

REVIEW

New trends in the management of diverticulitis and colonic diverticular disease

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ABSTRACT

Colonic diverticular disease is a chronic disorder presenting with a variety of abdominal symptoms and recurrent episodes of acute diverticulitis. It is close linked to age so its prevalence has risen notably during the last decades in western countries, increasing costs related to medical attention. Recently, several works have provided evidence to a series of measures that could improve the outcomes as well as reduce expenses associated to this process.

The aim of the present review is to expose a view of the new trends in the management of diverticulitis and colonic diverticular disease, based on the highest clinical evidence available.

Key words: Primary anastomosis. Colonic diverticular disease. Acute diverticulitis. Laparoscopic peritoneal lavage. Routine colonic evaluation.

ABBREVIATIONS

AD: Acute diverticulitis; C-AD: Complicated acute diverticulitis; CT-scan: Computed tomography scan; HP: Hartmann's procedure; NPV: Negative predictive value; PPV: Positive predictive value; RCT: Randomized clinical trial; Sn: Sensitivity; Sp: Specificity; UC-AD: Uncomplicated acute diverticulitis.

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INTRODUCTION

Colonic diverticular disease is a chronic entity with a wide variety of abdominal symptoms that eventually may course with recurrent episodes of acute diverticulitis (AD). The prevalence of colonic diverticulosis is not influenced by genre and increases with age. In this sense, the rise of life expectancy explains the accumulation of cases in Western countries. It is estimated that the prevalence of this disease can exceed 60 % in subjects above 80 years old, of which, up to 25 % will suffer at least one episode of AD during their lifetime (1-3). The classic therapeutic algorithm is based on the Hinchey classification, the use of antibiotics and the Hartmann's procedure (HP) during the acute phase; and elective colectomy in recurrent cases (Fig. 1). In contrast, a large number of papers published in the last decade have led to open new horizons in the management of this entity.

The aim of the present review is to expose an overview, based on the highest evidence available, of new trends in the management of diverticulitis and colonic diverticular disease.

MATERIAL AND METHODS

A bibliographic search was conducted using "diverticulitis" as search term in *PubMed.gov* (*NLM*). The search was limited to the last five years (from December 2014) and no other limits were imposed. At first, references not related to colonic diverticulosis, as well as those that offered no modification to the example of classic algorithm (Fig. 1) were excluded. In a second time, we selected works with level of evidence 1 or 2, according to the criteria of the Oxford Centre for the Evidence-Based Medicine (OCEBM) (Table I), and classified them within the different sections of this manuscript. These references formed the core of each section.

