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Why Does Diverticulitis Perforate?

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Abstract

Diverticular disease is a common entity in the western world with an increasing incidence globally. This probably reflects both an increase in detection and an ageing population. The pathophysiology of diverticular disease is likely multifactorial involving dietary habits, changes in colonic pressures and motility, and colon wall structural changes. Not only has the understanding of the natural history of the disease become more complex than previously believed but the treatment algorithms have also evolved. Management paradigms are changing and are increasingly challenging, particularly for complicated diverticulitis. While the prevalence of diverticulitis is increasing, its pathogenesis and natural history have received little attention. The aim of this article is to review the current literature regarding the pathogenesis of diverticular perforation and highlight the fact that there is limited data regarding its pathophysiology.

Keywords

Diverticulitis, Perforation, Pathophysiology

Introduction

Diverticular disease of the colon is an increasingly common diagnosis in western countries with a frequency that increases with age [1-5]. This is likely a reflection of an increase in the aging population, changes in diet, and an increase in detection of disease with widespread colonoscopic screening. Diverticular disease is currently one of the five most costly gastrointestinal disorders in the United States [6] with associated rates of inpatient admission and surgical interventions steadily increasing over the past 20 years [7].

The implicated origins of colonic diverticulosis are largely unknown. Although alterations in colonic wall resistance and motility as well dietary deficiency of fiber have been postulated, confirmatory evidence remains insufficient. Most patients with diverticulosis do not have symptoms and only a minority develops diverticulitis. The exact etiology of diverticulitis also remains unknown. Although mechanical obstruction of the diverticular lumen is thought to contribute to the inflammatory process, the majority of surgical specimens fail to demonstrate this finding [6]. Immunologic hypotheses have also attempted to explain the occurrence of diverticulitis but are limited because of the lack clinical correlation [4-5]. Presenting signs and symptoms will largely depend on the size of the perforation, and these may range from localized abdominal pain and minimal free intraperitoneal air to acute abdomen with abscess or feculent peritonitis. The Hinchey classification, which is the most important and widely used classification system for diverticulitis, categorizes patients based on the anatomic location of a diverticular abscess and the source of peritonitis [8] (Table 1). This classification system also serves as a surrogate in the diagnostic and treatment algorithms of acute diverticulitis. While the prevalence of perforation has increased from 2.4 per 100,000 in 1986 to 3.8 per 100,000 in 2000 according to one study [9], the majority of patients with perforated diverticulitis do not require emergent operative treatment.

Table 1: Hinchey classification for perforated diverticulitis

Hinchey stage	Features
Stage I	Diverticulitis with paracolonic abscess
Stage II	Diverticulitis with distant abscess (pelvic or retroperitoneal)
Stage III	Purulent peritonitis
Stage IV	Feculent peritonitis

Pathophysiology of Diverticulitis

The pathogenesis of diverticulitis is not entirely understood. It is presumed that factors responsible for diverticula formation, including insufficient dietary fiber intake, colonic pressure and motility changes, and colonic wall structural alterations, may also contribute to subsequent inflammatory episodes. Although many clinicians quote that approximately 10 to 25 percent of people with diverticulosis develop diverticulitis and that the majority of patients who develop diverticulitis will only experience a single episode, exact numbers are unknown and little has been studied regarding the natural history of diverticular disease.

Formerly, the pathophysiology of diverticulitis was thought to be similar to that of appendicitis in which a fecolith either lodges within the neck of the diverticulum or abrades the mucosal surface of the sac leading to inflammation, proliferation of bacteria, diverticulum distension, and localized ischemia [10]. However, this concept has been questioned based on anatomic studies that have shown inflammation with micro perforation in the absence of a fecolith [11-13]. Diffuse ischemia of a colonic segment with diverticulosis has also been described as a contributing factor in the development of diverticular inflammation [13-15], especially in colonic segments with multiple diverticula that alter the intramural vascular distribution [16]. Additionally, an imbalance of the colonic microflora has been suggested as a pathogenic factor in both diverticulosis and

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diverticulitis [17]. Dietary modifications during the past century may have affected the colonic microflora, including decreases in fiber intake that can increase levels of bacteroides and decreased levels of bifidobacteria [18].

Diverticular Perforation

Perforation is the cardinal feature of diverticulitis. This is particularly true for phlegmonous diverticulitis in which histopathologic assessment reveals micro perforation [19]. Micro perforations are most commonly located at the fundus of the diverticulum and may also result in purulent peritonitis and abscess [12,13]. Although larger colon wall perforations in the setting of diverticulitis have historically been thought to be associated with diverticular abscess and feculent peritonitis, this has not been proven. Additionally, the timing of colon wall perforation in the setting of diverticulitis and factors associated with the size of the perforation are poorly understood.

