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Updates in Diverticular Disease

Adam W. Templeton¹ and Lisa L. Strate²

¹Department of Medicine, Division of Gastroenterology, University of Washington, Seattle, WA, USA

²Department of Medicine, Division of Gastroenterology, University of Washington, Seattle, WA, USA

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Introduction

Diverticulosis is common, appearing in 15 % of individuals in their 5th decade of life and gradually increasing to 70 % by the 9th decade [1]. Among patients with diverticulosis, 15–25 % are posited to develop diverticulitis in their lifetime [2], although a recent study suggests that this proportion may be much lower (1-2 %) [3]. A smaller subgroup will experience diverticular bleeding, and a less well-defined group will suffer from symptoms attributed to their diverticulosis in the absence of diverticulitis. Recent work by Peery and colleagues suggests that diverticulitis and diverticulosis together are the 6th leading gastrointestinal (GI) diagnosis given for outpatient clinic visits in the US, and diverticulitis and diverticular bleeding are the most common principal GI discharge diagnoses for inpatient hospitalizations [4]. The prevalence of diverticular disease appears to be increasing. In a study of the Nationwide Inpatient Sample (NIS), a stratified sample of all hospital discharges in the US, Nguyen et al. found that hospitalization rates increased between 1998 and 2005 (61.8/100,000 to 75.5/100,000), particularly in those less than 45 years of age [5]. This article will focus on recent notable work in the field and promising future directions of study.

In this article, we will refer specifically to diverticulosis, diverticulitis, and diverticular bleeding when possible. The term diverticular disease will be used only when it is not possible to distinguish between these entities. To ensure adequate capture of recent literature, a Boolean search of PubMed was performed using the search terms "diverticulosis" and "diverticulitis" from January 2011 through March 2013. Additional

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Corresponding Author: Lisa L. Strate, MD, Harborview Medical Center, 325 Ninth Avenue, Seattle WA 98104, USA, UW Box Number 359773, P: (206) 744-7058, F: (206) 744-8698.

Co-author: Adam Templeton, MD, Digestive Diseases Center, University of Washington, 1959 NE Pacific Street, Seattle WA 98105, USA, UW Box Number 356424, P: (206) 598-4303, atempleton@medicine.washington.edu

articles were identified through a review of referenced articles. Notably, in the last decade, there has been considerable growth in the literature. We cannot hope to cover all of the recent work; however, we will touch on the latest updates in diverticular epidemiology and cover the evolving management of acute and recurrent diverticulitis.

Updates in Risk Factors

Historically, advancing age and inadequate dietary fiber were regarded as the major risk factors for diverticulosis and its complications, diverticulitis, and diverticular bleeding. In recent years, increased study of the risk factors for diverticular disease has challenged existing pathophysiologic concepts, and prompted new lines of investigation. For example, in the past, patients with diverticulosis were advised to avoid nuts, seeds, and corn under the assumption that these poorly digested foods incite diverticular obstruction or trauma leading to diverticulitis or bleeding. However, a detailed study of over 50,000 men followed for 18 years found that intake of these foods did not increase the risk of diverticulitis or bleeding. Men who consumed the most nuts and popcorn actually had a decreased risk of diverticulitis when compared to men with the lowest intake [6]. In addition, several large-scale studies have found that obesity is a consistent risk factor for diverticulitis and diverticular bleeding [7–9], potentially as a result of low-grade systemic inflammation. Below, we discuss recent and exciting updates in risk factors for diverticulosis, diverticulitis, and diverticular bleeding.

Genetic Factors

Diverticulosis and its complications have traditionally been ascribed to environmental factors. The contribution of genetic factors to the development of diverticular disease was recently evaluated in two large, population-based studies in Scandinavia.

In a Swedish cohort of over 100,000 twins, of whom 2,296 were hospitalized with a diagnosis of diverticular disease (diverticulosis, diverticulitis, or bleeding), the odds-ratio (OR) of the sibling developing the disease was 7.15 for monozygotic twins and 3.2 for dizygotic twins. The authors calculated that 40 % of the liability to diverticular disease was due to inherited factors, while 60 % was attributable to non-shared environmental factors [10].

Similar results were found in a nationwide study from Demark. Siblings of patients who received a diagnosis of diverticular disease were found to be three times more likely to be diagnosed with diverticular disease when compared to the general population. The risk was higher in siblings of cases who were likely to have had diverticulitis or diverticular bleeding. In a separate analysis of twins, the odds-ratio in monozygotic twins was approximately three times higher than in dizygotic twins (14.5 vs. 5.5), and heritability analysis suggested that 53 % of the liability to diverticular disease is attributable to genetic factors [11]. Interestingly, the younger the index case at diagnosis, the greater the risk was for a sibling to develop the disease. This suggests there may be a "young onset" cohort of diverticular disease with greater genetic susceptibility.