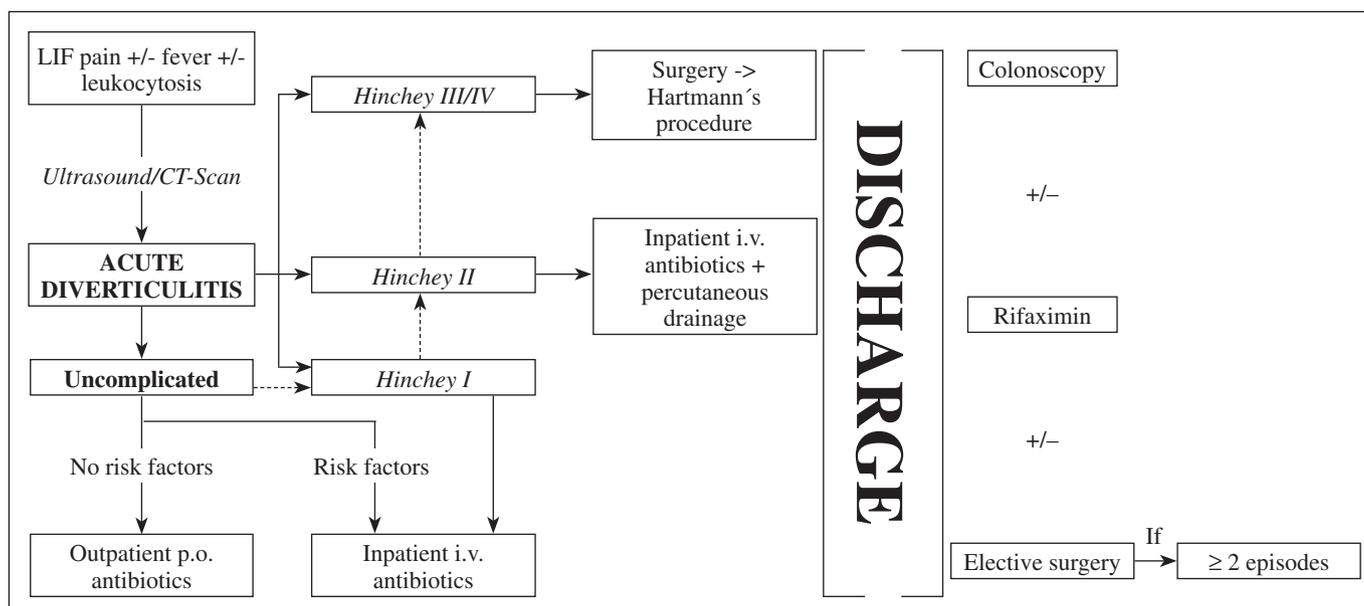


Fig. 1.

Since surgical approach should not influence therapeutic indication and there is plenty of evidence in the literature that laparoscopic surgery in experienced hands is comparable or even superior to open surgery in almost any scenario, the use of laparoscopy was not an objective of the present review.

RESULTS

Bibliographic search diagram is shown in figure 2. In the following paragraphs, the findings and conclusions of papers exposing new trends in the management of AD and colonic diverticular disease are discussed.

Diagnostic scores and severity scales

The diagnosis of diverticulosis can be established by barium enema, colonoscopy or even computed tomography (CT-scan) (4); however, a majority of patients will be diagnosed with diverticular disease during the first episode of AD. In the diagnosis of AD, clinical signs and symptoms play a key role on the suspicion and request of complementary tests. In this regard, AD is a condition with a high rate of clinical misdiagnosis (between 34 % and 68 %) what has motivated the development of at least two diagnostic scores based on clinical parameters (5,6).

Of these, the first one was published in 2010 by Laméris et al. who prospectively analyzed 1,021 patients with abdominal pain, identifying by logistic regression, three items associated with the diagnosis of AD (pain with tenderness in the left lower quadrant, absence of vomiting and

C-reactive protein > 50 mg/dL) (6). Likewise, based on data from the clinical history, physical examination and laboratory tests; Andeweg et al. identified seven variables (age > 50 years, previous episode of AD, increased pain with movement, tenderness in the left lower abdomen, absence of vomiting and C-Reactive protein > 50 mg/dL) from which constructed a diagnostic nomogram. According to these authors, this tool could discriminate up to 86 % of patients with AD, a figure similar to ultrasound (90 %) (5). Both diagnostic scores were externally validated in an independent cohort by Kiewiet et al., obtaining values of sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) as shown below: a) Laméris et al. (6) (PPV: 81 %-100 %; NPV: 47 %-66 %; Sn 24-37 %; Sp: 93 %-100 %); and b) Andaweg et al. (5) (PPV: 89 %-92 %; NPV: 47 %-76 %; Sn: 14-48 %; Sp: 98 %-99 %).

However, commonly used diagnostic radiological imaging presents better diagnostic performance than these clinical tools. To this respect, although ultrasound has demonstrated good (Sn) and (Sp) (92 % and 90 %, respectively), at present, CT-scan shows better values (94 % and 99 %, respectively) and is considered the gold standard for the diagnosis of AD (7,8).

Given the diagnostic performance of such scores, these would be particularly useful when they are positive. Their authors argue that the use of these scores might reduce the number of complementary tests requested for AD. However, from our point of view, shared by other authors (9), is precisely in patients with positive test in whom radiological imaging would be more useful since it could determine the severity of the AD, an essential factor in the therapeutic approach.

Table I. Levels of evidence and grades of recommendation of the OCEBM (March 2009)

