Review article

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Recent updates on classification and unsolved issues of diverticular disease: a narrative review

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Recently, a paradigm shift has occurred in the classification of diverticular disease and the understanding of its pathogenesis. Diverticular disease is now defined as a variety of clinically significant conditions such as diverticulitis, diverticular bleeding, symptomatic uncomplicated diverticular disease, and segmental colitis associated with diverticulosis. Low-grade inflammation, visceral hypersensitivity, abnormal intestinal motility, and genetic factors have emerged as the key contributors to the pathogenesis of diverticular disease. Routine antibiotic use is no longer recommended for all cases of diverticulitis, and simple recurrence is not an indication for surgical treatment. Early colonoscopy with proper preparation is recommended for the treatment of diverticular bleeding, although recent studies have not shown significant efficacy in preventing recurrence. The roles of dietary fiber, nonabsorbable antibiotics, 5-aminosalicylates, and probiotics in the prevention of diverticular disease are controversial and require further investigation.

Keywords: Diverticular disease; Diverticulitis; Diverticulum; Etiology; Therapy

Introduction

Colonic diverticulosis is defined as a protrusion of the mucosa and submucosa through a weak portion of the muscle layer [1]. Although the underlying mechanism of diverticulosis has not been fully elucidated, decreased stool volume due to a low-fiber diet, delayed colon transit, constipation, and increased intraluminal pressure due to overcontraction have been implicated [2-4].

Although the prevalence of colonic diverticulosis is lower in Asia than in Western countries, it has increased with an aging society and westernized food culture [5]. Diverticular disease is sometimes considered synonymous with diverticulosis; however, the exact definition of diverticular disease is a condition that combines clinically significant symptoms, including diverticulitis and diverticular bleeding [6-8]. In this review, we discuss the classification and unresolved issues associated with diverticular diseases in terms of diagnosis, treatment, and prevention.

Classification

Diverticulosis can be classified as asymptomatic or symptomatic. Symptomatic diverticulosis is similar to diverticular disease. Asymptomatic diverticulosis is usually detected incidentally during radiologic or colonoscopic evaluation [1]. According to a previous report, diverticulosis is more common in the left colon in Western countries, and not all colonic walls protrude (pseudodiverticulum) [1]. In contrast, in Asia, diverticulosis usually presents as a true diverticulum, which is more common in the right colon and does not increase with aging [1]. However, these differences decrease over time in Asians who move to Western countries, indicating the significant impact of diet and lifestyle [9].

A precise definition of the clinical significance of asymptomatic

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diverticulosis is lacking, making indications for treatment controversial [10]. Symptomatic diverticulosis or diverticular disease includes diverticulitis, diverticular bleeding, symptomatic uncomplicated diverticular disease (SUDD), and segmental colitis associated with diverticulosis (SCAD) (Fig. 1) [9].

1. Diverticulitis

Diverticulitis can be defined as acute or chronic inflammation of the diverticulum and is the most common complication (4%–15%) of diverticulosis [11,12]. Diverticulitis develops when fecaliths obstruct the sac owing to mucosal irritation, low-grade inflammation, and congestion [10]. Diverticulitis can be classified based on the presence or absence of complications [13]. Uncomplicated diverticulitis is an inflammation of the diverticulum and its surrounding wall, whereas complicated diverticulitis presents with an abscess, perforation, fistula, stricture, or obstruction. Diverticulitis has a prevalence of 12% to 15% [14,15].

Most cases of diverticulitis are acute episodes; however, approximately 5% to 10% of cases show prolonged symptoms. The typical symptoms of acute diverticulitis include localized abdominal pain (mostly in the left lower quadrant in Western countries and the right lower quadrant in Asia) [16,17].

2. Diverticular bleeding

Diverticular bleeding is one of the main causes of acute lower gastrointestinal bleeding. According to a previous study, approximately 30% to 65% of lower gastrointestinal bleeding cases are related to diverticula [18]. A bleeding incidence of 10% to 15% has been reported in patients with diverticulosis [7,8,19]. Bleeding is thought to develop from the herniated exposed vasa recta that protrudes over the dome of the diverticulum [1]. Diverticular bleeding is more common in the right-sided colon because the wall is thinner and the neck of the diverticulum is wider [20-22].

