 2015;87:203–20. http://dx.doi.org/10.1515/pjs-2015-0045; Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, Casetti T, Colecchia A, Festi D, Fiocca R, Laghi A, Maconi G, Nascimbeni R, Scarpignato C, Villanacci V, Annibale B. *Italian consensus conference for colonic diverticulosis and diverticular disease.* United European Gastroenterol J. 2014;2:413–42. http://dx.doi.org/10.1177/2050640614547068

[16] Andersen JC, Bundgaard L, Elbrønd H, Laurberg S, Walker LR, Støvring J; Danish Surgical Society. *Danish national guidelines for treatment of diverticular disease.* Dan Med J. 2012;59:C4453. PubMed PMID: 22549495

The colonic diverticular disease is a complex, multifactorial medical condition, the intestinal microbiota having an important role in its etiopathogenesis. Data from the literature shows a depletion of the intestinal flora with antiinflammatory properties, such as Clostridium cluster IV, Clostridium cluster IX, Fusobacterium and Lactobacillaceae, in patients with diverticular disease, these floral changes being associated with immune mucosal activation. Based on this information, therapeutic strategies targeted at the intestinal microbiota have been developed: administration of dietary fiber, probiotics or Rifaximin[17].

a. Fibers

The therapeutic effect of the fibers is not fully known, although their administration through diet or supplements is encouraged in order to control the symptomatology of uncomplicated diverticular disease.

The beneficial effect of the fibers can be explained by their properties:

- Increase the residue mass, stimulating intestinal transit;
- It acts as prebiotic in the colon by favoring the proliferation of the sanogenic species of the intestinal flora: bifidobacteria and lactobacilli.

The intestinal flora changes rapidly with the diet.

However, there is no evidence of the therapeutic benefits of fiber-rich diet in the therapeutic control of the diverticular disease.

Based on the data provided by the medical literature, the therapeutic guidelines in Denmark and Poland support the effectiveness of fiber dietary supplements, the italian researchers estimating the effect of fiber supplements as controversial in the therapeutic treatment of uncomplicated symptomatic diverticular disease[18].

b. Probiotics

The probiotics can alter the balance of the intestinal flora, having a positive effect through their anti-inflammatory properties and by maintaining adequate bacterial colonization in the digestive tract, inhibiting bacterial overgrowth and etiopathogenic mechanisms. Recent studies support the effectiveness of probiotics, however, given the design of these studies, the validity is

[17] Spiller RC. *Changing views on diverticular disease: impact of aging, obesity, diet, and microbiota.* Neurogastroenterol Motil. 2015;27:305–12. http://dx.doi.org/10.1111/nmo.12526

[18] Pietrzak A, Bartnik W, Szczepkowski M, Krokowicz P, Dziki A, Reguła J, Wallner G. *Polish interdisciplinary consensus on diagnostics and treatment of colonic diverticulosis.* Pol Przegl Chir. 2015;87:203–20. http://dx.doi.org/10.1515/pjs-2015-0045; Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, Casetti T, Colecchia A, Festi D, Fiocca R, Laghi A, Maconi G, Nascimbeni R, Scarpignato C, Villanacci V, Annibale B. *Italian consensus conference for colonic diverticulosis and diverticular disease.* United European Gastroenterol J. 2014;2:413–42. http://dx.doi.org/10.1177/2050640614547068; Andersen JC, Bundgaard L, Elbrønd H, Laurberg S, Walker LR, Støvring J; Danish Surgical Society. *Danish national guidelines for treatment of diverticular disease.* Dan Med J. 2012;59:C4453. PubMed PMID: 22549495; Spiller RC. *Changing views on diverticular disease: impact of aging, obesity, diet, and microbiota.* Neurogastroenterol Motil. 2015;27:305–12. http://dx.doi.org/10.1111/nmo.12526; Binda GA, Cuomo R, Laghi A, Nascimbeni R, Serventi A, Bellini D, Gervaz P, Annibale B; Italian Society of Colon and Rectal Surgery. *Practice parameters for the treatment of colonic diverticular disease: Italian Society of Colon and Rectal Surgery (SICCR) guidelines.* Tech Coloproctol. 2015;19:615–26. http://dx.doi.org/10.1007/s10151-015-1370-x

limited so that no final conclusions can be drawn. Most international therapeutic guidelines do not recommend the use of probiotics, given the insufficient data provided by literature[19].

c. Rifaximin

Rifaximin is a low resorbable antibiotic (high concentrations in faeces) used for the treatment of various gastrointestinal disorders (eg, acute bacterial diarrhea syndrome, portal-hypertensive encephalopathy) with a broad spectrum of action.

