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REVIEW

Inflammation management in acute diverticulitis: current perspectives

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Abstract: The pathogenesis of diverticular disease and acute diverticulitis is still unclear and many different hypotheses have been formulated. Seemingly, there are several related factors such as chronic inflammation, gut microbiome, obesity and the immunogenic properties of fat tissue and diet. Inflammation plays a pivotal role in diverticular disease and acute diverticulitis. The aim of the present review is to investigate the role of inflammation in diverticular disease as well as in mild and complicated acute diverticulitis with a focus on current research and treatment perspectives.

Keywords: acute diverticulitis, inflammation, diverticular disease.

Introduction

Colonic diverticulosis is an increasingly common condition in the aging western population. Prevalence is as high as 71.4% in those aged over 80 years, with an equal sex distribution and a preferential localization to the left colon, when compared with Asian countries where diverticulosis is typically right sided. The term diverticulosis refers to the presence of diverticula due to the out-pouching of mucosa and muscularis mucosa through the muscularis propria at sites of vascular penetration.[1] Diverticular disease comprehends a large spectrum of manifestations varying from the presence of persistent abdominal symptoms without verifiable inflammation (symptomatic uncomplicated diverticular disease [SUDD]) to a significant and symptomatic inflammatory process (segmental colitis associated with diverticulosis and diverticulitis.[2] According to the latest figures, 1%–4% of patients with diverticulosis progress to diverticulitis. Acute diverticulitis is a serious and potentially life-threatening condition. It can be classified as "mild" or "severe" according to Ambrosetti CT criteria or according to the modified Hinchey classification (Table 1). In ~85% of cases, diverticulitis can be treated conservatively, while a 15% of cases require surgical intervention or percutaneous drainage.[3] It is regarded as the most common cause for colorectal perforation and is associated with a substantial mortality rate during emergency surgery, which is estimated around 10% in Hinchey III and Hinchey IV stage.

The aim of the present review is to provide an overview of the actual knowledge on pathogenesis and treatment of diverticular inflammation in uncomplicated and complicated situations.

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Table 1 Acute diverticulitis classifications

Stage	Description
Modified Hinchey classification	
0	Mild clinical diverticulitis
Ia	Confined pericolic inflammation or phlegmon
Ib	Confined pericolic abscess
II	Pelvic, distant intra-abdominal or retroperitoneal abscess
III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis
Ambrosetti's classification	
Mild	-Wall thickening >5 mm
	-Pericolic fat stranding
Severe	-Abscess
	-Extraluminal air
	-Extraluminal contrast

Pathogenesis of diverticular inflammation

The process leading to diverticulitis was traditionally linked to that causing appendicitis with the diverticulum becoming obstructed by inspissated stool eventually leading to its perforation. Recently, advances in research have shed a new light on this condition shattering the dogma of tradition and suggesting different approaches to its management.

Some authors have demonstrated the presence of chronic low-grade inflammation in the mucosa harboring diverticula in patients who did not suffer from acute diverticulitis.[4] Further studies have confirmed the presence of microscopic colitis on biopsy material in diverticular disease, with the degree of inflammatory infiltration seemingly related to the severity of the condition.[5] Notably, a systematic appraisal of clinical, radiological, laboratory and endoscopic aspects of 50 consecutive cases of diverticulitis found that, in uncomplicated forms, inflammation was mostly confined to the mucosa with no signs of pericolonic disease at CT, much to the detriment of the micro-perforation theory.[6] The consequences of inflammation are muscular hypertrophy and enteric nerve remodeling leading to visceral hypersensitivity and altered motility.[7,8] At molecular level, recent studies have identified increased amounts of matrix metalloproteinases and pro-inflammatory cytokines as well as alterations in neuropeptides and in the serotoninergic signaling pathways.[9–11] Voluptuary habits typically linked to inflammation such as smoking and consuming alcohol have also been associated to this condition. Several studies have demonstrated an augmented incidence of acute diverticulitis in smokers and alcohol consumers.[12] The use of non steroidal anti inflammatory drugs (NSAIDs), such as aspirin, also seems to play a role in the development of acute diverticulitis. A large population study with 22 years of follow-up demonstrated a higher incidence of acute diverticulitis in patients treated with aspirin.[13] This could be due to direct topical injury and/or to impaired prostaglandin synthesis with mucosal impairment and enhanced permeability to toxins and bacteria.