<i>Levels of evidence OCEBM (March 2009)</i>		
1a	Therapy	SR (with homogeneity) of RCTs
	Diagnosis	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers
1b	Therapy	Individual RCT (with narrow Confidence Interval)
	Diagnosis	Validating cohort study with good reference standards; or CDR tested within one clinical center
1c	Therapy	All or none (the same result in all or none cases)
	Diagnosis	Absolute SpPins (diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis) and SnNouts (diagnostic finding whose sensitivity is so high that a positive result rules-out the diagnosis)
2a	Therapy	SR (with homogeneity) of cohort studies
	Diagnosis	SR (with homogeneity) of level > 2 diagnostic studies
2b	Therapy	Individual cohort study (including low quality RCT; e.g., < 80 % follow-up)
	Diagnosis	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases
2c	Therapy	"Outcomes" research; ecological studies
	Diagnosis	
3a	Therapy	SR (with homogeneity) of case-control studies
	Diagnosis	SR (with homogeneity) of 3b and better studies
3b	Therapy	Individual case-control study
	Diagnosis	Non-consecutive study; or without consistently applied reference standards
4	Therapy	Case-series (and poor quality cohort and case-control studies)
	Diagnosis	Case-control study, poor or non-independent reference standard
5	Therapy	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Diagnosis	
<i>Grades of recommendation</i>		
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies	
C	Level 4 studies or extrapolations from level 2 or 3 studies	
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	

CDR: Clinical decision rule; RCT: Randomized clinical trial; SR: Systematic review. *Adapted from "Levels of Evidence 1" Oxford Centre for Evidence-Based Medicine (OCEBM), Levels of Evidence Working Group (March 2009) (www.cebm.net).

Finally, it has been proposed several alternatives to the Hinchey classification (10), some of which might even be useful to select patients candidates for outpatient treatment (11). Nonetheless, to date, this scale described for the first time in 1978 (12), subsequently modified by Wasvary et al. in 1999 (13), and adapted to the findings of CT-scan in recent years (4) continues to be the most widely used.

Uncomplicated acute diverticulitis: Antibiotic therapy and outpatient treatment

Traditionally, treatment of uncomplicated AD (UC-AD) has been based on intravenous antibiotics and digestive rest. However, in recent years, various authors have considered the possibility of manage this condition through treatment with oral antibiotic and liquid diet from the beginning (14-20).

Biondo et al. (18) conducted a randomized clinical trial (RCT) in which 132 patients diagnosed with UC-AD received the same scheme of oral or intravenous antibiotic. After 60 days of follow-up, no difference in quality of life or rate of treatment failure (4.5 % vs. 6.1 %, respectively) was observed. In contrast, the average cost of inpatient treatment was 1,124 € higher than in the ambulatory group. These results are consistent, both in terms of safety and effectiveness (14,15,17,19,21), as well as efficiency (14,15,21), with other lower evidence studies previously published.

Unlu et al. (17) reached the same conclusion after a retrospective analysis of 312 patients with a median follow-up of 48 months. These authors highlight the importance of a rigorous analgesic control, since according to their findings; the main reason of hospital readmission is the persistence of pain without other type of complication. The results of these and other studies have been grouped