Taking into account the pharmacological properties, Rifaximin is indicated for the treatment of uncomplicated symptomatic diverticular disease[20]:

- Inhibits the bacterial growth;
- Increases the resistance to bacterial infections;
- Modulates different bacterial species (Lactobacillus spp and Bifidobacterium spp), leading to an eubiotic effect;
- Controls the bacterial metabolism;
- Presents anti-inflammatory activity.

A metaanalysis study reported that 64% of patients treated with Rifaximin and fiber supplements presented no symptoms at one year of follow-up compared to 36% of patients receiving only fiber supplements[21].

Recent studies support the efficacy of cyclically administered Rifaximin in conmbination with fiber dietary supplements in remission of symptomatology and reduction of disease severity. However, randomized placebo-controlled trials are required to establish the therapeutic dose, the mode of administration (continuous or cyclic) and its efficacy alone or in combination with probiotics.

d. Mesalazine

Mesalazine, or 5-aminosalicylic acid, is an anti-inflammatory agent especially used as a first-line therapy in patients with inflammatory bowel disease (ulcero-hemorrhagic rectocolitis or Crohn's disease).

The anti-inflammatory effect of Mesalazine is not completely understood, the possible mechanisms involved being represented by[22]:

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[19] Lahner E, Bellisario C, Hassan C, Zullo A, Esposito G, Annibale B. *Probiotics in the treatment of diverticular disease: a systematic review.* J Gastrointestin Liver Dis. 2016;25:79–86. http://dx.doi.org/10.15403/jgld.2014.1121.251.srw

[20] Descombe JJ, Dubourg D, Picard M, Palazzini E. *Pharmacokinetic study of rifaximin after oral administration in healthy volunteers.* Int J Clin Pharmacol Res. 1994;14:51–6. PubMed PMID: 7836025

[21] Bianchi M, Festa V, Moretti A, Ciaco A, Mangone M, Tornatore V, Dezi A, Luchetti R, De Pascalis B, Papi C, Koch M. *Metaanalysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease.* Aliment Pharmacol Ther. 2011;33:902–10. http://dx.doi.org/10.1111/j.1365-2036.2011.04606.x

[22] Desreumaux P, Ghosh S. *Review article: mode of action and delivery of 5-aminosalicylic acid – new evidence.* Aliment Pharmacol Ther. 2006;Suppl1:2–9. http://dx.doi.org/10.1111/j.1365-2036.2006.03069.x; Andrews CN, Griffiths TA, Kaufman J, Vergnolle N, Surette MG, Rioux KP. *Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome.* Aliment Pharmacol Ther. 2011;34:374–83. http://dx.doi.org/10.1111/j.1365-2036.2011.04732.x; Barbara G, Cremon C, Barbaro MR, Bellacosa L, Stanghellini V. *Treatment of diverticular disease with aminosalicylates: the evidence.* J Clin Gastroenterol. 2016;Suppl1:S60–3. http://dx.doi.org/10.1097/MCG.0000000000000611

• Reducing the synthesis of prostaglandins and proinflammatory cytokines;
• Inhibition of neutrophil chemotactism and activation of the transcriptional nuclear factor kB (responsible for the production of proinflammatory cytokines);
• Activating nuclear receptors that down-regulate inflammation;
• Changing luminal pH, favoring the proliferation of beneficial bacterial species.

Mesalazine is used in the treatment of uncomplicated symptomatic diverticular disease for its anti-inflammatory effect. The search in the databases listed in the subchapter "Material and Method" revealed only two double-blind and case-control studies that analyzed the effectiveness of Mesalazine in the treatment of the first episode of the disease and in maintaining clinical remission. These studies demonstrated a symptom recurrence rate of 0% in Mesalazine and probiotic patients, 13.7% in Mesalazine, 14.5% in probiotic-only patients, and 46% in the placebo group[23].