These inflammatory changes could be at the base of the continued symptoms and altered bowel habits that are described following acute attacks in symptomatic uncomplicated diverticular disease (SUDD). In this context, diverticular disease should no longer be considered an asymptotic condition hampered by occasional acute episodes. It should, instead, be considered a form of inflammatory bowel syndrome where a long-term history of chronic inflammation may lead to diverticulitis, first uncomplicated (confined to the bowel wall) and then complicated.

While diverticulosis is more common in the aging population and equally distributed between the two sexes, diverticulitis episodes are seemingly more common in the younger age groups, where the prevalence rate of male patients is more. Obesity, an increased BMI or increased circumference and waist-to-hip ratio are linked to an enhanced risk of developing diverticulitis and its complications;[14] interesting hypothesis were put forward regarding the immunologic role of the fat tissue surrounding the viscera.[15] The role of a reduced dietary fiber intake in both diverticulosis and diverticular disease has been much re-dimensioned. Although the original Painter theory was supported by a few studies, there seems to be a lack of robust favorable evidence and presence of some contradictory reports.[16] Common advice that was given to patients with diverticular disease to consume a low residue diet, and especially to avoid nuts, corn and popcorn in order to prevent diverticula inflammation and bleeding, has also been proved unfounded.[17] Some authors have argued that the type of fiber more than the amount itself may influence inflammatory response by altering the intestinal microbiome, an element that is gaining growing attention among experts. The composition of gut microbiota is characteristic of each individual and may be influenced by many different factors.[18] The gut mucosal barrier has protective functions and is involved in controlling cell proliferation and in the homeostasis of the immune system. It also has metabolic functions such as the fermentation of dietary residues in short chain fatty acids. Gut microbiome is known to be altered in a number of pathologic conditions such as colonic cancer, appendicitis and, notably, Inflammatory Bowel Disease.[19] Recent studies have identified significant changes in the microbiome of patients suffering from diverticular disease such as an excess of mucus degrading species.[20] A significant difference in the levels of *Akkermansia muciniphila*, which produces a variety of products of fermentation, was also noted.[21] Overall, these changes may cause both mucosal

inflammation and gut sensitivity and motility changes that are found in diverticular disease. The amount and composition of dietary fibers and obesity, factors that are both associated with diverticular disease and diverticulitis, have also been found to be linked with microflora alterations. This has brought to the formulation of a new hypothesis that encompasses the roles of chronic low-grade inflammation and altered gut microbiota as the possible causes behind diverticular disease and its chronic symptoms and as the potential triggers of acute diverticulitis.[22]

Antibiotic therapy in acute uncomplicated diverticulitis

The traditional standard treatment for acute uncomplicated diverticulitis included bowel rest, intravenous fluids and intravenous antibiotics. The use of antibiotics was based on the long-standing (and currently much questioned) premise that diverticulitis was caused by microcolonic perforation; however, antibiotic therapy has now become controversial. A recent extensive meta-analysis has shown that evidence in support of this kind of therapy is scarce and of low quality.[23] The authors found no randomized controlled trial (RCT) studies in support of antibiotic treatment, and there is only one small, retrospective study that showed no difference in time to recovery and risk of recurrence. These findings were confirmed by a further observational study and by one vast multicenter trial.[24,25] The latter randomized a group of 623 patients to treatment with or without antibiotics and showed no difference with regard to rate of complication or need for surgery and similar trends for subjective outcomes such as abdominal pain and tenderness, concluding that antibiotic therapy neither accelerates recovery nor prevents complications in acute uncomplicated diverticulitis. There were some methodological drawbacks of this study such as the high number of cases of recurrent rather than primary diverticulitis, the long accrual period and the non-standardized antibiotic therapy, which may have resulted in performance bias and further research was deemed necessary. In 2017, a second multicenter RCT was conducted, which included 528 patients, who at their first episode of acute diverticulitis were randomized to either observation alone or antibiotic treatment according to a well-defined scheme.[26] The study showed longer initial admission and a higher rate of antibiotic-related adverse events in the antibiotic group. No differences were found in time for recovery, complications, ongoing diverticulitis, sigmoid resections, recurrence, rate of readmission and mortality. Based on these results, the authors concluded that antibiotics can be safely omitted in patients with a first episode of uncomplicated (Hinchey Ia) left-sided diverticulitis. Similar results were found for Hinchey Ib diverticulitis. However, since the trial lacked power to detect smaller subgroup effects and there are no other reports in literature, the authors concluded that observational treatment should be, for the moment, limited to Hinchey Ia cases until larger Hinchey Ib samples have been examined.