In summary, these studies highlight the importance of genetic factors in the development of diverticulosis, its complications, or both. Further studies are needed to elucidate the genetic basis and its contributions to diverticular disease.

Fiber

Over 40 years ago, Painter and Burkitt put forth their hypothesis that a "low-residual diet", one that was high in processed sugars and low in fiber, was responsible for the development of colonic diverticula [12]. This hypothesis was based mainly on observational data. For

example, diverticular disease was poorly described before 1880, yet by the early part of the twentieth century, diverticula and their complications were common in developed nations and rare in underdeveloped nations. Despite a paucity of data, this fiber hypothesis remains dogma and patients with diverticular disease are frequently advised to increase their dietary fiber intake [13,14]. Two recent studies have attempted to address the importance of dietary fiber in the development of diverticulosis and its complications.

In a prospective cohort study, Crowe et al. queried 47,000 UK subjects regarding dietary factors and assessed their risk of admission to hospital or death from diverticular disease [15]. Individuals who were in the highest fifth of dietary fiber intake (>25.5 g/ day for women and >26.1 g/day for men) had a 42 % lower risk of hospitalization for diverticular disease compared with those in the lowest fifth (<14 g/day for men and women) (RR 0.58; 95 % CI 0.46–0.78). Additionally, persons who were self-reported vegetarians had a 31 % lower risk (0.69 RR, 95 % CI 0.55–0.86) of developing diverticular disease. Interestingly, low fiber alone did not explain the lower risk for vegetarians.

In the US, Peery and colleagues studied 2,014 subjects who underwent a screening colonoscopy for colorectal cancer and then assessed their dietary intake by questionnaire [16]. A total of 878 patients (41 %) were noted to have diverticulosis on their colonoscopy report. Contrary to long-held belief, the authors found that increased fiber consumption increased the risk of diverticulosis in a dose-dependent fashion. After adjusting for other variables such as age, race, and body-mass-index, individuals in the highest quartile of total fiber intake had an increased prevalence ratio (1.30; 95 % CI, 1.13–1.50) compared to the lowest quartile. In addition, frequent bowel movements were positively associated with diverticulosis.

These studies suggest that fiber consumption may have differing effects on the development of diverticulosis and diverticular complications. The work by Peery et al. challenges the concept that low fiber diets and constipation contribute to the development of diverticulosis and opens the door for new pathoetiologic concepts. However, it is premature to recommend against dietary fiber given its other health benefits.

Medications

Medications, most prominently nonsteroidal anti-inflammatory drugs (NSAIDs), have been identified as potential risk factors for diverticulitis and diverticular bleeding [17]. Two recent large-scale studies have helped define and quantify the risk of diverticular complications associated with the use of NSAIDs and other medications.

Strate and colleagues followed 47,000 male health professionals over a 22-year period including detailed assessment of aspirin and NSAIDs [18]. They found that aspirin and NSAIDs were associated with an increased risk of both diverticulitis and diverticular bleeding. This was true even after adjusting for other known or possible risk factors. The magnitude of bleeding risk was similar for NSAID and aspirin users (hazard ratio 1.70 and 1.74, respectively). However, the risk of diverticulitis was somewhat greater among NSAID users than aspirin users (hazard ratio 1.72 and 1.25, respectively).

Humes et al. addressed the relationship between a number of medications and the risk of perforated diverticulitis using the nationwide UK General Practice Research Database [19]. In this study of 899 incident cases and 8,980 matched controls, the authors found that perforated diverticulitis was more common in patients taking opiate analgesics (OR 2.16; 95 % CI 1.55–3.01) and oral corticosteroids (OR 2.74; 95 % CI 1.63–4.61). In addition, patients taking statins were at a decreased risk (OR 0.44; 95 % CI 0.20–0.95). These findings were significant even after controlling for smoking, comorbidity, and BMI, all of which were

These results help identify patients at risk for developing diverticular complications, although it remains unclear whether interventions targeting these medications or other modifiable risk factors will be of preventative benefit.

Management of Diverticulitis

Parks and others in the late 1960s and 1970s set the precedence for the management of acute diverticulitis, including the use of broad-spectrum antibiotics in all patients and surgical resection in patients with complicated diverticulitis (abscess, fistula) or more than two attacks of diverticulitis [20]. Over the last few decades, the surgical management of diverticulitis has moved to less invasive and aggressive approaches. The American Society of Colon and Rectal Surgeons (ASCRS) now recommend an individualized approach to elective surgery for diverticulitis and laparoscopic management when possible.[21] There are several trials ongoing in Europe evaluating laparoscopic peritoneal lavage without immediate colon resection for select patients with perforated, non-feculent diverticulitis [22,23]. In addition to changes in surgical management, recent work also challenges the long-standing recommendation that antibiotics should be used for all patients with acute diverticulitis.

