Current Gastroenterology Reports (2019) 21: 46
https://doi.org/10.1007/s11894-019-0715-4

GASTROENTEROLOGY IN GERIATRIC PATIENTS (S CHOKHAVATIA, SECTION EDITOR)

Diverticular Disease in the Elderly

Mona Rezapour[1] · Neil Stollman[2]

Published online: 25 July 2019

Abstract
Purpose of Review While few diseases are limited solely to the elderly, diverticular disease is clearly more prevalent with increasing age and therefore the aim of this review is to focus on the clinical implications of diverticular disease in the elderly.
Recent Findings Diverticulitis in the elderly is best managed with an individualized treatment approach including considerations for selective antibiotic usage even in uncomplicated disease. Furthermore, due to the increased prevalence of ischemic colitis in the elderly and the similarities in presentation with diverticular hemorrhage, there needs to be a high index of suspicion and appropriate evaluation for ischemic colitis in patients with hematochezia, particularly if they have abdominal pain.
Summary The elderly are a vulnerable population where the index of suspicion for complications of diverticular disease should be high.

Keywords Diverticular disease · Elderly · Diverticulitis · Diverticulosis · Older age · Colitis

Introduction

Diverticulosis is defined by the presence of sac-like herniation of the colonic mucosa through the muscularis mucosa at sites of vascular weakness (Image 1) [1]. Diverticular disease of the colon is the most common incidental lesion found on routine colonoscopy [2]. It is ranked in the top 10 leading diagnoses in the outpatient setting and 11th as the leading cause of death [3••]. Diverticulitis ranks 6th as the most common gastrointestinal diagnoses in US hospitals in 2014 [3••]. According to Peery et al., in 2015, the total annual US expense due to diverticulosis and diverticulitis was more than $5 billion [3••], the majority of which is due to inpatient hospital stay with emergency room visits ranked second [3••]. Diverticular disease is the most common disease of the colon affecting the Western world without an overall gender bias [4].

Although diverticulosis is often asymptomatic (Fig. 1) and incidentally found, a subset of patients will present with clinical manifestations including acute uncomplicated diverticulitis, complicated diverticulitis with perforation, abscess, strictures or fistulas, symptomatic uncomplicated diverticular disease (SUDD), and diverticular bleeding and segmental colitis associated with diverticulosis (SCAD) (Fig. 1) [1, 3••, 5–7]. Overall, about 80–85% of individuals with diverticulosis will remain asymptomatic [2]. Acute diverticulitis occurs in about 4–5% of those with diverticulosis [7, 8], of which 85% will manifest as uncomplicated disease [9]. The prevalence of diverticulosis increases progressively with age, affecting about 60% of adults over 60 years of age [5, 6]. The prevalence of diverticular disease in those under 40 is about 5% [4, 10]. The main aim of this review is to understand the clinical implications of diverticular disease, with attention to the elderly patient.

Pathogenesis

The pathogenesis of colonic diverticulosis remains largely unknown and likely multifactorial and complex. Several factors have been postulated to play a role including colonic motility and wall structure, genetics, diet, inflammation, and the microbiome.

Colonic diverticula form between the taeniae coli in areas of weakness in the muscularis mucosa where blood vessels

This article is part of the Topical Collection on *Gastroenterology in Geriatric Patients*

✉ Neil Stollman
Neil@Stollman.com

[1] Division of Gastroenterology and Hepatology, University of Miami, Miami, FL, USA

[2] Alta Bates Summit Medical Center, East Bay Center for Digestive Health, 300 Frank H Ogawa Plaza, Suite 450, Oakland, CA 94612, USA

penetrate the colonic wall [1]. In 1971, Burkitt first described the etiology of diverticular disease [11, 12] and postulated that fiber-depleted diets cause increased intracolonic pressures and also slow transit time through the colon [11]. This hypothesis, accepted as dogma for decades, was recently challenged by a report that hard stools, less frequent stools, and straining or sense of incomplete evaluation were not associated with diverticulosis [13]. The precise role of fiber in the pathogenesis of diverticulosis (as compared with its role in complications, as per below) remains unclear.