Although the studies show positive results regarding the effectiveness of Mesalazine, the data related to the optimal dose, treatment modalities (cyclic or continuous) or initial results are heterogeneous, so valid conclusions can not be drawn. These discrepancies lead to a lack of uniformity in the recommendations of the various therapeutic guidelines. Thus, German guidelines support the efficacy of Mesalazine as the only form of treatment in uncomplicated symptomatic diverticular colonic disorder, while Italian guidelines do not consider Mesalazine as a valid therapeutic option in the management of this pathology. Complex randomized trials are needed to determine whether Mesalazine is an effective therapeutic method and, if so, what is the optimal regimen of administration.

3. Acute diverticulitis

a. Pharmacologic management

Acute diverticulitis involves inflammation of the colon diverticula and, in certain situations, of pericolic structures. Patients with acute diverticulitis have localized pain in the left lower abdominal quadrant, fever and leukocytosis, alteration of intestinal transit, nausea, vomiting, urinary symptoms and high serum levels of inflammatory markers. Abdomino-pelvic computer tomography should be considered as a first-line investigation method, taking into account its high sensitivity and specificity in assessing uncomplicated and complicated forms of the disease. This imaging technique allows quantification of the degree of severity based on the Hinchey modified classification (Table II).

[23] Kruis W, Meier E, Schumacher M, Mickisch O, Greinwald R, Mueller R; German SAG-20 Study Group. *Randomised clinical trial: mesalazine (Salofalk granules) for uncomplicated diverticular disease of the colon – a placebo-controlled study.* Aliment Pharmacol Ther. 2013;37:680–90. http://dx.doi.org/10.1111/apt.12248; Tursi A, Brandimarte G, Elisei W, Picchio M, Forti G, Pianese G, Rodino S, D'Amico T, Sacca N, Portincasa P, Capezzuto E, Lattanzio R, Spadaccini A, Fiorella S, Polimeni F, Polimeni N, Stoppino V, Stoppino G, Giorgetti GM, Aiello F, Danese S. *Randomised clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease—a double-blind, randomised, placebo-controlled study.* Aliment Pharmacol Ther. 2013;38:741–51. http://dx.doi.org/10.1111/apt.12463

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Table II. Hinchey classifications: initial and modified.

Hinchey classification	Modified Hinchey classification
	0. Uncomplicated symptomatic diverticular disease
I. Pericolic abscess or phlegmona	I a. Pericolic inflammatory process
	I b. Pericolic abscess
II.Pelvic, intraabdominal or retroperitoneal abscess	II. Pelvic, intraabdominal or retroperitoneal abscess
III.Generalized purulent peritonitis	III. Generalized purulent peritonitis
IV. Generalized fecaloid peritonitis	IV. Fecaloid peritonitis

Abdominal ultrasound performed by an experienced imagist is a sensitive and specific diagnostic technique in acute diverticulitis, yet computed tomography has a better sensitivity than abdominal ultrasound. Recent studies propose a diagnostic protocol in acute diverticulitis by which computed tomography is indicated only after a negative or uncertain abdominal ultrasound examination[24].

Most episodes of acute diverticulitis evolve without complications, 15% developing complications such as abscesses, fistulas, obstructions or perforations. The rate of recurrence of the acute diverticulitis is between 15 and 30%, however, the first episode generally presents the highest degree of severity. Thus, according to data from a retrospective study, in a follow-up period of 9 years, the rate of recurrence of acute diverticulitis was 13.3%, approximately 4% developing a second recurrence. In this study, non-operative management was performed in 80% of the cases, emergency colectomy being performed in 20% of the patients[25].

Smoking, sedentary and poor diet in fibers are risk factors for the occurence of acute diverticulitis[26].