Antibiotics in Acute Uncomplicated Diverticulitis

Limiting the use of antibiotics and the duration of treatment once antibiotics are initiated is increasingly important with the emergence of multi-drug resistant bacteria and the rise of *Clostridum difficile*. In the case of diverticulitis, some authors speculate that diverticulitis may be an inflammatory rather than infectious condition, which may not be best addressed with antibiotics [24]. In addition, there is little evidence supporting the benefit of antibiotics in the treatment of acute, uncomplicated diverticulitis. Notably, two retrospective series found similar outcomes in patients with acute, uncomplicated diverticulitis treated with and without antibiotics [25,26].

In a recent multicenter trial in Sweden and Iceland, 623 patients with CT-confirmed acute, uncomplicated, left-sided diverticulitis were randomized to antibiotics versus no antibiotics [27]. The investigators found no difference in the number of patients who developed perforation and abscess (1.9 vs. 1 %; p = 0.302); recurrent diverticulitis necessitating readmission to hospital at 1 year was the same in both treatment groups (16 %); and only ten patients in the no antibiotic arm received antibiotics due to increasing symptoms or inflammatory markers. Per protocol and intention-to-treat analyses yielded similar results.

Overall, the few existing studies suggest that a subset of patients with acute uncomplicated diverticulitis can be managed safely without antibiotics [28]. This approach has already been embraced in Europe where a survey found that 90 % of Dutch surgeons and gastroenterologists manage mild diverticulitis without antibiotics [29]. In addition, recently published Danish national guidelines for treatment of diverticular disease do not recommend routine antibiotics for uncomplicated diverticulitis in patients without sepsis, significant comorbidity, pregnancy or immunosuppression [30]. Another large, multicenter trial of antibiotics versus no antibiotics is currently ongoing in Europe and promises to shed more light on this issue [31].

Diverticulitis and Irritable Bowel Syndrome

Patients with diverticulosis are more likely to report abdominal pain and altered bowel habits [32–35], suggesting that some patients with diverticulosis will have bothersome symptoms even in the absence of imaging or endoscopic visualization of inflammation. In a recent article, Cohen and colleagues [36] retrospectively reviewed a Veterans Administration dataset of subjects who were given a diagnosis of diverticulitis and had no previous diagnosis of functional bowel disease or psychiatric disease. These subjects were then compared to randomly identified controls. The researchers found that subjects were 4.7 times more likely to receive a diagnosis of irritable bowel syndrome than controls (95 % CI = 1.6–14.0; p = 0.006), 2.4 times more likely to receive a diagnosis of any functional bowel disorder (95 % CI = 1.6–3.6; p < 0.001) and 2.2 times more likely (CI 1.4–3.6; p < 0.001) to receive a new diagnosis of mooddisorder. They termed this entity post-diverticulitis irritable bowel syndrome (PDV-IBS). Confirmatory study is necessary; however, this retrospective review lends credence to the concept that in a subset of patients, diverticulitis can take a chronic and symptomatic course.

Diverticulitis and Colon Cancer

The signs and symptoms of colon cancer may masquerade as diverticulitis and repeated episodes of diverticular inflammation may predispose patients to the subsequent development of colon cancer [37]. These possibilities have led to the recommendation that patients undergo a colonoscopy following resolution of an episode of acute diverticulitis. Data on the relationship between diverticular disease and colon cancer are sparse and conflicting [37–43]. In a recent 15-year nationwide case–control study in Sweden, the odds of receiving a diagnosis of colorectal cancer after admission for diverticular disease was substantially elevated at 31.49 (95 % CI 19-52). However, after 12 months, this risk returned to baseline and colon cancer mortality did not differ between those with and without diverticular disease [39]. This suggests that diverticular disease does not increase the risk of colon cancer and that early diagnoses were the result of initial misdiagnoses or surveillance. This database study does not make clear how many patients underwent imaging at the time of diagnosis. In our current era of CT scanning, CT may be a sensitive enough tool for differentiating colon cancer from acute diverticulitis. Several retrospective case series suggest that this is the case [41-43]; however, at this point there is little highquality data to refute the current practice of screening colonoscopy following an episode of diverticulitis.

Conclusions

The study of diverticulosis and its complications is in an exciting period of growth. Recent studies have challenged long-held assumptions that nuts, corn, and seeds provoke diverticulitis and bleeding, and that low-fiber intake leads to the development of diverticulosis. In addition, we have learned that diverticular disease has a heritable component, and that a subset of patients may develop chronic symptoms following a self-limited attack of acute diverticulitis. The management of acute diverticulitis also continues to evolve. Experience from centers in Europe suggests that antibiotics may not be needed in some patients with acute uncomplicated diverticulitis and that less invasive surgical approaches to complicated diverticulitis may be feasible. These exciting and paradigm-shifting developments in the epidemiology and management of diverticulosis, diverticulitis, and diverticular bleeding are likely to spur new research that furthers our understanding of the pathophysiology and management of diverticulosis and its complications, diverticulitis and diverticular bleeding.

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