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Epidemiology, Pathophysiology, and Treatment of Diverticulitis

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Abstract

Diverticulitis is a prevalent gastrointestinal disorder that is associated with significant morbidity and health care costs. Approximately 20% of patients with incident diverticulitis have at least 1 recurrence. Complications of diverticulitis, such as abdominal sepsis, are less likely to occur with subsequent events. Several risk factors, many of which are modifiable, have been identified including obesity, diet, and physical inactivity. Diet and lifestyle factors could affect risk of diverticulitis through their effects on the intestinal microbiome and inflammation. Preliminary studies have found that the composition and function of the gut microbiome differ between individuals with vs without diverticulitis. Genetic factors, as well as alterations in colonic neuromusculature, can also contribute to the development of diverticulitis. Less-aggressive and more-nuanced treatment strategies have been developed. Two multicenter, randomized trials of patients with uncomplicated diverticulitis found that antibiotics did not speed recovery or prevent subsequent complications, and guidelines now recommend antibiotics for only specific patients. Elective surgical resection is no longer recommended solely based on number of recurrent events or young patient age and might not be necessary for some patients with diverticulitis complicated by abscess. Randomized trials of hemodynamically stable patients who require more emergent surgery for acute, complicated diverticulitis that has not improved with antibiotics provide evidence to support primary anastomosis vs sigmoid colectomy with end colostomy. Despite these advances, more research is needed to increase our understanding of the pathogenesis of diverticulitis and to clarify treatment algorithms.

Lay Summary

Diverticulitis is a prevalent condition of the colon. New evidence indicates that diet and lifestyle may interact with the gut microbiota to initiate inflammation. Less aggressive treatment paradigms are under active investigation.

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Keywords

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Diverticular disease, once a rarely diagnosed medical curiosity, is now one of the most common gastrointestinal disorders among inpatients and outpatients.[1–3] Painter and Burkitt first documented a large increase in the prevalence of diverticular disease beginning at the time of the industrial revolution and differences in prevalence between Western and Eastern countries.[4] These observations led to the hypothesis that diverticular disease resulted from dietary fiber deficiency. According to this theory, a diet low in fiber resulted in small-caliber stools, increased intracolonic pressures, and herniation of the colonic mucosa through the muscular layers adjacent to the vasa recta. Diverticulitis was thought to ensue when a diverticulum became obstructed with stool, resulting in fecal stasis, mucosal trauma, and ischemia. Diverticular disease was readily attributed to fiber deficiency, surgery and antibiotics became the primary treatments for diverticulitis, and research in the field stagnated.

In the past 2 decades, there has been a resurgent interest in diverticular disease. Modern imaging techniques and the widespread use of flexible endoscopy have enabled more accurate diagnosis of diverticulitis and asymptomatic diverticulosis, increasing our understanding of their epidemiology. The discovery that diverticulitis is not a progressive led to new and less-aggressive surgical and medical approaches.[5, 6] Recognition that diverticulitis shares many risk factors with other inflammatory diseases has prompted new theories of pathogenesis and opportunities for research and treatment. We review the latest data and concepts regarding the epidemiology, pathophysiology, and treatment of diverticulitis of the colon.

Terminology

“Diverticular disease” is used to describe asymptomatic diverticulosis and the spectrum of complications of colonic diverticulosis. However, because the term indicates the presence of symptoms or complications, diverticular disease is more appropriate for diverticulitis and other complications of diverticulosis such as bleeding, rather than for asymptomatic diverticulosis. In addition, diverticula can occur in the small bowel and other areas of the intestinal tract. This review focuses on diverticulitis and complicated diverticulitis (diverticulitis with abscess, perforation, stricture, obstruction and/or fistula) of the colon. Other complications of diverticular disease not covered in this review include segmental colitis associated with diverticular disease (SCAD), an uncommon manifestation that shares many clinical and histologic features with inflammatory bowel diseases (IBD),[7] and symptomatic uncomplicated diverticular disease (SUDD). SUDD is most commonly defined as gastrointestinal symptoms in the setting of diverticulosis without evidence of overt inflammation or diverticulitis.[8] However, definitions vary, there is significant overlap of symptoms with irritable bowel syndrome (IBS), and the diagnosis is controversial. Some patients develop chronic abdominal symptoms following an episode of diverticulitis, a syndrome sometimes referred to as post-diverticulitis functional bowel disease.[9]

Epidemiology

The lifetime risk of diverticulitis in a person with diverticulosis was reported to range from 10% to 25%.[10] However, these estimates predate the routine use of flexible endoscopy, and therefore, an accurate assessment of prevalence. In addition, the diagnosis of diverticulitis was made on clinical grounds. Modern estimates based on colonoscopy and computed tomography (CT) indicate that fewer than 5% of individuals with diverticulosis develop diverticulitis (Figure 1).[11] Nonetheless, because more than 50% of Americans older than 60 years of age have diverticulosis, diverticulitis is highly prevalent.[12] Annually, in the United States (US), there are more than 2.7 million outpatient visits and 200,000 inpatient admissions for diverticulitis at a cost of more than $2 billion.[1, 3] The incidence of diverticulitis has increased over time and increases with patient age.[13, 14] However, the relative increase in diverticulitis in recent decades has been greatest in young patients. For example, from 1980 through 2007, the incidence of diverticulitis in individuals 40–49 years old increased by 132%.[13]

Diverticulitis is more common in men than women until the 6th decade, when it becomes more common in women. [13, 14] The prevalence of hospitalization for diverticulitis in the US is greatest in whites (62/100,000), similar in African Americans and Hispanics (approximately 30/100,000), and lowest in Asians (10/100,00).[14] Individuals living in urban areas are more likely to be hospitalized for diverticulitis than those in rural areas,[15] as are those with lower income and educational levels.[16] Diverticulitis is more common in developed countries, but could be increasing in other parts of the world.[17] After immigration, non-Western individuals have a lower risk of hospitalization for diverticular disease than Western natives, although risk increases with time since immigration.[18]

Progression of diverticulosis and diverticulitis

Complications of diverticulitis occur in approximately 12% of patients. The most common complication is phlegmon or abscess (approximately 70% of patients with complications) followed by peritonitis, obstruction, and fistula.[13] Mortality following complicated diverticulitis (diverticulitis with phlegmon, abscess, perforation or fistula) is increased compared to uncomplicated diverticulitis, and is highest among individuals with perforation or abscess.[13, 19] In a population-based cohort study in the United Kingdom, mortality at 1 year was 20% in patients with perforated diverticulitis compared to 4% in age- and sex-matched controls.[19]

A small percentage of patients (4%–10%) have ongoing or smoldering diverticulitis, defined as ongoing diverticulitis (pain with increased white blood cell counts or markers of inflammation, fever, or CT evidence of inflammation) despite antibiotic treatment or re-exacerbation after cessation of treatment.[20, 21] An estimated 8% of patients with incident disease have recurrences within the first year after complete recovery from the incident episode, and 20% have recurrences within 10 years. The risk of recurrence increases with subsequent episodes. After a second episode, the risk is 18% at 1 year and 55% at 10 years, and after a third episode it is 40% at 3 years.[13] These estimates are derived from a population-based cohort of all patients with diverticulitis. Most other estimates of recurrence are derived from selected populations, such as those who were hospitalized for treatment. In

addition to the number of recurrences, risk factors for recurrence include young age at onset,[22, 23] severity of the incident event,[24–26] extent of colon involvement, family history of diverticulitis,[25] smoking, male sex, and obesity.[27]