Until 10 years ago, antibiotics were considered as mandatory therapeutic agents in the management of acute diverticulitis, even in mild forms, based on the idea that diverticulitis is the consequence of obstruction of a diverticulum, secondary mucosal abrasion, microperforation and

[24] Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, Casetti T, Colecchia A, Festi D, Fiocca R, Laghi A, Maconi G, Nascimbeni R, Scarpignato C, Villanacci V, Annibale B. *Italian consensus conference for colonic diverticulosis and diverticular disease.* United European Gastroenterol J. 2014;2:413–42. http://dx.doi.org/10.1177/2050640614547068; Andersen JC, Bundgaard L, Elbrønd H, Laurberg S, Walker LR, Støvring J; Danish Surgical Society. *Danish national guidelines for treatment of diverticular disease.* Dan Med J. 2012;59:C4453. PubMed PMID: 22549495; Spiller RC. *Changing views on diverticular disease: impact of aging, obesity, diet, and microbiota.* Neurogastroenterol Motil. 2015;27:305–12. http://dx.doi.org/10.1111/nmo.12526; Binda GA, Cuomo R, Laghi A, Nascimbeni R, Serventi A, Bellini D, Gervaz P, Annibale B; Italian Society of Colon and Rectal Surgery. *Practice parameters for the treatment of colonic diverticular disease: Italian Society of Colon and Rectal Surgery (SICCR) guidelines.* Tech Coloproctol. 2015;19:615–26. http://dx.doi.org/10.1007/s10151-015-1370-x

[25] Broderick-Villa G, Burchette RJ, Collins JC, Abbas MA, Haigh PI. *Hospitalization for acute diverticulitis does not mandate routine elective colectomy.* Arch Surg. 2005;140:576–81. http://dx.doi.org/10.1001/archsurg.140.6.576

[26] Strate LL. *Lifestyle factors and the course of diverticular disease.* Dig Dis. 2012;30:35–45. http://dx.doi.org/10.1159/000335707

bacterial translocation[27]. This etiopathogenic concept has been replaced by a recent hypothesis which points out that acute diverticulitis is an inflammatory, not infectious pathology. Randomized, prospective, case-control and retrospective studies have shown no benefit of using antibiotics in the treatment of uncomplicated acute diverticulitis, suggesting that the use of antibiotics should be strictly limited to complicated cases[28].

A Cochrane review evaluated the effectiveness of antibiotic therapy in cases of uncomplicated acute diverticulitis, with results supporting recommendations from recent European and American guidelines to individualise the indication of the antibiotic therapy. Thus, administering antibiotics to patients with uncomplicated acute diverticulitis may be indicated for patients with sepsis or severe infections, or those with severe concomitant disease or immunosuppression[29].

The need for hospitalization is a topic discussed in recent studies, the results of these studies revealing a high degree of safety and efficacy of the ambulatory treatment in acute uncomplicated diverticulitis[30].

The management of complicated acute diverticulitis depends on the severity and complexity of the disease stage, hospitalization, food rest, and surgery being, in some cases, a necessity. The broad spectrum antibiotic therapy indicated in the management of acute complicated diverticulitis includes: Ciprofloxacin (500mg twice daily per os or 200mg twice daily intravenously) in combination with Metronidazole (250-500mg 3 times per day or 500 mg 3 times daily intravenously); Amoxicillin - Clavulanic acid (650mg-1g twice daily per bone or 1, 2, 3, 4-times daily intravenously). Clindamycin or Metronidazole may also be used in combination with Trimethoprim / Sulfamethoxazole or Gentamicin[31]. Patients with complicated forms of acute diverticulitis without surgical indication require hospitalization, hydroelectrolytic rebalancing and administration of an antibiotic effective on aerobic and anaerobic bacteria[32].

b. Surgical management

The therapeutic algorithm in the management of the acute diverticulitis is shown in figure 1.