Genetics

Along with environmental factors, recent data now also point to genetic factors playing a role in the pathogenesis of diverticular disease. This has been supported by various epidemiological data on twins, migrants living in high prevalent regions, and anatomic location of disease. In terms of location of disease, it has been observed that while in the Western world, the primary location of diverticular disease is in the left colon 90% of the time, Asian patients present with diverticular disease in the right colon 55–71% of the time [14–16]. Twin studies in Swedish and Danish registries both show that the development of diverticulosis in twin siblings is significantly higher than the general population and greater in monozygotic than dizygotic twins [17, 18•]. Both studies reported a 40–50% contribution from heritability to the development of diverticular disease [17, 18•]. Lastly, specific single nuclear polymorphisms in the TFNSF15 gene have been found to be a marker of diverticulitis severity requiring surgical intervention [19], also supporting a genetic component.

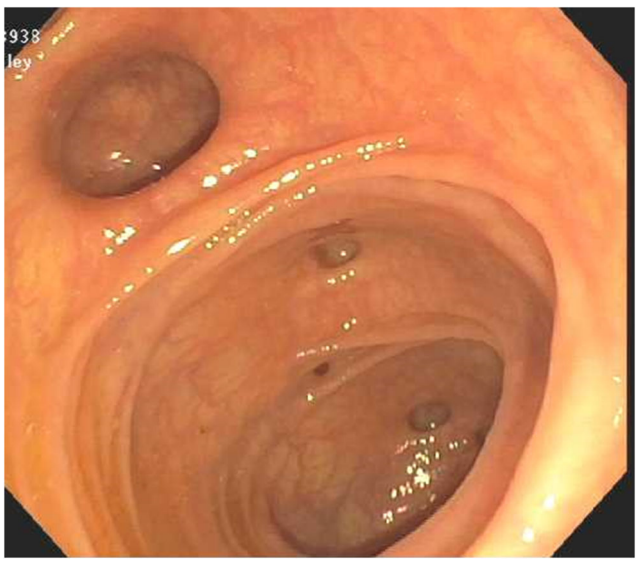

Image 1. Diverticulosis on colonoscopy

Dietary Fiber

As mentioned above, the role of dietary fiber in the pathogenesis of diverticular disease is controversial. The previous paradigm that low dietary fiber intake resulted in higher intracolonic pressures and therefore diverticulum formation has been more recently challenged [5, 20]. Peery et al. studied the relationship between dietary fiber intake and bowel habit and found that constipation was not associated with diverticulosis and further that there was no association between dietary fiber intake and risk of diverticulosis development [5, 13]. This single study has methodologic limitations, however, and we believe this remains an unanswered question, although the role of dietary fiber intake in the development of diverticular disease complications has been more defined. Several studies have now shown low dietary fiber intake increases the risk of developing symptomatic diverticular disease, and increases hospital admissions and death from diverticular disease [21–23]. Therefore, the American Gastroenterology Association (AGA) guidelines on the management of diverticulitis strongly suggest a high-fiber diet in patients with a history of acute diverticulitis [24•].

Role of Microbiome

The gut microbiome has been implicated in numerous disease states and it has been hypothesized that gut microbiota could be involved in the development of symptoms and complications associated with diverticular disease as well [25]. The mechanism hypothesized is that dysbiosis of luminal microbiota together with mucosal barrier breakdown and bacterial translocation leads to an inflammatory response [25]. Barbara et al. examined the microbiome and the metabolome of patients with diverticular disease and found that patients with diverticula had a greater than 70% increase in colonic macrophages (an indicator of mucosal inflammation) and also found a depletion of *Clostridium* Cluster IV in patients with diverticular disease [25]. *Clostridium* Cluster IV is a group of anti-inflammatory and butyrate-producing bacterial species which have also been implicated in the pathogenesis of IBD and IBS [26, 27]. This result highlights that patients with diverticular disease may have depletion of anti-inflammatory gut bacteria, which is associated with an increase in mucosal inflammation [25]. Other descriptive reports have cataloged various associations, but causality is difficult to establish.