Diverticular bleeding is usually painless and is self-limiting in most cases [23]. Bleeding is brisk in some patients with hypotension and tachycardia, requiring resuscitation and transfusion.

Diagnosis can be confirmed by colonoscopy when there is a single diverticulum with obvious evidence of bleeding, such as active bleeding, exposed vessels, or adherent clots. However, the probability of detection is less than 15% to 20% [8,24].

3. Symptomatic uncomplicated diverticular disease

SUDD is suspected when patients complain of nonspecific abdominal pain with no evidence of inflammation in the diverticulum by endoscopy or radiology [1]. Pain is typically colicky but can be continuous and improves after defecation. Changes in bloating and bowel habits may also occur. Considering these symptoms, distinguishing SUDD from irritable bowel syndrome (IBS) can be challenging. A recent study reported a prevalence of up to 15% for SUDD in diverticulosis, with classifications including SUDD, IBS-like SUDD, and post-diverticulitis SUDD [25].

The suggested pathogenesis of SUDD includes visceral hypersensitivity, low-grade inflammation, changes in gut microbiota, and abnormal colonic motility following an episode of diverticulitis [26-30]. Due to their overlapping pathogeneses and clinical symptoms, the current treatments for SUDD and IBS are similar, including fiber intake and antibiotics such as rifaximin [31,32]. Mesalamine, probiotics, and antispasmodics can also be considered as treatment options, although their indications have not yet been established [31].

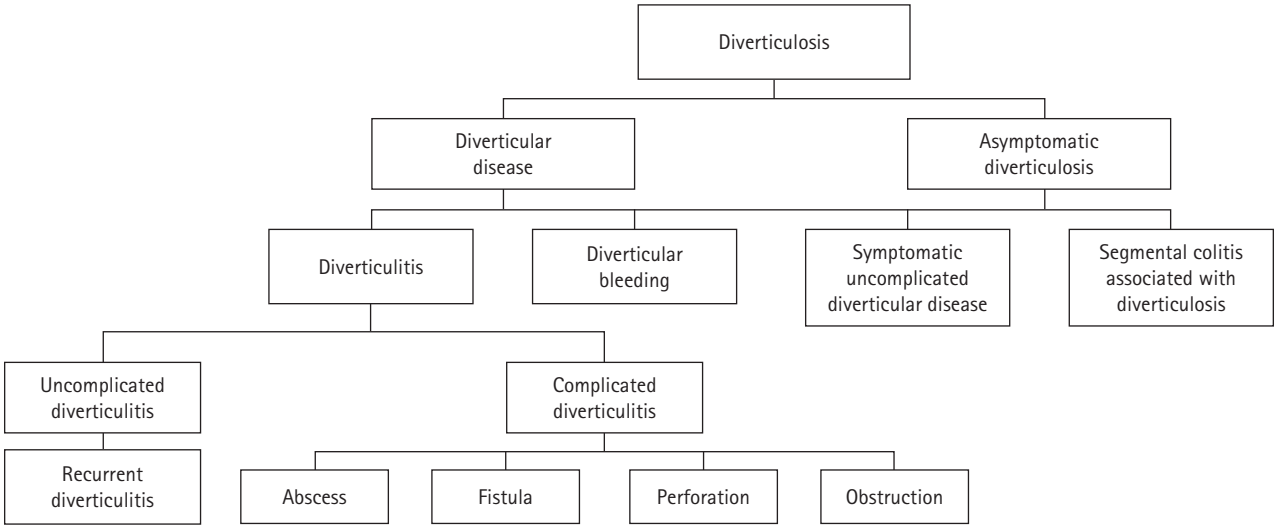

Fig. 1. Classification of diverticulosis and diverticular disease.

4. Segmental colitis associated with diverticulosis

SCAD is known as diverticula-associated colitis and is diagnosed when there is chronic inflammation in an area of colonic diverticulosis without involvement of the diverticular orifice. The estimated prevalence of SCAD in diverticulosis is 1% [33,34]. Various clinical symptoms, including bleeding, diarrhea, and abdominal pain, can occur simultaneously. Endoscopy can reveal erythema, friability, and erosion, and computed tomography (CT) can reveal inflammation around the diverticula. Typically, inflammation spares the rectum and ascending colon [34]. The evidence for treatment is limited; however, antibiotics such as ciprofloxacin and metronidazole with mesalamine or oral steroids can be considered [35,36].