Diverticulitis was once thought to be a progressive disease with an increasing risk of complications as the number of episodes increased. This belief informed guidelines for aggressive surgical intervention. However, complications, with the exception of fistula formation, occur more commonly during the first episode of diverticulitis than after subsequent episodes.[28] For example, in a prospective study of 900 patients, the risk of free perforation was 25% at the first episode and decreased to zero after the 4th episode.[29] In another prospective study, only 4% of patients developed complicated diverticulitis within 2 years of presentation with uncomplicated diverticulitis.[30] The reduced risk of subsequent perforation is believed to be due to occlusion of microperforations by nearby tissues or organs during the initial inflammatory episode. Population-based data also indicate that the risk of recurrence after complicated diverticulitis treated medically is similar to the risk following uncomplicated diverticulitis.[13] Nonetheless, retrospective studies reporting a high rate of recurrence following medical treatment of complicated diverticulitis continue to dictate surgical treatment.[24, 31, 32]

Chronic manifestations

Patients with a history of diverticulitis can develop chronic manifestations aside from recurrent or smoldering diverticulitis, stricture, and fistula. In a randomized controlled trial (RCT) of antibiotics vs no antibiotics for treatment of uncomplicated diverticulitis, approximately 40% of patients with CT- confirmed diverticulitis had mild to moderate abdominal pain and/or changes in bowel habits at 1 year of follow up.[33] In a large retrospective study of US Veterans, the risk of IBS and functional bowel diseases were 5- and 2.5-fold higher, respectively, in patients with a history of diverticulitis than without.[9] Patients with diverticulitis were also more than twice as likely to develop mood disorders.[9] A study that evaluated quality of life in patients with a history of diverticulitis found that negative psychological, social as well as gastrointestinal, symptoms are common after resolution of the acute episode, and that patients attribute these symptoms specifically to prior diverticulitis.[34] Although functional symptoms without overt inflammation appear to be common following a diagnosis of diverticulitis, it is less clear whether patients with diverticulosis without a history of diverticulitis can develop chronic symptoms (such as SUDD). Many studies of SUDD included patients with prior diverticulitis and it is difficult to distinguish SUDD from IBS.[8] In a large, prospective colonoscopy study, no association was found between diverticulosis and IBS.[35]

There may be long-term, extra-intestinal implications of diverticulitis. In a nationwide study in Sweden, individuals with diverticular disease had a modest increase in risk of thromboembolic events compared with matched controls.[36] It should be a priority to increase our understanding of the long-term, global effects of diverticulitis on health and quality of life.

Risk factors

Modern studies have confirmed and expanded the role of diet and other modifiable lifestyle factors in the natural history of diverticulitis (Table 1). Lifestyle factors associated with increased risk include Western dietary patterns (high in red meat, fat, and refined grains) and red meat consumption alone.[37, 38] Obesity, and central obesity in particular, increases the risk of diverticulitis.[39–42] Smoking is also associated with an increased risk of diverticulitis —particularly complicated diverticulitis.[43–46] On the other hand, dietary fiber intake and prudent diets (high in fruits, vegetables, and whole grains) reduce the risk of diverticulitis.[38, 47, 48] Nuts and seeds do not appear to increase the risk, and in a large, prospective cohort nuts and popcorn were associated with reduced risk of diverticulitis.[49]. Physical activity (particularly vigorous activity, such as running) is associated with decreased risk.[39, 50, 51] It is not clear whether alcohol use affects risk of diverticulitis.[43, 52]

A study examining the joint contribution of multiple lifestyle risk factors on risk of incident diverticulitis found that adherence to a low-risk lifestyle decreased the risk of diverticulitis by nearly 75%. A low-risk lifestyle was defined as fewer than 4 servings of red meat per week, at least 23g of fiber per day, 2 hrs of vigorous activity per week, body mass index 18.5–24.9, and no history of smoking. Assuming causal associations, it was estimated that a low-risk lifestyle could prevent half of diverticulitis cases.[53] These findings highlight the importance of diet and lifestyle modification in the prevention of diverticulitis.

Several medications have been associated with increased risk of diverticulitis. Prospective cohort and case-control studies have found a consistent positive association between nonsteroidal anti-inflammatory drug (NSAIDs) use and diverticulitis.[54–57] The association appears to be stronger for non-aspirin NSAIDs than for aspirin.[57] Non-aspirin NSAIDs also appear to be more strongly associated with complicated or perforated diverticulitis than with uncomplicated disease.[57] Opiate analgesics as well as corticosteroids are also associated with diverticulitis and perforated diverticulitis.[56] Several medications have been associated with a decreased risk of diverticulitis including statins, calcium channel blockers, and metformin, although these studies were at risk of bias and confounding—further studies are needed.[56, 58, 59] A case–control study comparing 25(OH)D levels and risk of diverticulitis, as well as a study of ultraviolet light exposure, identified low vitamin D levels as a risk factor for diverticulitis.[15, 60, 61] Medication use, particularly NSAID use, is generally one of the easiest targets for risk factor modification.

Immunosuppression is thought to increase the risk of diverticulitis. The risk associated with corticosteroids is well-defined. However, studies of other forms of immunosuppression such as chemotherapy, organ transplant, and renal failure have been small, retrospective, and heterogeneous with respect to the type and degree of immunosuppression and associated risk for diverticulitis. Although the mechanism of increased risk is unclear, it is plausible that impaired healing contributes to perforation, and the lack of an immune response might mask signs and symptoms. Although their symptoms may be less pronounced, immunocompromised patients appear to be more likely to present with complicated disease, and are therefore more likely to require surgical intervention than their non-immunocompromised counterparts.[62] It is unclear whether these patients are more likely to

develop recurrent disease, but poor outcomes during recurrent episodes, including death, appear more likely.[62, 63]

Pathophysiology

The pathophysiology of diverticulitis is incompletely understood. Long-standing but unproven theories suggest that diverticulitis results from obstruction and trauma to a diverticulum with subsequent ischemia, microperforation, and infection.[64] This theory led to the wide-spread belief that patients with diverticulosis should avoid eating nuts and seeds, and the widespread use of antibiotics for diverticulitis treatment. However, more recent studies indicated that nut and seed consumption do not increase risk of diverticulitis,[49] and that antibiotics may not hasten recovery or improve outcomes.[21, 33] These findings have led to models of diverticulitis pathogenesis that involve chronic inflammation and alterations in the gut microbiome (see Figure 2).