Histologically, diverticulitis with perforation is characterized by an intensive inflammatory infiltrate of the colonic wall consisting mainly of activated macrophages characterized by CD68+/CD163+ expression [19-21]. Despite appropriate medical treatment and a good clinical response, this inflammatory infiltrate has been shown to persist; which may play a role in the chronicity of symptoms seen in these patients [19].

The exact cause of colonic wall perforation in the setting of diverticulitis remains largely unknown but four hypotheses have been postulated:

1) Mechanical hypothesis, where a fecolith or food particle obstructs the lumen of a false diverticula causing excessive rise in intradiverticular pressure and focal necrosis, similar to what occurs in acute appendicitis. This process has not been proven and is now questioned given that the majority of anatomic studies on diverticulitis specimens lack the presence of a fecolith or food particle [11-13].

2) Enzymatic matrix metalloproteinase (MMP) hypothesis, where a disruption of the balance between MMPs and their inhibitors (tissue inhibitors of metalloproteinases or TIMPs) leads to defective remodeling of the colonic extracellular matrix, which may predispose the colon wall to perforation. Diverticular perforation has been seen more frequently in colonic specimens with MMP/TIMP imbalance compared to those without it. At present, the etiology of this imbalance is still unknown [21,22].

3) Immunosuppression hypothesis, where drug-induced immunosuppression (especially with corticosteroids) has been associated with a more virulent type of disease [20,23]. A recent investigation has suggested that the glucocorticoid induced Tumor Necrosis Factor (TNF)-alpha receptor (GITR) might represent a molecular link between steroid use and complicated forms of acute sigmoid diverticulitis [21]. This receptor was found overexpressed in macrophages of patients with complicated diverticulitis [20]. Corticosteroids seem to be a risk factor for diverticular perforation irrespective of the route of administration, and even low doses seem to play a role [20,24-25].

4) Ischemia hypothesis, where alterations of the intramural vascular distribution secondary to multiple diverticula may predispose the colon wall to acute vascular injury and perforation [13-16]. Diverticular perforations with multiple diverticula have been reported in the absence of diverticular inflammation, which may support this theory [15].

Although not one single hypothesis is widely accepted, many investigators favor a combination of the above. It is my personal opinion that diverticulosis originates from a weakened colonic wall caused by increased luminal pressures, altered motility and structural changes of the colon wall, mainly defective collagen remodeling. I also believe that it is this "defective or altered structure" of the colon wall that serves as a chemotactic stimulus, and therefore, leads to recurrent or persistent inflammation and perforation.

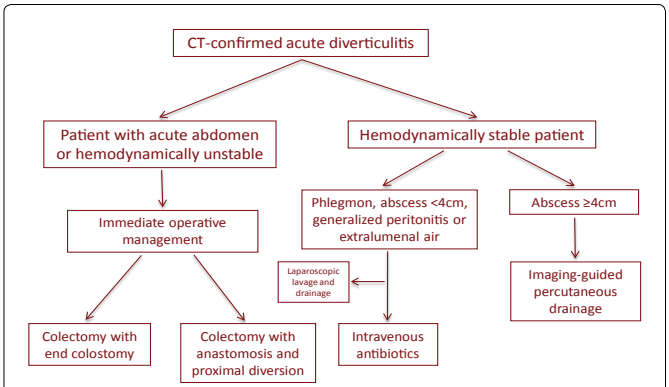

Figure 1: Treatment algorithm for patients with acute diverticulitis

Clinical Presentation and Significance of Perforation

Little is known regarding the occurrence of diverticular perforation, as well as its impact on the natural history of diverticular disease. Formerly it was thought that the number of episodes of diverticulitis increased the risk of diverticular perforation. However, it has been shown that for the majority of patients experiencing diverticular perforation, this was the first episode [23]. Although recurrence is common following medical management of an initial attack, perforated recurrence is uncommon [19,23]. A first episode of uncomplicated diverticulitis is actually thought to be protective for future perforation in following attacks.

As for the impact of perforation on the outcomes of patients who require operative treatment, a recent retrospective study including 148,874 patients undergoing segmental colectomy for diverticulitis from 1998 to 2010 showed that perforated diverticulitis with peritonitis (Hinchey 3-4) increased mortality with an odds ratio of 1.6 [26].