Anti-inflammatory compounds

Anti-inflammatory compounds in SUDD

Mesalamine is a 5-aminosalicylic acid preparation employed in the treatment of inflammatory gastrointestinal disorders. It is known to be effective in inducing and maintaining remission in ulcerative colitis and preventing relapse after surgically induced remission in Crohn's disease. Although its molecular action has not been fully elucidated, mesalamine seems to exert an inhibitory activity on the inflammatory cascade, reducing the production of interleukin-1 and free radicals.[27] The potential benefit of mesalamine administration has been mostly evaluated in the context of SUDD and in prevention of acute episodes. Several randomized studies investigated the role of mesalamine in treatment of SUDD symptoms and in prevention of recurrences.[28–37] Their results were summarized in a systematic review by Picchio et al.[38] When compared with placebo or high-fiber diet, mesalamine seemed to obtain better results in symptom relief. However it should be noticed, as shown in Table 2, that the included trials have different design, different treatment and different follow-up durations. No data are available to meta-analyze results. Moreover it should be noticed that the definition of SUDD is still unclear: despite Tursi et al proposing some objective criteria to define SUDD with an endoscopic-based score, the majority of the studies available did not apply this criteria and the definition of SUDD is very variable giving a high heterogeneity among the studies.[39]

Anti-inflammatory compounds in acute diverticulitis

Meanwhile, the effect of mesalamine on acute inflammation has been little researched. One small retrospective series suggested a possible role for mesalamine in modulating acute inflammatory response in patients suffering from uncomplicated diverticulitis.[40] In this single-center cohort study, 50 patients with a CT-confirmed diagnosis of acute uncomplicated diverticulitis received 3.2 g/d of mesalamine or standard therapy from the day of admission. Mesalamine administration was associated with a trend toward a faster resolution of inflammation (by means of C-reactive plasma level over time) as well as with an earlier reintroduction of food intake and a shorter hospital stay.

Table 2 Randomized studies on mesalamine in SUDD

Study ID	Included patients	Study's interventions	Number of patients	Endpoint	Follow-up	Results	Note
Kruis et al[31]	SUDD	Mesalamine 3 g/d vs placebo	56+61	Pain intensity reduction	1 month	No difference	
Tursi et al[34]	SUDD	Mesalamine vs mesalamine + *Lactobacillus casei* vs *L. casei* vs placebo	51+55+54+50	Prevention of SUDD recurrence	12 months	Mesalamine and *L. casei* reduced recurrences; better in combination	
Smith et al[36]	SUDD	Mesalamine vs placebo	18+14	Symptoms relief and inflammatory genes expression	3 months	Reduction with mesalamine	Study unpublished
Trepsi et al[37]	SUDD	Mesalamine vs placebo	81+85	Prevention of recurrence and complications	5 years	Significant reduction with mesalamine	
Di Mario et al[33]	SUDD	Mesalamine 800 vs mesalamine 1600 vs rifaximin 400 vs rifaximin 800	39+43+40+48	Symptoms relief	3 months	Mesalamine similar to rifaximin	**Duplicate publication
Tursi et al[35]	SUDD	Mesalamine vs mesalamine + *L. casei* vs *L. casei*	27+29+29	Prevention of SUDD recurrence	12 months	Mesalamine + *L. casei* better than single agent	
Comparato et al[32]	SUDD	Mesalamine 800 vs mesalamine 1600 vs rifaximin 400 vs rifaximin 800	66+69+67+66	Symptoms relief	12 months	Mesalamine similar to rifaximin	**Duplicate publication
Stollman et al[28]	Uncomplicated acute diverticulitis	Mesalamine vs mesalamine + *Bifidobacterium infantis* vs placebo	40+36+41	Symptoms relief at 3 months	12 months	No differences among groups	
Parente et al[29]	Previous uncomplicated acute diverticulitis	Mesalamine vs placebo	45+47	Diverticulitis recurrence	24 months	No difference	
Raskin et al[30]	Previous uncomplicated acute diverticulitis	Mesalamine 1,2 vs mesalamine 2,4 vs mesalamine 4,8 vs placebo	291+290+299+289	Diverticulitis recurrence	24 months	No differences	

Note: **Duplicate publication.
Abbreviation: SUDD, symptomatic uncomplicated diverticular disease.