Chronic inflammation

Several studies have associated diverticulitis with a chronic inflammatory state. The most convincing evidence, although indirect, is that many risk factors for diverticulitis are associated with chronic, systemic inflammation. For example, obesity, physical inactivity, and a Western diet are risk factors for other diseases believed to be caused by chronic inflammation, including cardiovascular disease and diabetes—these risk factors increase levels of biomarkers of inflammation.[65–67] Increased expression of matrix metalloproteases and histamine, which are associated with intestinal inflammation, have also been linked to diverticulitis.[68, 69] Intestinal mucosal inflammation observed in patients with SCAD has morphological and clinical overlap with IBD,[7]. Findings from a case series study indicated that patients with diverticulosis, particularly those with abdominal symptoms or SUDD, have microscopic inflammation.[70, 71] However, SCAD and SUDD are separate manifestations of diverticular disease, and, in a study of more than 600 individuals undergoing screening colonoscopies, after adjustment for potential confounders, there was no association between diverticulosis and levels of immune markers or cytokines implicated in IBD and IBS. In addition, there was no association between diverticulosis and IBS and no difference in mucosal inflammatory markers between diverticulosis patients with and without abdominal symptoms, although the subset with symptoms was small.[35] Therefore, diverticulosis itself may not be associated with mucosal inflammation, and functional symptoms in patients with diverticulosis might not be related to inflammation or even to diverticulosis itself. However, these studies did not investigate whether patients who later developed diverticulitis or had recurrent diverticulitis had subclinical mucosal or systemic inflammation.

Altered microbiomes

Alterations in the gut microbiota are implicated in the pathogenesis of many intestinal disorders. Diet and lifestyle factors may induce alterations in the gut microbiome that lead to mucosal inflammation and diverticulitis.[72, 73] Several lines of evidence support a role for gut microbiota in diverticulitis. Acute diverticulitis involves micro- or macro-perforation with translocation of commensal bacteria across the colon mucosal barrier, sometimes resulting in

frank infections, including abscess formation and peritonitis. The standard treatment for diverticulitis is antibiotics.[74] Worldwide differences in the prevalence of diverticular disease mirror geographical differences in gut microbial composition.[4, 75–77] Diet and lifestyle risk factors for diverticulitis affect the gut microbiome. For example, obesity and a Western dietary pattern are linked to decreased microbial diversity in the intestine and changes in the microbiome composition and its functions.[78–81] On the other hand, diets high in fiber increase gut microbiome diversity and richness.[82–84] Dietary fiber is an important source of energy for intestinal microbes, which metabolize complex carbohydrates into short-chain fatty acids (SCFAs).[85] SCFAs increase the production of mucus and antimicrobial peptides and mediate immune homeostasis, intestinal barrier function, and proper levels of cell proliferation.[86]

Preliminary studies indicate that the composition of the intestinal microbiome differs in patients with vs without diverticular disease. Most studies have focused on the microbiota of patients with SUDD. In general, these studies have found decreases in bacteria that produce SCFAs and in Akkermansia, a mucin-degrading bacteria that promotes epithelial barrier integrity and suppresses inflammation.[70, 87, 88] However, it is difficult to extrapolate findings from studies of SUDD to diverticulitis given the controversy surrounding the diagnosis of SUDD and the lack of similarities in pathophysiology. A large study of the mucosal adherent bacteria in incidental diverticulosis (n=226) vs no diverticulosis (n=309) found only weak associations with the phylum Proteobacteria and the family Comamonadaceae. It concluded that mucosal adherent bacteria are unlikely to contribute to development of diverticulosis.[89]

Several studies have examined the intestinal microbiomes of patients with diverticulitis. A PCR analysis of surgical resection specimens from patients with diverticulitis found higher levels of Bifidobacterium than in patients with colon cancer or IBD.[90] Daniels et al studied the microbiomes of patients with acute diverticulitis who underwent colonoscopies vs controls. The authors performed PCR amplification of the 16S–23S rDNA interspace region of specific phyla and found the diversity of Proteobacteria to be higher in patients with diverticulitis. The Enterobacteriaceae family, which includes *Escherichia coli,* had the highest degree of discrimination—also observed in studies of patients with IBD.[91] Lower levels of Clostridiales (which produce SCFAs) such as Lachnospiraceae and of Erysipelotrichaceae (also decreased in patients with IBD)[92, 93] were found in cases with a history of diverticulitis compared to controls with asymptomatic diverticulosis. PICRUSt analysis predicted that microbes involved in carbohydrate metabolism and biosynthesis of secondary metabolites were significantly decreased in cases.[94] Overall, changes in the intestinal microbiome associate with development of diverticulitis and symptoms associated with diverticulosis (such as SUDD). Bacteria involved in SCFA metabolism, mucosal barrier function, and potentially invasive bacteria appear to be particularly important. However, it is difficult to determine whether changes in the fecal microbiome are causally associated with diverticulitis. In small, cross-sectional studies, diet and lifestyle changes following diagnosis and treatment with antibiotics may have altered gut microbiota profiles.

Genetics

Two large, Scandinavian twin or family studies provided evidence that genetic factors affect risk for diverticular disease. In these studies, the odds of developing diverticular disease if a co-twin had the disease was significantly higher among monozygotic twins than dizygotic twins and higher in non-twin siblings than the general population. Statistical modeling estimated that genetic factors accounted for 40%–50% of risk for diverticular disease.[95, 96] These studies could not clearly distinguish diverticulitis from diverticulosis. However, results were similar the analysis was restricted to complicated diverticulitis.[96]

A genome-wide association study in Iceland and Denmark identified variants in genes (*ARHGAP15, COLQ*, and *FAM155A*) that associated with diverticular disease. Variants in *FAM155A* associated specifically with diverticulitis.[97] A variant in *ARHGAP15* is associated with phagocyte function and inflammation. Maguire et al used the UK Biobank to perform a retrospective genome-wide association study of 28,000 patients admitted to the hospital with diverticular disease. The authors identified 42 risk loci, 8 of which were replicated in a separate cohort. Candidate risk loci contained genes that regulate immunity, the extracellular matrix, cell adhesion, membrane transport, and intestinal motility. The previously identified associations with *ARGAP15*, *COLQ*, and *FAM155A* were confirmed in this study. [98] Two small studies of patients with diverticulitis who required surgery found an association with several single-nucleotide polymorphisms in the *TNFSF15* gene.[99, 100] Variants in this gene, which encodes for a cytokine in the tumor necrosis family, have been associated with severe forms of IBD. A study of 5 members of a family with early-onset diverticulitis identified a rare single-nucleotide polymorphisms in the laminin subunit beta 4 (*LAMB4*).[101] Laminins are part of the extracellular matrix and involved in development of the enteric nervous system.

Alterations in colonic neuromusculature

Localized high-pressure zones in the colon were originally believed to lead to formation of diverticula at weak spots in the colonic musculature. This might account for the observation that diverticulosis occurs most frequently in the sigmoid, where the colon is less distensible, than the proximal colon and rectum. Furthermore, diverticula are not found in the rectum, which functions as a reservoir and is highly distensible, and where the tenia coli flare to create an additional, circumferential layer to the bowel wall. Alterations in the enteric nervous system, connective tissue, smooth muscle, and colonic motility are believed to contribute to the development of diverticulosis and functional symptoms in the setting of diverticulosis.[102] It is less clear if these neuromotor abnormalities are involved in the development of diverticulitis.