[27] Jacobs DO. Diverticulitis. N Engl J Med. 2007;357:2057–66. http://dx.doi.org/10.1056/NEJMcp073228

[28] Rezapour M, Ali S, Stollman N. *Diverticular disease: an update on pathogenesis and management.* Gut Liver. 2017 May 12. http://dx.doi.org/10.5009/gnl16552

[29] Shabanzadeh DM, Wille-Jørgensen P. *Antibiotics for uncomplicated diverticulitis.* Cochrane Database Syst Rev. 2012;11:CD009092. http://dx.doi.org/10.1002/14651858.CD009092.pub2

[30] Sartelli et al. *WSES Guidelines for the management of acute left sided colonic diverticulitis in the emergency setting.* World Journal of Emergency Surgery (2016) 11:37. DOI 10.1186/s13017-016-0095-0

[31] Pietrzak A, Bartnik W, Szczepkowski M, Krokowicz P, Dziki A, Reguła J, Wallner G. *Polish interdisciplinary consensus on diagnostics and treatment of colonic diverticulosis.* Pol Przegl Chir. 2015;87:203–20. http://dx.doi.org/10.1515/pjs-2015-0045

[32] Binda GA, Cuomo R, Laghi A, Nascimbeni R, Serventi A, Bellini D, Gervaz P, Annibale B; Italian Society of Colon and Rectal Surgery. *Practice parameters for the treatment of colonic diverticular disease: Italian Society of Colon and Rectal Surgery (SICCR) guidelines.* Tech Coloproctol. 2015;19:615–26. http://dx.doi.org/10.1007/s10151-015-1370-x

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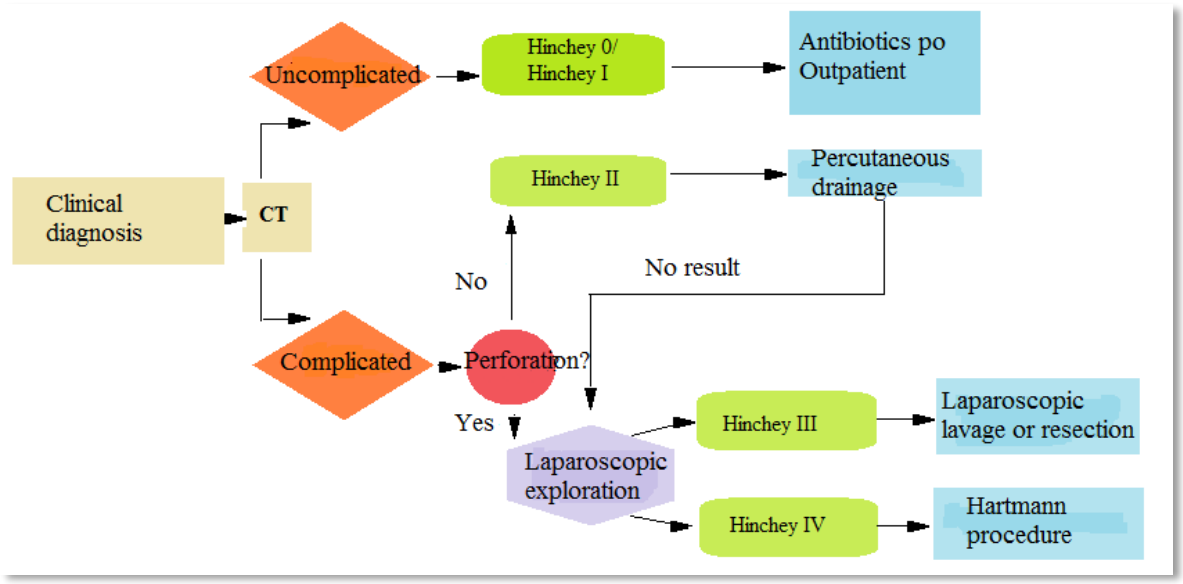

Figure 1. The therapeutic algorithm in the management of the acute diverticulitis (adapted from Sartelli et al.[33]).

Laparoscopic peritoneal lavage, especially in patients with acute diverticulitis Hinchey III, is a controversial topic of study, considering the patient's favorable response, low recurrence rates, however, associating a high risk of peritoneal abscess formation.

As it can be seen from Figure 1, for patients with acute diverticulitis complicated by pericolic abscess or inflammation (Hinchey II), the percutaneous peritoneal drainage or the laparoscopic lavage and drainage are indicated. If clinical and imaging data support a Hinchey III stage (generalized purulent peritonitis), laparoscopic lavage and peritoneal drainage with or without resection of the affected colon can be chosen. For patients with colonic perforation and faecal peritonitis, the Hartmann surgical procedure is indicated,through which the affected colon is resected and a temporary colostoma is made; after complete remission of the inflammatory process the stoma can be reintegrated into digestive transit through a second surgical operation[34].