Role of Inflammation

One postulated theory for the pathogenesis of diverticular disease is chronic inflammation. However, studies evaluating the role of low-grade inflammation in the pathogenesis of diverticular disease have been conflicting [6, 28–33]. There is evidence that suggests that neuromuscular dysfunction which plays a role in the pathogenesis

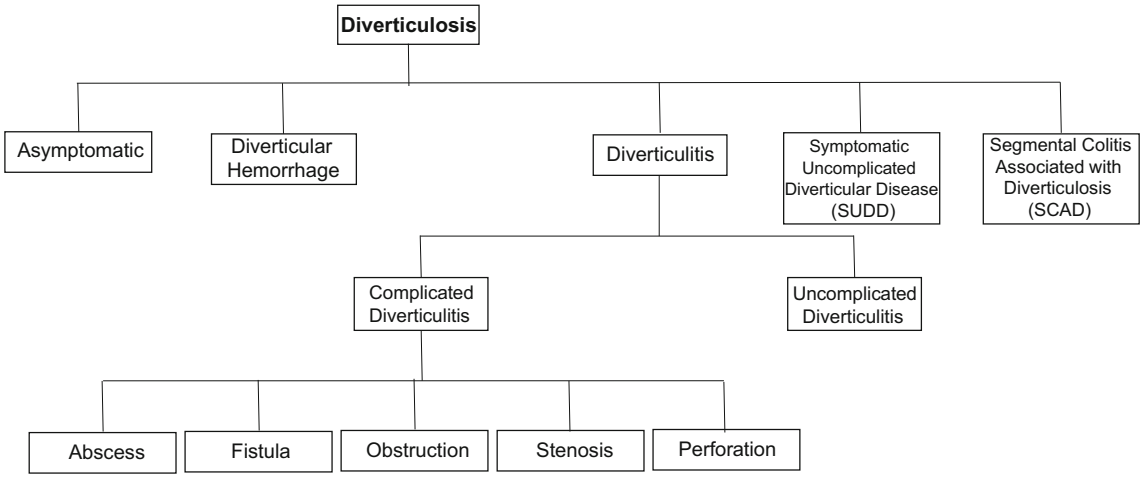

Fig. 1 Classification of diverticular disease

of diverticular disease is the end result of low-grade inflammation [34]. However, Peery et al. evaluated 619 patients undergoing screening colonoscopy with sigmoid biopsies and found that there was no association between colonic diverticulosis and mucosal inflammation [33]. They specifically found that patients with diverticulosis were less likely to express IL-6 which is an inflammatory cytokine [33]. Furthermore, Jarbrink-Sehgal et al. found that there was no association between symptomatic diverticulosis and serologic or mucosal inflammation [6]. Other studies, however, have demonstrated evidence for subclinical inflammation in patients with symptomatic disease, by way of downregulation of cyclooxygenase-2/PGE_2 and upregulation of 15-PGDH in colonic mucosa [35]. This, like the role of fiber, is another area of uncertainty [36, 37].

Natural History

The true natural history of diverticular disease remains unknown, largely due to the fact that diverticulosis is silent and often an incidental finding on screening colonoscopy. In addition, the few studies conducted to evaluate the natural history of diverticular disease are limited to the colorectal cancer screening age population of 50–75 years [38]. The suggested lifetime risk of acute diverticulitis was thought to be around 10–25% [38]. However, more recent analysis shows that this risk is about 4–5% [8, 39, 40]. Recent studies suggest that acute diverticulitis occurs in about 1.5–6 per 1,000 person-years and diverticular bleeding occurs in about 0.46 per 1,000 person-years. The risk of diverticulitis and recurrent diverticulitis was found to be higher in younger patients [8, 41]. Age ≥ 70 and bilateral diverticulosis were found to be risk factors for hemorrhage [39].

Clinical Presentation

Diverticular disease is usually an asymptomatic disease or becomes clinically overt and manifests as acute diverticulitis [42, 43•]. About one-fourth to one-fifth of patients with asymptomatic diverticulosis will develop symptoms without any complications, which is a manifestation of SUDD [37]. SUDD presents with nonspecific abdominal pain, abdominal bloating, and change in bowel habits without otherwise any evidence of macroscopic inflammatory process [37]. The presentation of SUDD makes it difficult to distinguish it from irritable bowel syndrome (IBS) [43•]. However, patients with SUDD appear to have microscopic inflammatory infiltrates as compared with healthy controls [44].