Early-onset diverticulosis occurs in patients with connective tissue disorders, supporting a role for connective tissue defects in the formation of diverticulosis[103–105]. Alternations in collagen composition and content as well as connective tissue metabolism have been identified in colons of patients with diverticulosis.[106] Reduced numbers of ganglionic and neuronal cells[107], as well as imbalances in neurotrophic factors and neuropeptides such as serotonin and acetyl choline, are also found in patients with diverticular disease.[108–110] These alternations might cause symptoms in patients with diverticulosis.[111] Motility studies

of patients with diverticulosis have, in general, found increased motility indices and propulsive activity.[112] It is not clear whether these neuromuscular alterations predate the formation of diverticulosis or diverticulitis, and therefore contribute to disease development, or are a result of processes that occur after diverticulosis formation.

Treatment

Antibiotics, dietary modification, and pain control have been the mainstays of treatment for patients with uncomplicated diverticulitis; surgical resection has been the cornerstone for treatment of complicated diverticulitis and recurrence. However, these interventions are based largely on dogma and expert opinion rather than data. Traditional surgical recommendations were comfortingly definitive but ultimately have not been supported by evidence. Although more recent data and technology advances have reduced risk through less-invasive treatment, clinical guidelines have become more difficult to define due to the need for individualized treatment.[74] The concept that diverticulitis is an inflammatory as well as an infection-associated disease have sparked interest in new medical and surgical treatment paradigms. In general, there has been a shift towards less-aggressive medical and surgical management.

Pharmacologic agents

Two RCTs and several observational studies have challenged the need for antibiotic treatment for patients with uncomplicated diverticulitis (Table 2). The antibotika vid okomplicerad divertikulit study group randomly assigned 623 patients with CT-proven uncomplicated diverticulitis from 10 centers in Sweden and Iceland to groups given intravenous followed by oral antibiotics (carbapenem or piperacillin and tazobactam followed by oral metronidazole combined with either ciprofloxacin or cefadroxil) or intravenous fluids alone. Patients were followed for 12 months.[33] In the diverticulitis: antibiotics or close observation (DIABLO) study, 570 patients with CT-proven uncomplicated diverticulitis (Hinchey 1a or 1b; supplementary table 1) from 22 centers in the Netherlands were randomly assigned to groups given amoxicillin-clavulanic acid (intravenously, for least 48 hrs, and then oral) or placebo and followed for 6 months.[21] Each study found that antibiotics did not hasten recovery or prevent subsequent surgery or complications.

Based on these findings and growing concerns about antibiotic-related complications and resistance, several European guidelines have stopped recommending antibiotics for uncomplicated diverticulitis.[113–115] The American Gastroenterological Association's 2015 guideline gave a conditional recommendation for selective rather than routine use of antibiotics in uncomplicated diverticulitis in the absence of severe disease, immunocompromise, pregnancy or significant comorbidity,[116] noting the low quality of evidence including inadequate power to assess risk of serious complications.[117] In a subsequent analysis of 2-year follow-up of the DIABLO trial, rates of progression to complicated or recurrent diverticulitis were similar.[118] However, higher proportions of patients in the placebo group underwent elective surgery (7.7%) than in the antibiotic group (4.2%; P=.09), and the indications for surgery in the placebo group were more frequently

obstruction and recurrent diverticulitis. Furthermore, the risk of elective surgery in the placebo group might have been underestimated. The proportion would increase to 10% if patients who were censored after enrolling in another trial of elective surgery vs conservative management were included in the analysis.[119] Therefore, the long-term safety of withholding antibiotics from patients with uncomplicated diverticulitis is uncertain; larger long-term follow-up studies are needed before well-supported consensus treatment guidelines can be developed. Nonetheless, data indicate that the risk of serious complications after acute uncomplicated diverticulitis is low (4%) whether or not patients receive antibiotics.[118] The decision to withhold antibiotics from stable, immunocompetent, adherent patients with uncomplicated diverticulitis involves shared decision making and close follow up (see Figure 3). This option may be particularly appealing to patients with recurrent diverticulitis who have had mild episodes and repeated exposure to antibiotics.

Other approaches that have been studied for uncomplicated diverticulitis, although with less rigor, include shorter treatment courses, oral vs intravenous antibiotics, and outpatient vs inpatient management. A small RCT indicated that the treatment failure rate was similar in patients receiving 4 days vs 7 days of antibiotics.[120] Small studies have also demonstrated that outpatient treatment (with antibiotics) is safe in select patients with uncomplicated diverticulitis who can tolerate oral intake and do not have significant comorbid disease[121, 122]. A trial is underway to compare outpatient treatment with vs without antibiotics.[123]

Unfortunately, there are few data to guide dietary recommendations and pain management for patients with acute diverticulitis. Patients have been instructed to consume a clear-liquid or low-residue diet. A prospective, uncontrolled study of an unrestricted diet in 86 patients with uncomplicated diverticulitis concluded that this was well-tolerated, although 8% had serious adverse events and 20% had ongoing symptoms.[124] A multicenter trial is underway to evaluate an unrestricted vs a progressive diet in uncomplicated diverticulitis. Most guidelines do not address pain control. NSAIDs and opiates are associated with increased risk of incident and complicated diverticulitis but have not been studied in patients with acute disease.

Selection is key to management of outpatients with diverticulitis. The diagnostic accuracy of diverticulitis based on clinical grounds alone has been reported to be low (diagnoses of diverticulitis are incorrect for as many as 60% of cases), and clinical decision tools are imperfect.[125] CT or ultrasound imaging is required for identification of complicated diverticulitis (Figure 3). A multi-slice CT with intravenous contrast identifies patients with diverticulitis with 95% sensitivity and 96% specificity.[126] In Europe, ultrasound is frequently used and identifies diverticulitis with 94% accuracy, but is operator dependent.[127] Ultrasound-based strategies would reduce radiation exposure—particularly in patients with recurrent disease, but further studies are needed.

Pharmacologic agents might be used to prevent recurrence of diverticulitis. Patients with incident diverticulitis have an approximately 10% risk of recurrence within 1 year—risk increases substantially with each subsequent episode.[13] Even after a segmental colectomy, as many as 15% of patients have recurrences; 10%–20% of patients have serious post-operative

complications and as many as 20% report no relief in symptoms of pain and bloating.[117, 128–130] A medical means to prevent recurrence would be transformative. Several medications have been tested under the premise that diverticulitis is an acute inflammatory disorder. Six trials have evaluated the efficacy of mesalamine in the prevention of recurrent diverticulitis in more than 2000 patients.[131–134] Unfortunately, none of these trials found a significant difference in the rate of recurrent diverticulitis. However, there may be other indications for mesalamine in diverticulitis. A small retrospective study of patients with acute uncomplicated diverticulitis found that mesalamine led to faster recovery, and uncontrolled studies indicate benefits to patients with SUDD.[135, 136] Other pharmaceutical agents that have been tested for prevention of recurrent diverticulitis include rifaximin and probiotics.[137, 138] However, these studies have been small and of low quality.[117] Pharmacologic agents are needed to reduce risk of recurrent diverticulitis.