Mesalamine has also been studied in preventing recurrence of acute diverticulitis after a first episode. Khan et al published a letter containing results of a meta-analysis that demonstrated that mesalamine has no role in prevention of acute diverticulitis:[41] however it should be noticed that two of the included studies considered as recurrent only diverticulitis episodes requiring surgery and not episodes of mild inflammation; results should be interpreted with caution. Moreover, heterogeneity of data is very high and the level of evidence available is low. Table 2 summarizes the results of all available randomized trials on administration of mesalamine in SUDD.

Probiotics in SUDD

The role of probiotics as modulators of immune system and chronic inflammation has been investigated. At the moment, probiotics are considered as a third choice for the treatment of SUDD and no evidences exist in the treatment and prevention of acute diverticulitis. Some studies, summarized by Elisei and Tursi in a systematic review, seem to demonstrate a role in reduction of SUDD recurrence.[42]

Complicated acute diverticulitis

Complicated acute diverticulitis comprehends all forms of acute inflammation of the sigmoid colon bearing diverticula with a localization not restricted to the intestinal wall or pericolic fat. It can be characterized by the presence of near or distant abscess (stages Ib and II) or by the presence of purulent or fecaloid diffuse peritonitis (stages III and IV).

In these stages of pathology, the acute process is no more confined to the sigmoid colon and can no longer be considered as an isolated inflammatory process. The acute inflammation of the diverticular wall, consisting only of mucosa

and submucosa without a muscular layer, leads to parietal edema with disaggregation of the normal stratification with micro-perforations or macro-perforations and bacterial translocation and subsequent peritoneal or extraperitoneal (based on the diverticulum location) bacterial contamination.[43] When bacterial contamination over-reaches the peritoneal capacity to drain fluids and remove contaminants through the lymphatic system, it leads to intra abdominal sepsis and peritonitis.[44] Several factors contribute to the development of intraperitoneal sepsis and diffused peritonitis such as virulence, the characteristics and the bacterial load of the contaminant bacteria, the immune status of the patient and elements of the local environment such as the presence of fecal material and/or blood. The presence of bacteria-producing endotoxins in the peritoneal cavity induces a violent and intense activation of the inflammatory response with cytokine release and a cellular and humoral response. All of these alterations of the normal physiology of the peritoneum, with the release of cytokines, activation and mis-regulation of the immune response contribute to the development of a systemic inflammatory response syndrome that can also lead to multiple organ failure unless the septic source is timely removed and controlled.[44,45] Therefore, treatment of acute diverticulitis should be targeted to the control and removal of the septic source that maintains inflammatory response. According to the extent of inflammation and extension of the involvement of the peritoneal cavity, several approaches have been proposed. Antibiotic therapy is always mandatory due to the presence of bacterial contamination through the visceral wall systemic.[46,47]

Percutaneous drainage

In a considerable proportion of patients, acute diverticulitis associates with abscess formation, near (Hinchey Ib) or distant (Hincey II) to the diverticula according to the modified Hinchey classification.[48] The treatment of abscess requires antibiotic therapy. If the abscess is limited in size (generally <4 cm in diameter), systemic antibiotic therapy alone is considered safe and effective in removing the abscess and solving acute inflammation with a pooled failure rate of 20% and a mortality rate of 0.6%.[49] When abscess diameter is larger (generally >4 cm), antibiotics could fail to reach the needed concentration inside the abscess leading to an augmented failure rate.[50] Historically, the presence of big abscesses was considered an indication to surgery. In the late 1980s, with the development of US-guided techniques, percutaneous drainage of abscesses has been proposed an alternative to surgery, with exciting results.[51–54] The rationale of this technique is the drainage and removal the localized intra-abdominal bacterial contamination without the need for a surgical operation. Several studies have been published reporting the results of percutaneous drainage of abscesses; a recent systematic review including 684 patients with abscess (median diameter of 6.1 cm) calculated a failure rate of 20.8% with an associated mortality of 1.6%.[49] It should be noticed that, presently, there are no randomized studies available on the best treatment of intra-abdominal abscess from acute diverticulitis but only observational studies are available. When the patient's clinical conditions allow it (in the absence of severe sepsis and septic shock) and percutaneous drainage is not feasible, antibiotic therapy alone can be considered, keeping in mind the high failure rate and the subsequent need for surgical control of the septic source.