Risk of diverticular disease associated with aspirin and nonsteroidal anti-inflammatory drugs

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) directly injure the colonic mucosa and inhibit prostaglandin synthesis. They increase intestinal permeability and reduce barrier function. Therefore, diverticular disease develops due to the influx of gut microbiota and toxins into the colon [37,38]. In addition, these drugs can aggravate diverticular bleeding owing to mucosal ulceration and decreased platelet function [39].

The association between aspirin or NSAIDs and diverticular disease has been demonstrated in a longitudinal study [40]. This large prospective cohort study in the United States included 47,210 males from the Health Professionals Follow-up Study who worked in the medical field in 1986 and were aged 40 years to 75 years. Data on aspirin and NSAIDs use were evaluated every 2 years since 1986, and the history of diverticular disease was collected every 2 years since 1990. A total of 939 diverticulitis and 256 diverticular bleeding cases were reported during 22 years of follow-up. After adjusting for other risk factors of diverticular disease, participants who took aspirin at least two times per week showed a significantly higher risk of diverticulitis than those in the control group (hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.05–1.47), and the HR for diverticular bleeding was 1.70 (95% CI, 1.20–2.39). Another meta-analysis of 11 studies on NSAIDs indicated an association with diverticular perforation (odds ratio [OR], 3.4) and 12 studies indicated an association with diverticular bleeding (OR, 2.6) [41].

Management of colonic diverticulitis

1. Dietary restriction and bowel rest for colonic diverticulitis

Although many clinicians recommend diet restriction during the acute phase of diverticulitis, the evidence is scarce. Considering that food intake increases peristalsis and pressure on the intestine, a restricted diet could be beneficial. However, this is not always necessary in outpatient settings in the absence of fever or other severe symptoms. A clear diet can be attempted in these cases and advanced based on symptom improvement within 3 to 5 days [15,42].

2. Antibiotics in uncomplicated diverticulitis

Diet modification is the best management strategy for incidental asymptomatic diverticulosis, and fiber intake can reduce the risk of diverticular disease-associated hospitalization [43,44]. Mild cases of symptomatic uncomplicated acute diverticulitis can be treated with broad-spectrum antibiotics against anaerobic microorganisms in outpatient clinics for 7 to 10 days [45-48]. Regarding treatment duration, one study indicated no significant difference between the 4- and 7-day treatment courses [49].

Hospitalization with intravenous antibiotics and fluid treatment is required for patients with severe symptoms or for older adults. Approximately 75% of patients who are hospitalized with acute diverticulitis respond favorably to medical treatment [50,51]. Clinical guidelines recommend changing intravenous antibiotics to oral agents if patients show clinical improvement without fever for 24 to 48 hours and a decreased leukocyte count [52]. Antibiotics must target both aerobic and anaerobic microbes. The most used antibiotics in outpatient clinics are a combination of ciprofloxacin and metronidazole [53]. In patients who are hospitalized, a combination of intravenous ceftriaxone and metronidazole, piperacillin and tazobactam, or meropenem as a single agent, can be used for 7 to 10 days [54].

A recent multicenter randomized clinical trial of 623 patients with uncomplicated acute diverticulitis showed no significant difference in recurrence or complications for 1 year after the episode between patients treated with and without antibiotics [55]. A meta-analysis by Hjern et al. [56] also indicated no additional benefits of antibiotics for uncomplicated left-sided diverticulitis. Similarly, a recent meta-analysis revealed that conservative treatment without antibiotics reduced the number of hospitalization days in patients who were clinically stable with uncomplicated diverticulitis [57]. Considering the risks of antibiotic resistance, cost, and adverse events, more care should be taken regarding antibiotic treatment for uncomplicated diverticulitis based on these recent data. Therefore, recent practice guidelines recommend antibiotics for uncomplicated mild diverticulitis only in cases of American Society of Anesthesiologists class III or IV comorbidities, persistent symptoms longer than 5 days prior to presentation, and a C-reactive protein level of > 14 mg/dL or a white blood cell level of > 15,000 cells/L [15].