Immunosuppression predisposes to early appearance of complications, which requires colon elective resection after a first inflammatory episode as an optimal method of treatment for this category of patients.

Primary prevention strategies in acute diverticulitis

A higher intake of dietary fiber associates a lower risk of diverticular disease. Data from the literature suggest that Rifaximin, taken together with dietary fiber, reduces the risk of diverticulitis (primary prevention) in patients with uncomplicated symptomatic diverticular

[33] Sartelli et al. *WSES Guidelines for the management of acute left sided colonic diverticulitis in the emergency setting.* World Journal of Emergency Surgery (2016) 11:37. DOI 10.1186/s13017-016-0095-0
[34] Sartelli et al. *WSES Guidelines for the management of acute left sided colonic diverticulitis in the emergency setting.* World Journal of Emergency Surgery (2016) 11:37. DOI 10.1186/s13017-016-0095-0

disease. There is no clear information on the effect of Mesalazine in the primary prevention of acute diverticulitis.

Secondary prevention strategies for acute diverticulitis

Rifaximin seems to reduce the risk of recurrence of acute diverticulitis as recommended by European guidelines, but American guides suggest avoiding it. Studies on this subject have methodological limits and heterogenity of dosing or administration, so there are no clear data, requiring randomized case-control studies in order to determine the real benefit of Rifaximin in the secondary prevention of acute diverticulitis. The effect of Mesalazine on the risk of recurrence of acute diverticulitis is uncertain, according to a Cochrane review. There is a discrepancy in the therapeutic recommendations of international guidelines, some of which promoting the use of Mesalazine for secondary prevention, others avoiding the use of Mesalazine in this context[35].

There are some rare location for diverticular disease, like appendicular or cecal[36].

DISCUSSION

According to the results of recent studies, food fibers, probiotics, Rifaximin and Mesalazine represent therapeutic agents with a possible beneficial effect on the evolution of the diverticular colonic disease. Multiple therapeutic guidelines have been developed over the last 5 years, with uneven and varying recommendations.

There is no consensus regarding the therapeutic management of colonic diverticulosis or uncomplicated symptomatic diverticular disease. The therapeutic algorithm for acute diverticulitis with ot without complicationsis clearly outlined.

This review of the literature suggests the need to develop randomized case-control clinical trials to analyze optimal therapeutic methods depending on the clinical status of the patient (symptomatic or asymptomatic, with or without a history of acute diverticulitis).

CONCLUSION

- In order to be able to identify the optimal therapeutic strategy for each patient, a careful assessment of this is required based on clinical, laboratory and imaging data.
- Localized pain in the left iliac fossil and reactive C-reactive protein (PCR) ≥50mg / l are suggestive for the diagnosis of acute diverticulitis.
- Abdomino-pelvic computed tomography has high sensitivity and specificity and allows assessment of the severity of acute diverticulitis, thus organizing the therapeutic plan.
- Abdominal ultrasound represents an effective imaging alternative for the initial assessment of patients with suspected acute diverticulitis. It is an accessible method and can provide good results (highsensitivity and specificity) when performed by an experienced radiologis. For patients with suspected acute diverticulitis, performing abdominal and pelvic computed

[35] Carter F, Alsayb M, Marshall JK, Yuan Y. *Mesalamine (5-ASA) for the prevention of recurrent diverticulitis.* Cochrane Database Syst Rev. 2017;10:CD009839. http://dx.doi.org/10.1002/14651858.CD009839.pub2

[36] Constantin, Vlad D., Carâp, Alexandru, Nica, Anca A., Smaranda, Alexandru, Socea, Bogdan. *Appendiceal diverticulitis - A case report.* Chirurgia, 2017, 112(1): 82-84; Socea, Bogdan, Nica, Anca A., Smaranda, Cristian A., Carâp, Alexandru C., Socea, Laura I., Dimitriu, Mihai, Bratu, Ovidiu G., Moculescu, Cezar E., Bertești eanu, Șerban V.G., Constantin, Vlad D. *Solitary cecum diverticulitis – a surprising diagnosis.* Arch Balk Med Union, 2017, 52(4): 467-470

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tomography only after an inconclusive or negative echographic result is a safe and effective approach.