Surgery

Patients with a phlegmon or small abscess (Hinchey grade I or II) can be managed with bowel rest, antibiotics, and if appropriate with percutaneous drainage (Figure 3). Surgical treatment is rarely warranted due to the minimal opportunity to prevent recurrence or perforation. Specifically, after an incident diagnosis of uncomplicated diverticulitis in an otherwise healthy patient, the risk of recurrence is only 13%–23%, and risk of perforation or other complications in patients with disease recurrence is less than 6%.[5, 13] In a RCT of surgery vs conservative management of patients with ongoing and recurrent disease, fewer than 42% of patients actually had recurrence.[139] Surgical guidelines therefore urge caution with respect to surgical resection after uncomplicated diverticulitis.[5, 74] Moreover, among patients who underwent surgical resection, as many as 15% had a recurrence and as many as 25% have continued chronic pain without imaging evidence of inflammation.[20, 140, 141] The decision to move forward with surgery, therefore, should include a discussion with patients about the possibility of persistent or recurrent pain as well as the 10%–20% risk of surgical complications.[74] When surgeons and patients together decide for surgery, we recommend complete resection of the apparently affected portion of the colon with primary anastomosis to the rectum and avoidance of a diverting stoma unless the patient is immunocompromised or nutritionally depleted, specifically requests a stoma, or has unexpected surgical findings.

In patients with complicated diverticulitis, the need for operative intervention and type of operation are areas of active investigation. Patients with diverticula-associated fistula, by definition, have chronic disease and can almost always undergo an elective operation with a primary anastomosis. Increasingly, only patients who are hemodynamically unstable with severe sepsis and/or peritonitis require an urgent Hartmann procedure (a sigmoid colectomy with end colostomy). The rationale for colostomy in this case is that infection, inflammation, and shock will compromise healing of a descending colon–rectum anastomosis. However, this rationale has been based on tradition and expert opinion, rather than data. Even among patients with purulent or fecal peritonitis (Hinchey grade III–IV), the need for an urgent colostomy is increasingly questioned.

Patients with acute complicated diverticulitis who are hemodynamically stable but are not improving clinically after several days of conservative management will likely require an

operative intervention. Several recent surgical RCTs from Europe have compared the Hartmann procedure to anastomosis with diverting loop ileostomy, anastomosis without stoma, and laparoscopic lavage among patients with CT- or laparoscopically-diagnosed Hinchey III-IV diverticulitis (Table 2).[142, 143] These findings indicate the difficulty of applying RCT principles to studies of acute disorders that require surgery—recruitment was hampered, blinding was impossible, and rigorous technical standardization was not realistic. Several studies closed prematurely due to slow or inadequate recruitment.[139, 143] Each study used a different primary outcome, making it difficult to summarize or compare results. In general, however, post-operative complications, mortality, and stoma-free survival after a Hartmann procedure were equivalent or inferior to colectomy with a primary anastomosis with or without a diverting loop ileostomy. Investigators also found that diverting loop ileostomies were more likely to be closed within 12 months of the incident diagnosis than colostomies, supporting primary anastomosis over the Hartmann procedure.

Laparoscopic lavage, which initially appeared promising among small cohort studies, has not performed well and even led to early closure of the RCT LADIES-LOLA (LaparOscopic LAvage) group due to an increased need for unplanned urgent surgery, in spite of fewer stomas in the lavage arm than the surgical resection arm.[144] The Scandinavian diverticulitis trial similarly found more reoperations but ultimately a lower stoma rate in the lavage arm.[145] The diverticulitis-laparoscopic lavage trial found fewer operations and improved stoma-free survival in the lavage group, and, in contrast to the 2 previous studies, concluded that the use of lavage was feasible and safe.[146] Unfortunately, lavage has been studied only as a substitute for resection (definitive treatment) rather than as a bridge to resection (damage control) with a primary anastomosis.[147] At this time, the use of laparoscopic lavage is not recommended outside of clinical trials given its association with persistent and recurrent abdominal sepsis.

There are several special case patient profiles that deserve mention: young patients, the elderly, and those who are immunocompromised. Although epidemiologic trends indicate that younger patients comprise an increasingly large proportion of all patients diagnosed and have an increased risk of recurrence,[13, 14] there is no evidence that they fare worse than their older counterparts if treated non-operatively.[148] Similarly, the elderly are not more likely to experience recurrence. Based on nationally representative longitudinal data, more than 85% of inpatient cases were managed non-operatively and only 3% required a future operation. Odds of recurrence were even lower among those aged 80 years and older.[149] On the other hand, elective surgery in elderly patients is associated with higher rates of mortality, intestinal diversion and hospital readmission.[150] Therefore, aggressive intervention is not indicated based on young age, and conservative management is strongly recommended for stable elderly patients who are not suffering from obstructive symptoms or fistula.

Elective surgery for stable patients with resolved complicated diverticulitis or multiple recurrent episodes of disease might reduce the risk of further recurrence or ongoing symptoms. It is unclear whether immunocompromised patients are more likely to develop recurrent disease, but delayed diagnosis and poor outcomes during recurrent episodes, including mortality, appear to be more likely.[62, 63] Guidelines recommend a lower threshold for prophylactic surgery in the setting of ongoing immunocompromise.[74]

Although the indications for elective surgery for diverticulitis have become more nuanced and require an assessment of patient values and preferences, the goals of surgical treatment are unchanged. Surgical priorities focus on first controlling the source of infection, second reducing morbidity, and third increasing quality of life.[5] Controlling the source of infection requires resection of affected sigmoid colon, and not merely oversewing, or lavaging the area of abscess. The most important adverse outcomes of surgical treatment are persistent or recurrent abdominal sepsis, unplanned reoperation, and long-term colostomy or ileostomy. To minimize such events, we recommend surgical mobilization of the splenic flexure of the colon to achieve a tension-free and well-perfused anastomosis, complete resection of thickened or inflamed colon, ensuring that the distal anastomotic edge is rectum (not residual sigmoid) as indicated by flared tenia and no distal diverticula, and avoidance of the Hartmann procedure when feasible.[5] Increasing quality of life usually implies avoidance of a colostomy, although select patients may actually experience an improved quality of life with a colostomy. Concerns about impaired anastomotic healing should prompt consideration of a primary colon to rectum anastomosis with a diverting loop ileostomy given a reasonably clean surgical field.