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3. Indication for hospitalization and discharge criteria in diverticulitis

Patients with uncomplicated diverticulitis can be treated in an outpatient setting, unless they have significant comorbidities or are immunosuppressed [47,48]. According to a retrospective study, patients with mildly complicated diverticulitis (abscess < 4 cm or pneumoperitoneum < 2 cm) can also be safely treated in outpatient clinics with close follow-up [58]. However, another retrospective study revealed a 50% rehospitalization rate after discharge from the emergency department [59]. More studies on the indications for hospitalization in mildly complicated diverticulitis are needed.

Discharge can be considered when symptoms are well-controlled without complications and the patient tolerates diet, is immunocompetent, and has stable vital signs [15,60-62]. Postdischarge follow-ups are required, especially in patients who are discharged without antibiotic therapy.

Colonoscopy in diverticular disease

1. Colonoscopy after diverticulitis diagnosed by computed tomography

CT is the first and most widely used diagnostic modality because it is noninvasive and useful for evaluating inflammation around the diverticulum and detecting complications [63]. CT has an estimated sensitivity and specificity of 98% and 99%, respectively [64]. CT can be helpful in differentiating diverticulitis from other diseases such as colon cancer, appendicitis, epiploic appendagitis, ischemic colitis, and inflammatory bowel disease [64].

As CT can show the presence of a diverticulum with bowel wall thickening, pericolic infiltration, enhancement, abscess, obstruction, and lymph node enlargement in diverticulitis, differentiating diverticulitis from malignancy is sometimes difficult [65]. Therefore, colonoscopy is recommended to exclude the possibility of malignancy after an episode of diverticulitis, particularly in patients with no history of colonoscopy [66]. According to one systematic review evaluating the clinical utility of colonoscopy after acute diverticulitis diagnosed by abdominal CT, colonoscopy 4 to 8 weeks after a diverticulitis episode detected 15 cases of colon cancer and 38 cases of advanced adenoma [67].

As inflation with gas can result in colonic perforation, colonoscopy should be avoided during the acute phase. Therefore, colonoscopy is usually recommended at least 6 weeks after recovery from acute diverticulitis [68].

Urgent colonoscopy in diverticular bleeding

Although colonoscopy is a useful modality for diagnosing and treating colonic diverticular bleeding, it is challenging because the bleeding ceases spontaneously in 75% of cases [23]. After spontaneous hemostasis, identifying and treating the stigmata associated with a recent hemorrhage is difficult. Studies that indicated the effectiveness of colonoscopy within 24 hours of admission failed to show an improvement in the rebleeding rate within 30 days [69-71]. A recent multicenter randomized controlled study reported no significant difference in the stigmata of recent bleeding and rebleeding within 30 days between early (24 hours) and elective (> 24 hours) colonoscopy. Another study showed that elective colonoscopy could be performed except in cases of positive extravasation on CT [72]. Another difficulty associated with early colonoscopy is bowel preparation. Bowel preparation is essential for visualizing lesions; however, it is time-consuming.

Although it did not show significant efficacy in improving the rebleeding rate, early colonoscopy with proper bowel preparation could help detect the bleeding focus, which is usually suggested in practice [42].

Indications of surgical treatment in diverticular disease

1. Diverticulitis

The old concept that the risk of complications increases after one or two recurrences has changed. Recent evidence has shown that the risk does not increase despite multiple recurrences [73]. Moreover, most complications develop during the first or second episode, except for fistulas. Based on these results, a personalized approach considering the number of recurrences, severity, and patient condition has been suggested [73]. Surgical treatment should be reserved for patients with peritonitis or perforation [73].

2. Diverticular bleeding

Although diverticular bleeding is the most common cause of hematochezia in patients who are older (≥ 60 years), only 10% to 15% of patients with diverticulosis experience bleeding, and 3% to 5% of these cases are severe [74-77]. More than 50% of diverticular bleeding cases stop spontaneously and only 4.6% require endoscopic intervention [78]. Surgery is rarely required in such cases. The indications for surgery include the requirement for transfusion of more than six units within 24 hours [79], recurrent hemorrhage that is refractory or not indicated for nonsurgical treatment, or hemodynamic instability [80]. The mortality rate of emergency

surgery for uncontrolled bleeding is reportedly 10% to 20% [81,82].