- Immunosuppression may increase the rate of complications in patients with acute diverticulitis, elective colonic resection after a first episode of acute diverticulitis being indicated for immunocompromised patients.
- Antibiotherapy can be avoided in immunocompromised patients with uncomplicated diverticulitis and without systemic inflammatory manifestations.
- For patients requiring antibiotic therapy, per os administration may be approached.
- Outpatient therapeutic management is indicated for patients with uncomplicated acute diverticulitis without comorbidities. These patients should be clinically monitored and re-evaluated within 7 days to estimate the extent of remission of the inflammatory process. Reassessment may be performed on an interval less than 7 days if the general condition of the patient is impaired.
- Patients with minimal fluid or gaseous accumulation have indication for antibiotic therapy.
- Patients with diverticular abscesses <4-5 cm can be treated conservatively (antibiotic therapy only).
- Patients with large abscesses over 4-5 cm have indication for percutaneous drainage combined with antibiotic therapy. For cases where percutaneous drainage is not a feasible or accessible method, depending on the clinical condition of patients, conservative treatment (antibiotic therapy) can be tried, clinico-paraclinic monitoring being mandatory.
- For patients with conservatively treated diverticular abscesses, colonoscopic evaluation is required at 4-6 weeks.
- For patients with uncomplicated acute diverticulitis (CT scan) no colonoscopic reassessment is required.
- Patients aged ≥ 50 years should be included in colorectal cancer screening programs.
- Patients with diffuse pneumoperitoneum revealed by computer tomography images, without diffuse fluid collection, can be treated conservatively after careful selection of the cases. There is, however, a high risk of failure of treatment, thus requiring surgery. Clinical and imaging monitoring (repeat computed tomography depending on the clinical and paraclinical evolution of the patient) is mandatory.
- If there is no response to conservative treatment in patients with diffuse pneumoperitoneum and without intraperitoneal fluid collection, colon resection with anastomosis or colostoma, or Hartmann resection, depending on the clinical condition and comorbidities, is indicated.
- Laparoscopic lavage and peritoneal drainage should not be applied to patients with generalized peritonitis.
- Hartmann resection is indicated for the management of complicated cases of diffuse peritonitis, critically ill patients or with multiple comorbidities. For clinically stable patients without co-morbidities, primary resection with anastomosis with or without protecting stoma can be performed. Mechanical sutures are safe in diverticular disease[37].

[37] Costea, Dragoş, Carâp, Alexandru C., Socea, Bogdan, Udrişte, Cristian, Moculescu, Cezar E., Ciudin, Alex, Dimitriu, Liliana, Popa, Florian, Constantin, Vlad D. *Mechanical sutures for the surgical treatment of acute diverticulitis.* Arch Balk Med Union, 2013, 48(4): 366-370

- "Damage Control" surgery can be performed in unstable patients (septic shock) with generalized peritonitis secondary to acute perforated diverticulitis.
- Patient-related factors and not the number of previous diverticulitis episodes are the elements that should be taken into account when planning elective colonic resection in patients previously treated conservatively.
- After a conservatively treated episode, elective colonic resection is indicated for patients in the high-risk group, such as those immunocompromised.
- Colonoscopy can produce an iatrogenic perforation in acute diverticulitis that could be hardly recognized[38].
- After surgerical intervention, it is advisable to continue antibiotic therapy for a period of 4-6 days.

[38] Socea, Bogdan, Carâp, Alexandru, Smaranda, Alexandru, Moculescu, Cezar, Bobic, Simona, Dimitriu, Mihai, Socea, Laura, Constantin, Vlad D. *Delayed recognition of a sigmoid colon iatrogenic lesion following total abdominal hysterectomy in a patient with a previous episode of acute diverticulitis.* Proceedings of the 13th National Congres of Urogynecology, Urogyn 2016: 62-65

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