Once the clinical diagnosis of diverticulitis has been made, most patients are not diagnosed with diverticular perforation until an imaging study has been performed, most commonly a Computed Tomography (CT) of the abdomen and pelvis. One may have an increased suspicion of perforated diverticulitis when patients present with an acute abdomen, severe leukocytosis, or hemodynamic instability; however, these findings are not exclusive of perforated diverticulitis. The sigmoid colon is the most common site of perforation with diverticulitis. Although the sigmoid colon wall has been shown to have decreased elasticity and increased musculature when compared to the rest of the colon [27], these findings have never been directly implicated in diverticular perforation.

Once the diagnosis of diverticular perforation has been established, one must ask two important questions (Figure 1):

1) What is the clinical status of the patient? Patients who present with Systemic Inflammatory Response Syndrome (SIRS) or shock [28] and an acute abdomen require immediate abdominal exploration. This can be performed laparoscopically or open. Most patients with this clinical presentation undergo sigmoidectomy with end colostomy; with the expectation of markedly increased postoperative morbidity and mortality. Currently, many institutions are performing laparoscopic lavage and drainage as a minimally invasive approach with both temporal and curative intents. This therapeutic approach has been mainly reported in case series and institutional experiences and appears to be a safe and effective therapy for selected patients with complicated diverticulitis [29-31]. Randomized controlled trials are currently underway to better evaluate its role in the treatment of complicated diverticulitis [32,33].

The treatment algorithm for patients who are hemodynamically stable at the time of diagnosis of perforated diverticulitis varies

according to the physical exam and imaging findings. In this scenario, there is more time to plan the therapeutic approach and to evaluate the response to a given intervention. Patients who are hemodynamically stable with localized peritonitis associated with a phlegmon or evidence of a contained perforation may be managed non-operatively. When an abscess ≥4cm is present, percutaneous drainage is strongly recommended, especially when patients present with a pronounced systemic inflammatory response [33,34]. Close evaluation is mandated after non-operative treatment, given that 15 to 30 percent of patients have been reported to fail with this approach [35].

2) Is the perforation free or contained? Diverticular perforation may present as a large perforation with free communication to the peritoneal cavity and fecal peritonitis, or as a micro perforation with mild abdominal pain and a CT showing a phlegmon or small bubbles of free intraperitoneal air.

Large perforations with fecal peritonitis require operative treatment, most commonly a sigmoid colectomy with end colostomy. After sigmoidectomy, if the surgeon feels that the bowel ends are appropriate for reconnection and the peritoneal contamination is limited, primary colorectal anastomosis can be performed. This technique with a diverting loop ileostomy has shown comparable results to sigmoidectomy with end colostomy [36,37]. Gawlick and collegues [36] evaluated 2018 patients who underwent operative treatment for perforated diverticulitis. Of these patients, the majority underwent sigmoidectomy with end colostomy and 17 percent (n=340) underwent resection with anastomosis and diverting loop ileostomy. The two groups were comparable in demographics and disease presentation. Septic patients who underwent sigmoidectomy with end colostomy had significantly more wound infections (14.6% *vs.* 8.6%, *P*=0.02), but there were no significant differences in organ-space infection, dehiscence, return to the operating room, postoperative sepsis, or length of hospital stay. Binda et al. [37] randomized 90 patients with perforated diverticulitis and peritonitis to either sigmoidectomy with end colostomy or sigmoidectomy with primary anastomosis and diverting loop ileostomy. Although the trial was closed prematurely because of low accrual of patients, no significant differences were seen in overall postoperative morbidity or mortality. Upon follow up, patients who underwent end colostomy takedown had increased postoperative morbidity compared to those undergoing loop ileostomy reversal (23.5% *vs.* 4.5%, *P*=0.058).

Patients who are hemodynamically stable without generalized peritonitis and are found to have a left lower quadrant phlegmon or scattered free air on CT can be managed nonoperatively. In our experience these patients are at a higher risk for developing a diverticular abscess and a repeat CT of the abdomen and pelvis is recommended if signs and symptoms of infection persist.

Summary

Complicated diverticulitis with suspected or confirmed diverticular perforation is becoming an increasingly common disease presentation. However, the pathophysiology, clinical impact, and natural history of diverticular perforation are largely unknown. Theories have been postulated and risk factors have been identified but none completely explain the occurrence of diverticular perforation. Perforated diverticulitis has many clinical presentations that will largely depend on the size of the perforation, degree of peritoneal contamination, and inflammatory response. The majority of patients with perforated diverticulitis can be managed non-operatively with good results. Operative treatment, when necessary, is associated with increased morbidity and mortality. Laparoscopic lavage and colonic resection are minimally invasive approaches that are safe and associated with lower postoperative morbidity and mortality compared to open Hartmann's procedure and colectomy.

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