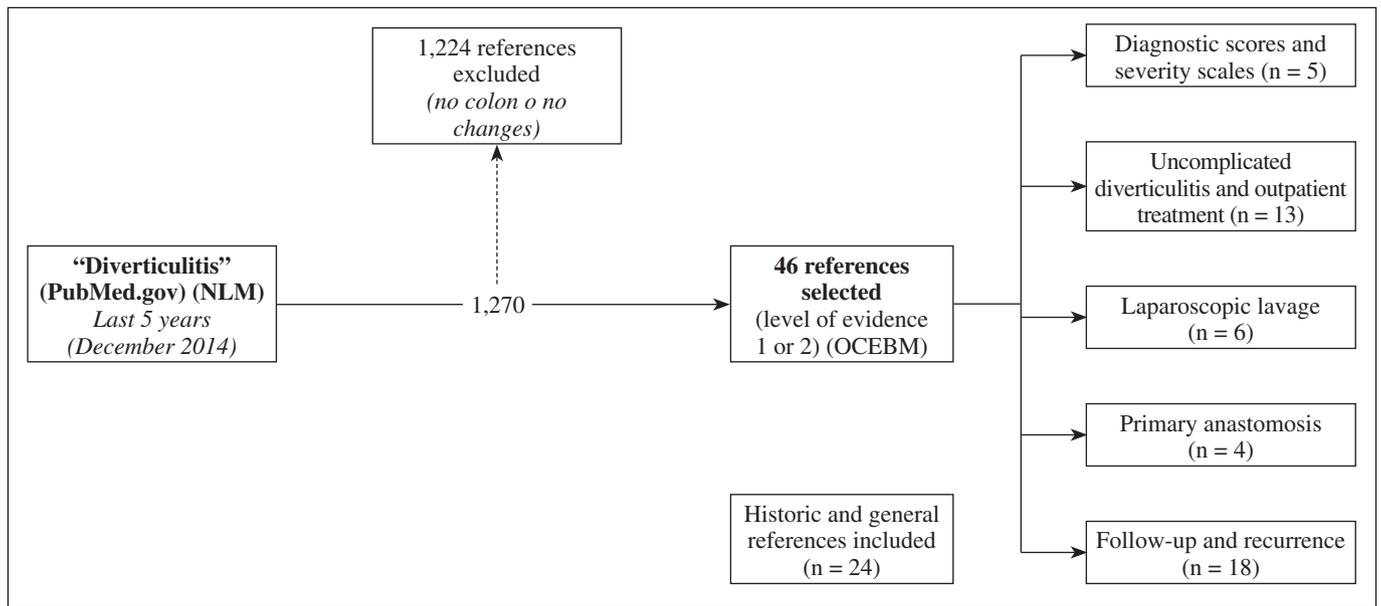


Fig. 2.

and analyzed in a systematic review that reported up to 97 % of success with outpatient treatment for UC-AD (22).

Another new trend in the management of UC-AD questions the need for antibiotic administration. Several publications have suggested this therapeutic approach (23-25). To date, the highest evidence to this respect has been published by Chabok et al. (26). These authors conducted a RCT involving 623 patients with UC-AD treated with or without antibiotic, concluding that there were no significant differences regarding complications of the inflammatory process (1 % vs. 1.9 %), recurrence (15.8 % vs. 16.2 %), need for resection (1.6 % vs. 2.3 %) and hospital stay (2.9 vs. 2.9 days), after one year of follow-up. Nevertheless, the rate of complication in the group without antibiotic could double that of those patients who were treated with antimicrobials (1.9 % vs. 1 %) (26). The sample size necessary to discriminate this difference as statistically significant is estimated on 5,000 patients approximately, hardly attainable in an RCT of these characteristics. Additionally, the clinical significance of that difference might not support the routine use of antibiotics in this scenario.

It should be highlighted that the success of these measures, which could reduce the healthcare costs associated with the process up to 60 % (21), is strongly influenced by the selection of patients. The majority of works considered as factors of exclusion for outpatient treatment or antibiotics-free: Renal or cardiac failure, diabetes mellitus, immunosuppression states or the absence of almost immediate response to the first dose of analgesic and antibiotic.

In brief, it could be concluded that outpatient treatment of UC-AD may be safe and effective in selected patients. However, further studies are necessary before leaving the routinary use of antibiotics in this entity.

Peritoneal laparoscopic lavage

The treatment of complicated AD (C-AD) has evolved over the years. Currently, there is consensus that C-AD Hinchey I should be initially treated with intravenous antibiotic, while Hinchey II can be managed safely and successfully by percutaneous drainage in those centers with availability (27-29). The controversy is generated in cases with Hinchey II and large abscesses or not accessible percutaneously, and Hinchey III/IV. In C-AD Hinchey IV almost all authors agree on the need to resect the affected colon, inflamed and perforated. However, regarding the surgical technique, some surgeons defend the creation of primary anastomosis and others of HP, discussion that will be objective in the next section.

In the remaining cases, i.e. C-AD Hinchey II with gas or inaccessible percutaneously and Hinchey III, several authors have proposed the laparoscopic lavage and drainage from the peritoneal cavity as an alternative to the HP, even in elderly patients (30).

The introduction of this strategy, which was first published in 1996 (31), is the result of numerous studies. In this regard, a systematic review that analyzed the outcomes of several studies on the use of peritoneal lavage in C-AD (321 patients from two prospective studies, nine retrospective and several case series) was published in 2010. The authors concluded that this strategy could control the systemic and abdominal sepsis in 95.7 % of cases, associating a morbidity and mortality of 10.4 % and 1.7 %, respectively (32). Furthermore, only 1.7 % of patients required a colostomy. In their results, the authors also expose that laparoscopic peritoneal lavage should not be considered in C-AD Hinchey IV, since up to half of these patients treated

by peritoneal lavage and drainage presented residual pelvic abscesses.