The evaluation of patients with acute presentation of abdominal pain and fever often involves risk stratification. Patients who have a low risk presentation are those without leukocytosis, elevated CRP or temperature, and without any signs of sepsis [43•]. Conversely, high risk presentations include patients with leukocytosis, high fever and CRP, and presence of complications of acute diverticulitis and comorbidities [43•]. This assessment and stratification will aid in determining which patient populations require antibiotics, hospitalization, and frequent evaluation of hemodynamic stability.

Diagnosis

Diverticular disease can be diagnosed clinically or endoscopically, or with the aid of radiographic imaging. The use of endoscopic and radiographic modalities is often needed in order to rule out other diagnoses that are in the differential and can have an overlap in presentation. These include ischemic colitis, colorectal carcinoma (CRC), and NSAID-induced

colitis especially in the elderly, in addition to infectious colitis and inflammatory bowel disease (IBD) [45•]. Therefore, besides the use of stool studies to rule out infectious etiologies, the use of endoscopic and radiologic modalities is paramount to obtaining the most accurate diagnosis and ultimately treatment.

Acute Diverticulitis

Barium enema had historically been widely used for the diagnosis of diverticular disease [46, 47]. There are, in fact, studies reporting the therapeutic benefits of barium enema in diverticular hemorrhage [48–50]. Adams explained that due to the massive bleeding associated with diverticular bleeding, the fragility of the patient population, and high operative risk, therapeutic barium enema is an effective mechanism to not only control bleeding but to be able to select appropriate patient populations that may require surgery [48]. The 2 postulated mechanisms underlying the therapeutic effects of barium enema are thought to be pressure by the barium solution producing a tamponade effect and direct hemostasis from the barium solution [48]. Nonetheless, this is not a currently recommended modality.

More recently, computed tomography (CT) has become the standard for diagnosing diverticular disease due mainly to its reproducibility, high diagnostic accuracy, and ability to have a comprehensive evaluation that includes severity grading and complication detection [46, 51]. CT and CT colonography (CTC) are effective in diagnosis, determination of extent of disease, and complications of diverticular disease [48, 51]. CTC and barium enema, however, are contraindicated in the setting of suspected acute diverticulitis due to pressure insufflation [52••]. CT of the abdomen and pelvis serves as the main modality to diagnose diverticulitis and its complications [52••]. In general, CT should be done with IV contrast for the diagnosis of diverticulitis in order to confirm and grade the severity of complications such as abscesses [52••]. However, where expertise is available, ultrasound is comparable in accuracy for the evaluation of diverticulitis and is likely advantageous in female patients of childbearing age [52••, 53, 54]. MRI is a radiologic modality that does not currently play a role in the evaluation of patients with acute diverticulitis except perhaps in the case of pregnancy in order to reduce radiation exposure [52••].

There are several radiologic scoring systems that are used to classify patients into either uncomplicated or complicated disease, an important distinction in frail elderly patients. These CT-based scores include the Hinchey, Ambrosetti, Buckley, and Neff classifications (Table 1) [55–58]. Most of these classifications grade the complications based on bowel wall thickening, fistula, stenosis, and abscess/phlegmon and its location within the abdomen and lastly peritonitis [55–58].

CTC requires the administration of room air or carbon dioxide and is therefore contraindicated in acute diverticulitis due to concern for extension of a microperforation [52••]. Similarly, colonoscopy is contraindicated in the acute setting in patients with acute diverticulitis for the same reasons [52••].

The role of colonoscopic evaluation after the resolution of acute diverticulitis is somewhat controversial, but most authorities, including the recent AGA guidelines, advocate for a colonoscopy electively after an attack of acute diverticulitis, if not recently done, to exclude a perforated cancer mimicking diverticulitis, in patients of appropriate risk profile [24•, 59–61].