Post-treatment recommendations

Guidelines recommend that a colonoscopy be performed 4–8 weeks following recovery from an episode of diverticulitis in patients who have not had a recent, high-quality colonoscopy even among those who were diagnosed via CT scanning.[116] This recommendation is based on multiple observational studies of patients with imaging-diagnosed diverticulitis that subsequently underwent colonoscopy. A pooled analysis indicated that 1 out of 67 patients initially diagnosed with diverticulitis would have a misdiagnosed colon cancer on follow up colonoscopy.[117] These cancers were almost exclusively located in the area of suspected previous diverticulitis. Patients with suspicious imaging or presentations were probably more likely to be referred for colonoscopy than those with a typical course, thereby biasing the results of such observational studies. In a randomized trial of antibiotics vs no antibiotics, 6 patients out of 893 screened for eligibility were initially felt to have a clinical presentation and imaging consistent with diverticulitis but were subsequently found to have colon cancer.[21]

Future Directions

Diverticulitis has a considerable impact on patients and the health care systems. Large, prospective cohort studies have identified the importance of diet, lifestyle, medication, and genetic factors in development. Increased understanding of the natural history of diverticulosis and diverticulitis has led to less aggressive management approaches, and findings from studies of inflammation and the intestinal microbiome have stimulated new avenues of research and treatment. Diverticular disease research has increased rapidly in the last 2 decades. An informal PubMed search for this article using the terms diverticulosis, diverticulitis, or diverticular disease found that the number of published articles increased 3.5-fold, from approximately 200 in 2000 to nearly 700 in 2017. Nonetheless, our understanding of the pathogenesis of diverticulitis is superficial, and treatment algorithms are still largely based on medical dogma and expert opinion.

RCTs have begun to guide evidence-based care of patients with diverticulitis. However, it is difficult to perform high-quality RCTs due to factors such as inadequate sample sizes to detect differences in infrequent but serious events, and inability to blind treatment allocation. Well-supported, definitive consensus treatment guidelines therefore do not exist, so clinicians must often use their judgment to select treatment. The fact that most major RCTs of medical and surgical treatment have been performed in Europe is a call to action for investigators in the US. The medical community has much to learn, and patients have much to gain from future research of this common, costly, and complicated disease (Table 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

IBD	inflammatory bowel disease
SCAD	segmental colitis associated with diverticular disease
SUDD	symptomatic uncomplicated diverticular disease
IBS	irritable bowel syndrome
NSAID	nonsteroidal anti-inflammatory drug
RCT	randomized controlled trial
SCFAs	short chain fatty acids
RR	relative risk
OR	odds ratio

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What You Need to Know

BACKGROUND AND CONTEXT

Diverticulitis of the colon is one of the most common gastrointestinal disorders in the outpatient and inpatient setting. Research on the epidemiology, pathophysiology and treatment of this disorder has accelerated over the past decade.

NEW FINDINGS

Sigmoid diverticulitis is increasingly prevalent, partly associated with the aging population, but also due to increased incidence among younger Americans. Recurrence occurs in approximately 20% of patients, and disease complicated by peritonitis is more common in the first episode. Diet, lifestyle and certain medications are risk factors for incident diverticulitis. The etiopathogenesis of diverticulitis is thought to involve diet and lifestyle factors, microbiota alterations, neuromuscular abnormalities and genetic predisposition. Randomized control trials indicate that antibiotics may not be helpful for uncomplicated diverticulitis. The decision for elective and even acute surgery should be individualized and primary anastomosis with or without a diverting loop ileostomy is safe in most situations.

LIMITATIONS

Observational studies have been limited by potential selection bias and surgical randomized trials have been hampered by difficulty with recruitment.

IMPACT

Data regarding risk for and treatment of diagnosis have illuminated previous misconceptions about diverticulitis. Much work remains, however, to better understand the pathophysiology of diverticulitis and the best means to prevent incident and recurrent disease as well as more definitive recommendations for management.

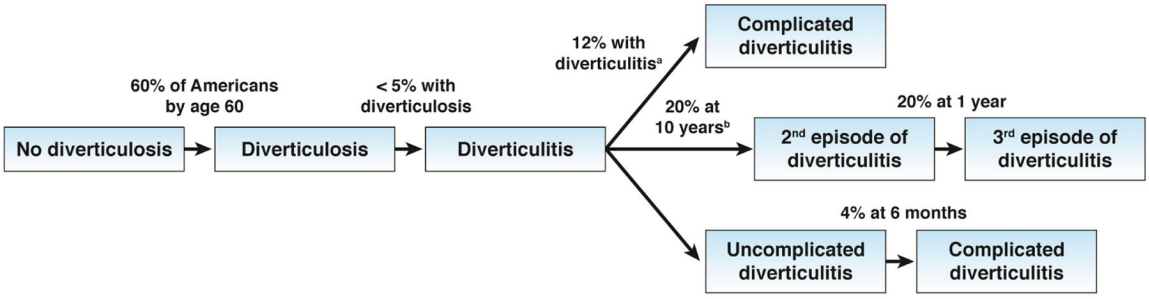

Figure 1.

Natural history of diverticulosis and diverticulitis. aThe majority of complications occur during the first or second episode of diverticulitis.[29, 30] bEstimates of recurrence are for all patients with diverticulitis regardless of the presence of complications and in the absence of prophylactic surgery. Of note, patients with complicated diverticulitis treated medically do not appear to be at increased risk of recurrent diverticulitis compared with uncomplicated diverticulitis. However, the risk of recurrence is significantly lower in those who undergo surgery for complicated diverticulitis.[14]