These results led to design two RCTs which are still in development: a) *Ladies trial* (33), a multicenter RCT that compares the laparoscopic lavage *versus* the resection plus primary anastomosis or HP in C-AD Hinchey III and IV, respectively; and b) the *DILALA trial* (34), a RCT focused on comparing the laparoscopic lavage *versus* the HP.

Preliminary results of the latter (*DILALA trial*), after analyzing 83 patients, suggest that laparoscopic lavage is short term safe and feasible in C-AD Hinchey III; resulting in less surgical time and shorter hospital and resuscitation stays, without differences in terms of morbidity and mortality with respect to the HP (35). In the same line, the authors of "Ladies trial" have published one of the retrospective studies on peritoneal lavage with best sample size and design (36). In this work, after reviewing 38 patients with C-AD Hinchey II with free gas or Hinchey III, these authors report that laparoscopic peritoneal lavage may control abdominal septic focus after one intervention in 79 % of cases, and after a reoperation in 92.1 %. Mortality rate associated with this strategy is 5.2 %. In addition, a logistic regression analysis revealed that the presence of co-morbidities, very high levels of C-reactive protein and high scores in the Mannheim scale of peritonitis are predictive factors of failure of this therapeutic approach (36).

In summary, peritoneal lavage and laparoscopic drainage, with the advantages inherent to a minimally invasive approach, could diminish the number of urgent laparotomies, bowel resections and stomas; therefore reducing the morbidity associated with the treatment of the urgent episode of C-AD Hinchey II/III. However, the final results of the RCTs currently ongoing are necessary for this approach to be generalized on daily practice.

Primary anastomosis in urgent surgery

Laparoscopic peritoneal lavage may be an alternative in cases of C-AD Hinchey III; however, other authors advocate by resection of the affected segment in both C-AD Hinchey III and IV. Traditionally, this scenario led invariably to HP; however, during the last years, several works have proposed as an alternative the realization of primary anastomosis with or without diversion stoma (37). In this regard, although some authors have published relatively low rates of postoperative complications without the use of diversion ileostomy (24 %-84 %), these works present significant selection bias by including patients with low surgical risk and C-AD Hinchey II/III (38-41). Thus, the current trend is to associate diversion ileostomy in cases in which primary anastomosis is performed.

In this line, several retrospective studies published in recent years have pointed out that primary anastomosis plus diversion ileostomy may have similar outcomes to HP in terms of overall morbidity and mortality (37,38,42,43).

In 2012, Oberkofler et al. presented the results of a RCT in which 62 patients with C-AD Hinchey III/IV were randomized to receive colon resection with primary anastomosis and diversion ileostomy, or HP (44). The analysis took into account the urgent procedure, the elective surgery for closure of stoma, and the global care process. When only the urgent intervention was considered, no difference between the two approaches was found in any variable (operative time, blood loss and number of transfusions, stay in ICU, hospital stay, complications, mortality and costs of the process). Conversely, when only the intervention for reversing the stoma was analyzed, the group presenting loop ileostomy (primary anastomosis) was favored with less surgical time (183 vs. 73 minutes), less hospital stay (9 vs. 6 days) and a lower rate of serious complications (3 vs. 0). Likewise, 90 % of the patients with ileostomy underwent surgery for reversing the stoma compared to 56 % in the group with colostomy. Finally, when evaluated both interventions together, only significant differences in operative time and overall number of complications, in favor of the group with primary anastomosis and diversion ileostomy were observed.

In view of these results, it cannot be firmly concluded that the realization of primary anastomosis with diversion stoma be superior to the HP; however, this strategy should be taken into account at least in selected cases of young patients with high probabilities of reversing the stoma.

Monitoring and prevention of recurrence

Most of the current clinical guidelines recommended to do a routine colonoscopy six weeks after a first episode of AD, due to the possible existence of an underlying malignant disease. Nonetheless, the more and more frequent use of high resolution CT-scan in the diagnosis of the acute episode and the results of several series that have evaluated the incidence of cancer in these patients (45-48) have led to some clinical guidelines no longer recommend this attitude (4).