Segmental resection should be considered only in confirmed bleeding foci, but the rebleeding rate is up to 14% [83]. Thus, a postoperative colonoscopy is needed to detect the bleeding focus and the presence of diverticulosis, and right or left colectomy should be performed. In cases of refractory bleeding from an undetectable focus, subtotal colectomy is required, with a high risk of complications and mortality [79].

High-fiber diet and various medications for prevention of diverticular disease

Traditionally, diverticulitis has been considered to develop due to obstruction of the diverticulum opening, fecal stasis, and bacterial overgrowth [84]. However, the concept of diverticular disease as a chronic inflammatory disease has recently emerged [85,86]. Microscopic low-grade inflammation around the diverticulum without evidence of gross inflammation, an association between the degree of inflammation and symptom severity, and increased proinflammatory cytokines such as tumor necrosis factor-α could indicate that chronic inflammation is critical in the development of diverticular disease [87]. In addition, changes in gut microbiota, visceral hypersensitivity, and abnormal bowel motility interact in a complex manner to cause diverticular disease [1]. Based on this understanding of pathogenesis, studies on the efficacy of 5-aminosalicylates (5-ASAs), rifaximin, and probiotics in preventing diverticulitis recurrence and improving chronic inflammation have been reported [88-90].

A high-fiber diet appears to reduce the long-term risk of diverticulitis recurrence [91,92], but a recent systematic literature review reported limited evidence [93]. Although the importance of dietary fiber has waned recently, it is still recommended for its potential preventive benefits [91]. It is reasonable to recommend a high-fiber diet because it reduces the risk of symptomatic diverticular disease, including diverticulitis and bleeding [44]. It also has favorable effects on various chronic diseases, such as cardiovascular disease, obesity, and diabetes [1].

Recently, other medications such as rifaximin, 5-ASAs, and probiotics have been suggested to prevent diverticulitis. Rifaximin (a nonabsorbable antibiotic) significantly reduced the symptoms of diverticulitis at 1 year [32]; however, a recent study failed to confirm the role of rifaximin in secondary prevention and its proper dosing [94].

In the case of mesalamine, there are conflicting data, with only one positive result compared with placebo [95-97]. A 2017 Cochrane review of seven randomized controlled trials found no significant differences in diverticulitis recurrence. However, the data quality was very low and significantly heterogeneous [98]. Although some studies have shown a tendency for improved symptoms and reduced recurrence [99], there has been insufficient evidence to recommend probiotics in the prevention of diverticulitis [100]. In addition to these medications for secondary prevention, general recommendations for the prevention of diverticular disease, especially diverticulitis, are summarized in Table 1, although the evidence is limited [101].

Conclusion

In addition to traditional concepts, chronic low-grade inflamma-

Table 1. Suggested recommendations for the prevention of diverticular disease

Recommendation	Criterion	RR (95% CI) of diverticular disease
High-fiber diet	Highest quintile	0.59 (0.46–0.78)
Increased nut consumption	> 2 times per week	0.80 (0.63–1.01)
Increased popcorn consumption	> 2 times per week	0.72 (0.56–0.92)
Reduced red meat consumption	Highest quintile	1.58 (1.19–2.11)
Decreased body mass index	≥ 30 kg per m^2	1.78 (1.08–2.94)
Increased physical activity	Highest quintile	0.75 (0.58–0.95)
Stop smoking	Current or ≥ 15 cigarettes per day	1.56 (1.42–1.72)
Stop NSAIDs	> 2 times per week	1.65 (1.36–2.01)
Stop corticosteroid	Current use	1.72 (1.40–2.11)
Stop opiates	Current use	2.16 (1.55–3.01)
Secondary prevention after diverticulitis		
Rifaximin	Promising but not yet recommended due to poor evidence	
Mesalamine		
Probiotics		

RR, relative risk; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.

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tion, alterations in the gut microbiota, visceral hypersensitivity, and abnormal intestinal motility have recently emerged as important factors in the pathogenesis of diverticular disease. Although guidelines based on recent clinical studies provide recommendations regarding the diagnosis, management, and prevention of diverticular diseases, controversies remain regarding dietary modifications, prophylactic medications, surgical indications, and the use of antibiotics for uncomplicated diverticulitis. Further studies are required to confirm these issues based on routine practice.

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Conflicts of interest

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