Laparoscopic lavage

When the peritoneal defenses cannot control bacterial contamination from a perforated/inflamed diverticulum and confine it into an abscess, diffuse peritonitis occurs.[44] Diffuse peritonitis can by characterized by the presence of purulent exudates (stage III according to the Hinchey classification) or diffused fecaloid material (stage IV). In these cases, surgical exploration is mandatory to control and remove the source of infection that maintains the inflammatory response. Traditionally, in case of peritonitis from acute diverticulitis, Hartmann procedure is the treatment of choice. However, emergency surgery is associated with high morbidity (30%–50%) and mortality (10%–20%).[55,56] Because of this, and in order to limit surgical intervention only to source control avoiding bowel resection and the confection of stoma, a laparoscopic approach with lavage, drainage and no resection has been proposed as an alternative in purulent diffused peritonitis (Hinchey III).[57] The first report of this technique in a large prospective cohort of patients showed a very low morbidity and mortality (4% and 3%, respectively) proving its feasibility. The procedure consists of explorative laparoscopy: if no macroscopic defects are found in the colonic wall, only an abundant lavage with warm saline water is performed, with no resection. The debate about this promising technique arose immediately and four RCTs have been launched to investigate the issue since. Presently, the results of three trials have been published, with contrasting results.[58–60] Immediately after publication, these results have been summarized in six different meta-analyses with similar findings.[61–66] When compared with emergency surgery with resection, laparoscopic lavage in Hinchey III acute diverticulitis shows a

comparable mortality (3% vs 3.5%) but is associated with a 17% failure rate with a significantly augmented need for reoperation due to the failure of the treatment and to intra-abdominal abscess formation. Long-term results were similar, with no difference in morbidity and mortality. This technique is associated with a lower number of patients receiving stoma.[67] Several controversies remain about this innovative approach: despite the low mortality and the promising long-term results associated to it, laparoscopic lavage fails in one of every five patients, exposing to a scarce source control and an increased risk of sepsis. For these reasons, laparoscopic lavage with drain should be considered as a valid alternative to colonic resection only in selected patients who can tolerate the failure of the treatment and the possible incomplete control of the septic source.

Damage control surgery

Emergency surgery has borrowed from Trauma surgery the concept of damage control. When the conditions of the patients are critical, surgical intervention must be quick to allow for the timely restoration of vital functions. In these cases, the abdomen can be left open in view of a planned re-intervention when it is stabilized.[68,69] The open abdomen, especially with drains or negative pressure wound therapy as a temporary abdominal closure technique allows an adjunctive function: several studies in swine models of abdominal sepsis demonstrated that vacuum-assisted closure allows for a more effective drainage of the abdominal cavity with better modulation of the inflammatory response and for a significant reduction in pro-inflammatory cytokines with a reduced rate of multiple organ failure and mortality.[70–73] The reduction of intra-peritoneal levels of pro-inflammatory cytokines is also associated with a reduction of circulating systemic cytokines with an improved cardiac, pulmonary and renal function.[71]

The concept of damage control laparotomy has also been proposed and studied in patients with disseminated peritonitis after diverticular perforation.[74–76] After the first laparotomy with resection and lavage, the two colonic stumps are abandoned and the abdomen is left open until the planned revision with anastomosis or stoma and closure if the situation allows it. This strategy in the setting of acute diverticulitis has been proposed for two reasons: to treat critically ill patients and to avoid stoma confection at the first laparotomy. Waiting for a reduction of the local inflammation might allow for a later anastomosis. Sohn et al performed a case–control study comparing traditional strategy vs damage control: there were no differences in morbidity and mortality but there was a significant reduction of stoma confection in the damage control group.[76] Despite this results, obtained in a relatively small number of patients, it should be kept in mind that open abdomen is associated with several drawbacks such as the formation of enteroatmospheric fistula and high costs; guidelines recommend this strategy only in critically ill patients who cannot withstand major surgery.[47]

Conclusion

In conclusion, the pathogenesis of diverticular disease and acute diverticulitis is a present and still evolving issue with several interesting perspectives. The role of chronic inflammation, the interaction of human microbiota with the mucosa and the immune system, the immunogenic role of fat tissue and the role of acute inflammation should be well defined and clarified. Inflammation plays a pivotal role in the development of diverticular disease and in the acute phase of diverticulitis. Several well-designed studies are needed to clarify the real pathogenesis of diverticular disease and the role of anti-inflammatory compounds in all the disease phases, from prevention to treatment.

Disclosure

The authors report no conflicts of interest in this work.

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