Of those studies that have addressed this issue (45-54), the review with the largest number of patients has been published by Sharma et al. (55). These authors, after the analysis of 11 studies involving patients diagnosed of AD by CT-scan with subsequent colonoscopy (five retrospective studies and prospective the remaining; a total of 1,970 patients) estimated that globally these patients presented: a) underlying carcinoma in 1.6 % (CI 95: 0.9 %-2.8 %) cases; and b) non-malignant polyps in 16.5 % (CI 95: 11.2 %-23.8 %). When the analysis was subdivided into UC-AD and C-AD, the proportion of cancer in the group without complication decreased to 0.7 % (CI 95: 0.3 %-1.4 %), rising to 10.8 % (CI 95: 5.2 %-21 %) in the case of C-AD. These figures, inherently low for patients who suffered UC-AD, become still less relevant when compared with data from a meta-analysis involving 68,324 patients of a screening program for colon cancer in asymptomatic subjects without risk fac-

tors (56). In this latest work, the proportion of cancer was estimated at 0.78 % (CI 95: 0.13 %-2.97 %) and at 19 % (CI 95: 15 %-23 %) for non-malignant polyps. This comparison allowed Sharma et al. conclude what previously pointed out by other studies (45-54): In the absence of other signs or clinical symptoms of cancer, routine colonoscopy may not be necessary in patients who suffered from UC-AD diagnosed by CT-scan. These patients could simply be included in screening programs for colorectal cancer. Nevertheless, Choi et al., after a retrospective study with 149 patients, warn that patients older than 50 years perhaps should be taken in particular consideration by a possible increased risk of advanced neoplasia (57).

On the other hand, from the 25 % of patients who are suffering symptomatic diverticular disease, between 7 % and 45 % of them will suffer recurrent episodes of AD. To this respect, special efforts are made to study measures for preventing recurrence of AD as well as improving chronic symptoms. To date, lifestyle measures (fiber intake, interruption of smoking, regular physical activity, and weight loss) and non-absorbable antibiotics as rifaximin have been proposed as possible effective measures on the reduction of the number of episodes of AD (4). Recently, based on the pathophysiological similarities that might share diverticular disease and inflammatory bowel disease, administration of other agents such as mesalamine, sodium butyrate, or probiotics have opened new horizons in the therapy of diverticular disease of the colon.

Regarding mesalamine, still in 2002, an Italian group published that long-term treatment associating this to rifaximin was superior to rifaximin alone improving chronic symptoms and decreasing the number of acute episodes (58). More recently, the results of the DIVA trial, a RCT that evaluated the effect of mesalamine ± probiotics for twelve weeks after a first episode of AD, have been published (59). Although none of these two schemes was superior to placebo in terms of rate of recurrence, a slight effect on chronic symptoms was observed. Similarly, the recent results of the phase III RCTs PREVENT1 (n = 590) and

PREVENT2 (n = 592) conclude that mesalamine is not superior to placebo preventing the recurrence of AD (60).

Another molecule that due to its anti-inflammatory role and ability to regulate the intestinal microenvironment may decrease the episodes of AD is sodium butyrate. According to a RCT, the administration of this short-chain fatty acid on a daily basis for twelve months could reduce significantly the number of episodes of AD (31.8 % vs. 6.7 %) and improve chronic symptoms (61).

Finally, the axiom that recommended elective surgery for resection after two episodes of AD is to date controversial, even in cases of C-AD (62). In 2006, the American Society of Colon and Rectal Surgeons stated that this indication should be made on a case-by-case basis and not taking into account only the number of episodes of AD (63). Other current clinical guidelines have adopted this trend (4), which is based on several facts: a) Elective surgery may present severe complications (64); b) the majority of patients with C-AD will do so in the first episode (64-66); c) only 5.5 % of patients with recurrent AD will require urgent surgery since the risk of perforation appears to decrease in this scenario (67); and d) even after resection, some patients will continue presenting discomfort and episodes of AD (65). On the contrary, patients with severe chronic symptoms or those with comorbid conditions such as chronic renal failure, collagenopathies or immunosuppression of any origin would constitute a group that could benefit from early elective surgery (4,68). Regarding elective surgery, current guidelines recommend to perform the most economic resection possible (63), which should extend at least to the proximal rectum in order to minimize the probability of postoperative recurrent AD (69,70).