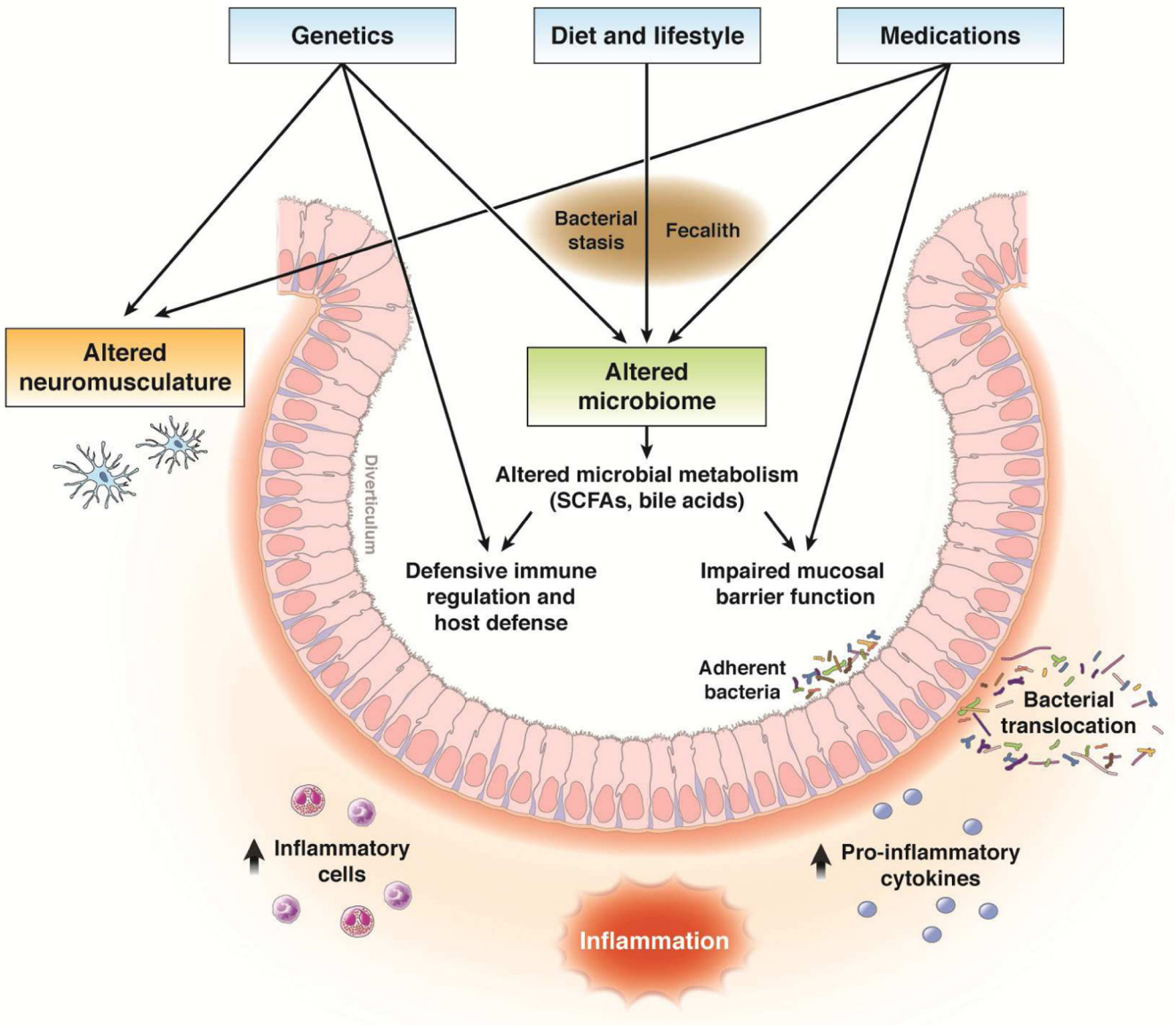

Figure 2.

Proposed pathophysiology of acute colonic diverticulitis. Diverticulitis is hypothesized to arise from the complex interaction of diet and lifestyle factors, medications, genetics, and the gut microbiome. Alterations in the gut microbiome composition (eg, ↓short chain fatty acid, SCFA, producers, ↑invasive pathogens) and function (↓SCFAs, altered bile acids) result in defects in the mucosal barrier and immune function leading to an inflammatory cascade and mucosal inflammation.

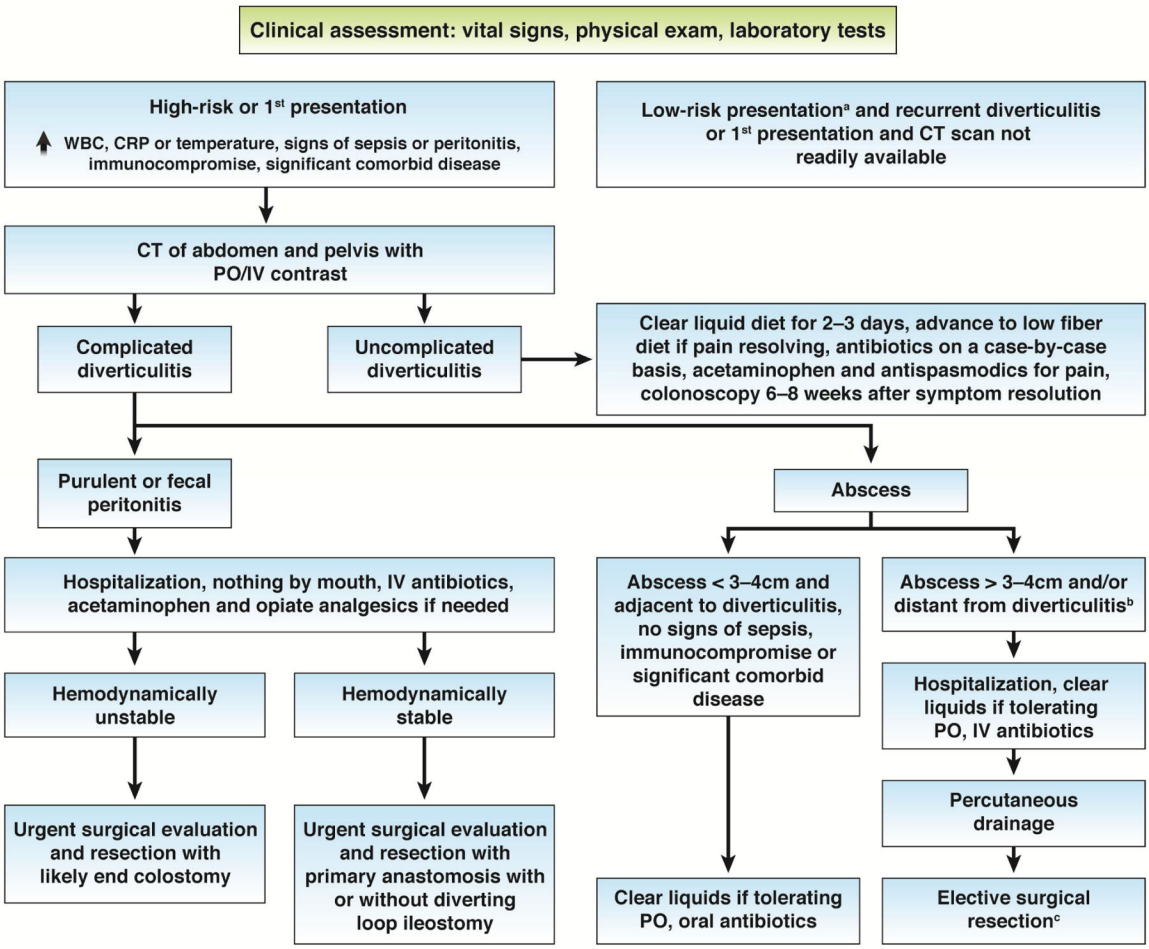

Figure 3.

Management algorithm for acute diverticulitis. Evaluation and treatment approach depends on the severity of presentation, presence of complications (peritonitis, abscess), and comorbid conditions. aLow-risk presentation includes no markedly elevated WBC, CRP, or temperature, no signs of sepsis or peritonitis, no immunocompromise or significant comorbid disease. bSuch as a pelvic abscess. cRecommended by current guidelines, but some evidence to suggest good outcomes without resection in selected patients. CRP, C-reactive protein; IV, intravenous; PO, per os; WBC, white blood cell count.

Table 1.

Risk Factors for Incident Diverticulitis

Risk Factor	Category	RR/OR[a]	References
Diet			
Fiber	Highest quintile	0.57–0.75	48, 49
Nuts	> 2 times/week	0.80	50
Popcorn	> 2 times/week	0.72	50
Vegetarian diet	Yes/no	0.69	49
Prudent dietary pattern[b]	Highest quintile	0.74	39
Western dietary pattern[c]	Highest quintile	1.55	39
Red meat	Highest quintile	1.58	38
Lifestyle			
Physical activity	Highest quintile	0.63–0.75	40, 51, 52
Body mass index (BMI)	BMI ≥ 30	1.33–4.4	40–42
Waist-to-hip ratio	Highest quintile	1.62	42
Smoking	Current or ≥ 15 cigarettes/day	1.23–1.89	41, 45, 46
Medications			
Non-aspirin NSAIDs	≥ 2 times/week	1.72	58
Aspirin	Ever or ≥ 2 times/week	1.25–1.32	57, 58
All NSAIDs	≥ 2 times/week	1.62	58
Corticosteroids	Current use	2.74	57
Opiate analgesics	Current use	2.16	57
Statins	Current use	0.44	57
Vitamin D	Highest quintile	0.49	61
Sibling with diverticular disease	Yes/no	2.92	97

[a]Effect estimates are from select, large, population-based cohort or case-controls studies with adjustment for confounding variables. The study outcomes include hospitalization for diverticulitis, symptomatic diverticular disease and diverticulitis managed in the inpatient or outpatient setting depending on the study.