DISCUSSION

In view of the evidence in favor of the new trends in the management of AD and diverticular disease of the colon (Table II), we are witnessing a gradual change

Table II. New trends with evidence

Measure	L.E., G.R.*	Type and number of studies [§]
Routine colonoscopy, only in cases of complicated diverticulitis or suspicious of cancer	1 a, A	3 SR, 5 RS
Outpatient treatment for uncomplicated acute diverticulitis	1 b, A	1 SR, 2 RCT, 3 RS
Treatment without antibiotics for uncomplicated acute episode	1 b, B	1 RCT, 1 RS
Laparoscopic peritoneal lavage for Hinchey II with gas or III	1 b, B	1 SR, 1 RCT, 2 RS
Resection with primary anastomosis and diversion ileostomy in Hinchey III/IV	1 b, B	1 RCT, 2 RS
Mesalamine may have a mild beneficial effect on chronic symptoms	1 b, B	1 RCT
Sodium butyrate may reduce the number of acute episodes and the intensity of chronic symptoms	2 b, B	1 RCT

RCT: Randomized clinical trial; RS: Retrospective study; SR: Systematic review. *Levels of Evidence (L.E.) and Grades of Recommendation (G.R.) according to "Levels of Evidence 1" Oxford Centre for Evidence-Based Medicine (OCEBM), Levels of Evidence Working Group (March 2009) (www.cebm.net). [§]Number of studies in the last five years.

in the diagnostic-therapeutic algorithm of this pathology, which may be modified with the inclusion of these measures in the near future (Fig. 3). Nevertheless, this evidence in the majority of cases is based on only one

RCT; therefore, new studies in the coming years must confirm the usefulness of these measures until they can be applied safely and efficiently in daily clinical practice.

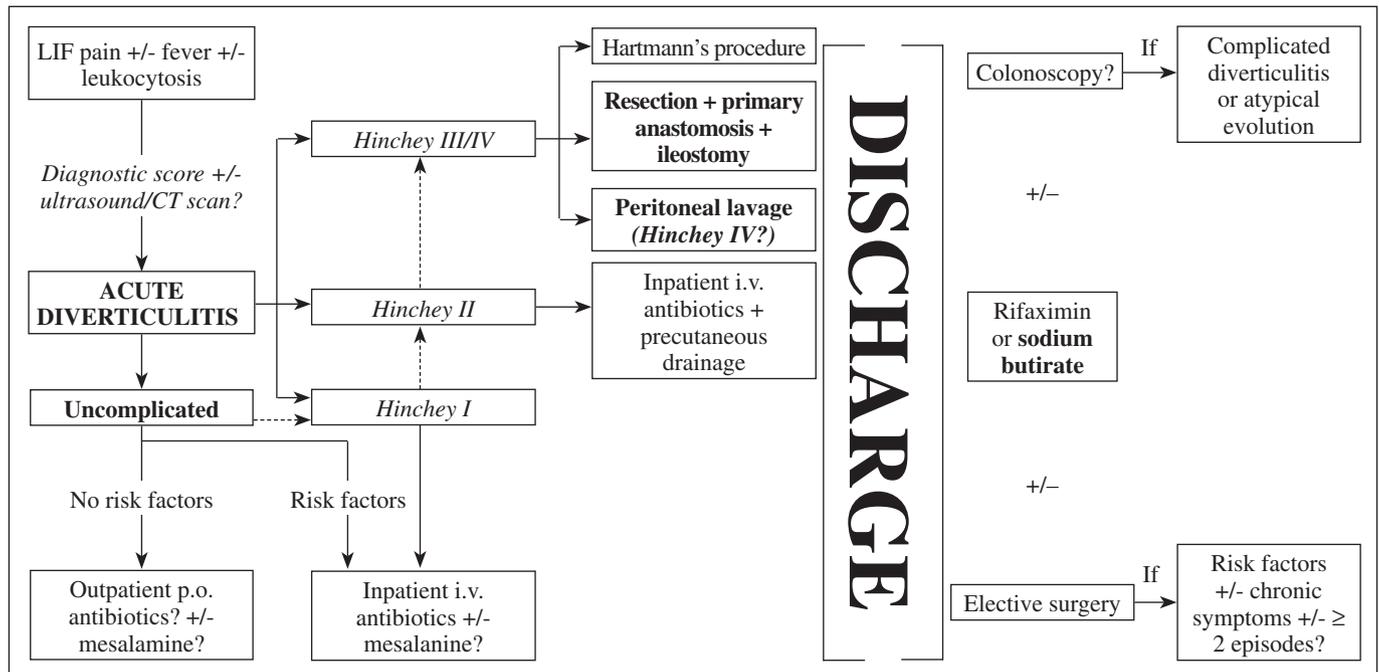


Fig. 3.

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