[b]Prudent dietary pattern is high in fruits, vegetables and whole grains

[c]Western dietary pattern is high in red meat, high-fat dairy, and refined grains

Table 2.

Selected Multi-center Randomized Controlled Trials of Treatment for Acute Diverticulitis

Study name	Author, year	Inclusion criteria	Intervention	Primary Outcome	Main findings
Medical Treatment					
AVOD	Chabok, 2012	CT-based uncomplicated left-sided diverticulitis; Hinchey 1a	IV carbapenem or piperacillin/tazobactam then oral metronidazole plus ciprofloxacin or cefadroxil (n=314) vs. IV fluids (n=309)	Complication rate	No difference in time to recovery, complications, recurrent diverticulitis
DIABLO	Daniels, 2016	CT-based left-sided uncomplicated diverticulitis; Hinchey 1a-1b	IV then PO amoxicillin- clavulanic acid (n=266) vs. observation alone (n=262)	Time to recovery	No difference in time to recovery, complications, recurrent diverticulitis
	Mora Lopez, 2017	Mild, CT-based uncomplicated diverticulitis; Neff grade 0	Oral amoxicillin, ibuprofen, acetaminophen (n=230) vs. ibuprofen and acetaminophen(n=230)	Readmission	Anticipated recruitment until July 2020 (NCT02785549)
Surgical Treatment					
ColonPerfRCT	Oberkofler, 2012	Hinchey III-IV	Sigmoidectomy with anastomosis and diverting ostomy (n=32) *vs.* Hartmann procedure (n=30)	Postoperative complication rate	No differences in postoperative complications. Discontinued due to significant difference favoring primary anastomosis with diverting ostomy and declining enrollment.
SCANDIV	Schultz, 2017	CT-based Hinchey grades I-IV	Laparoscopic lavage (n=101) *vs.* sigmoidectomy (n=98)	Severe postoperative complication within 90 days	Lavage did not reduce severe postoperative complications. The stoma rate was lower in the lavage group (14% vs. 42%; P<0.001). 4 cancers missed with lavage.
DILALA	Kohl, 2018	Laparoscopy-based Hinchey grade III	Laparoscopic lavage (n=43) *vs.* Hartmann procedure (n=40)	Reoperation within 24 months	Fewer patients in the lavage group than in the Hartmann arm had at least 1 reoperation within 12 months (42% *vs.* 67.5%, P = 0.012). Mortality and severe adverse events did not differ between groups.
DIVERTI	Bridoux, 2017	CT-based Hinchey grade III-IV	Primary anastomosis with diverting stoma (n=50) *vs.* Hartmann procedure (n=52)	Mortality within 18 months	Mortality did not differ Hartmann and primary anastomosis (7.7% vs. 4%; p = 0.4233). Morbidity and stoma reversal were comparable (39 vs 44%; p = 0.4233). At 18 months, 96% of PA patients and 65% of HP patients had a stoma reversal (p = 0.0001).
DIRECT	van de Wall, 2017	CT-, US-, or endoscopy confirmed diverticulitis with persistent pain > 3 months and/or 3+ recurrences/2 years	Elective laparoscopic or open sigmoidectomy (n=53) *vs.* conservative management (n=56)	Health-related quality of life	Prematurely terminated due to increasing difficulty with enrollment. Elective sigmoidectomy resulted in better quality of life than conservative management (Gastrointestinal Quality of Life Index mean difference 14.2, 95% CI 7.2–21.1, p<0.0001).
LADIES-LOLA arm	Vennix, 2015	Laparoscopy-based Hinchey grade III	Laparoscopic lavage (n=45) *vs.* sigmoidectomy (n=42)	Composite morbidity* and mortality	Prematurely terminated due to safety concerns in lavage arm.
LADIES-DIVA arm	2010-present	Laparoscopy-based Hinchey grade III-IV	Sigmoidectomy with anastomosis (n=118, anticipated) vs. Hartmann procedure (n=118, anticipated)	Stoma-free survival at 12 months	Anticipated recruitment until March 2017 (NCT01317485)

Study name	Author, year	Inclusion criteria	Intervention	Primary Outcome	Main findings
STELLA	Tartaglia, 2015-present	CT-based Hinchey grade II unresponsive to conservative therapy and grade III	Laparoscopic lavage (n=50 anticipated) vs. Laparoscopic sigmoidectomy (n=50 anticipated)	30-day morbidity, 30-day mortality, 30-day sepsis control 15-day re-intervention	Anticipated recruitment until December 2018 (NCT03008707)
DEBUT	Flum, 2016-present	CT-based Hinchey grades I-IV	No intervention prospective cohort (n=750)	Patient-reported symptom burden and quality of life	Anticipated recruitment until December 2019 (NCT02776787)

Table 3.

Areas of Unmet Need in Diverticular Disease

Epidemiology
Delineate factors associated with the rapid rise in diverticulitis incidence among young patients
Understand the long-term, global impact of acute diverticulitis on patients
Identify markers (clinical and biomarkers) of risk of disease progression/recurrence
Examine sex and racial differences in the incidence of diverticulitis
Define the natural history of diverticulitis in immunocompromised patients
Pathogenesis
Determine the role of systemic and mucosal inflammation in the development diverticulitis
Examine prospectively the gut microbiota and related metabolites in diverticulitis
Clarify risk genes within genetic risk loci associated with diverticulitis and determine mechanisms
Delineate the role of connective tissue and enteric nerve abnormalities in diverticulitis
Medical Treatment
Develop accurate clinical prediction tools to aide in the diagnosis and triage of acute diverticulitis
Examine the role of ultrasound in the diagnosis of diverticulitis (in the U.S.)
Define the long-term consequences of withholding antibiotics in uncomplicated diverticulitis
Compare dietary strategies in the treatment of uncomplicated diverticulitis
Study pain control strategies for complicated and uncomplicated diverticulitis
Surgical Treatment
Compare outcomes in patients undergoing surgery vs no surgery for recurrent diverticulitis
Understand long-term outcomes of medical vs surgical treatment of complicated diverticulitis
Identify predictors of postoperative complications
Identify predictors of resolution of symptoms following surgical resection
Determine the optimal timing of surgery among patient with persistent inflammatory symptoms
Evaluate the modern prognostic value of the Hinchey classification system
Prevention
Define the role of diet and lifestyle modification in the prevention of recurrent diverticulitis
Develop and test new pharmaceutical agents in the prevention of recurrent diverticulitis
Compare medical vs surgical approach to prevention of recurrent diverticulitis