Diverticular Hemorrhage

In cases of suspected diverticular bleeding, prompt diagnostic colonoscopy within 12–24 h after an effective prep is suggested [62]. When performed within 48 h of an acute presentation along with an adequate bowel preparation, the diagnostic yield of colonoscopy is about 48 to 90% in addition to shortening hospital stays [63]. When endoscopically visualized, hemostasis can be achieved with the aid of thermal contact therapy, epinephrine injection, or clip placement [64]. If there is delay associated with either bowel preparation or patient stability especially in the elderly population or difficulty with visualization of the bleeding source due to hemorrhage, CT angiography can aid in localization of bleeding source followed by catheter-based angiography for the treatment of bleeding [65–68].

Therapy

Antibiotics

It has long been felt that acute diverticulitis was due to obstruction of the neck of a single diverticulum, with a resulting localized microperforation. As such, antibiotics were felt to be an obligate foundation of acute diverticulitis treatment [69]. However, this paradigm has somewhat shifted with numerous studies including two large randomized trials showing no worse outcomes in patients with antibiotics withheld in acute uncomplicated diverticulitis [70–73]. Based on these studies, the AGA guidelines along with others now recommend the selective use of antibiotics in patients with acute diverticulitis, although the authors believe in erring on the side of caution in elderly patients with significant comorbidities [24•, 74].

Fiber

Dietary fiber does appear to play a role in the prevention of diverticular disease complications more than in the pathogenesis of diverticulosis itself [22], and as such, the AGA strongly

Table 1 CT classification of diverticulitis

Classification type	Hinchey classification	Ambrosetti classification	Buckley classification	Neff classification
I	Abscess	Localized sigmoid wall thickening (< 5 mm)	Wall thickening and/or fat stranding	Wall thickening and/or fat stranding
II	Contained pelvic abscess	Pericolic fat stranding	Wall thickening >3 mm and/or small abscess	Locally complicated diverticulitis
III	Purulent peritonitis	Abscess	Wall thickening >5 mm and/or perforation with free air and/or abscess > 5 mm	Localized pneumoperitoneum
IV	Fecal peritonitis	Extraluminal air		Abscess (< 4 mm)
V		Extraluminal contrast		Abscess > 4 mm in the pelvis
VI				Abscess in the abdominal cavity
VII				Significant pneumoperitoneum and/or intra-abdominal free liquid

recommends the use of a high-fiber diet after an episode of diverticulitis [24•].

Mesalamine

Mesalamine, an anti-inflammatory medication, has been investigated both to prevent recurrent diverticulitis and as a therapy for the treatment of patients with SUDD [75]. However, a large, phase 3 randomized, double-blind, placebo-controlled multicenter trial of 1,182 patients found that mesalamine did not reduce the rate of diverticulitis recurrence episodes, time to recurrence, or surgical intervention requirements [76]. This was confirmed by a meta-analysis that also found no evidence that mesalamine use can prevent the recurrence of diverticulitis [77]. In accordance with these findings, the AGA guidelines recommend against the use of mesalamine for diverticulitis prevention [24•]. Its role in SUDD is undefined.

Rifaximin

Rifaximin, a nonabsorbable, locally effective oral antibiotic, has been investigated mainly for its role in symptom relief in SUDD [24•, 78, 79]. The mechanism by which this is achieved is believed to be reduction of gut microbiota proliferation and therefore improving bacterial overgrowth [80]. A large meta-analysis of 1,660 patients found that the majority of patients on rifaximin were able to have symptomatic improvement [80]. However, the role of rifaximin in disease modification and prevention of complications including diverticulitis is unclear. Therefore, the AGA guidelines suggest against the use of rifaximin in SUDD [24•].

Probiotics

Alterations of the microbiome causing an inflammatory response have been postulated to be involved in the pathogenesis of diverticular disease. However, the microbiome alterations have not been fully characterized nor have causal associations been established. Further, data on the use of probiotics in the treatment of diverticular disease has only occasionally shown reduction in abdominal symptoms and not in the prevention of complications or future recurrent diverticulitis episodes [81]. Accordingly, the AGA guidelines recommend against the use of probiotics after acute uncomplicated diverticulitis [24•].

Complications

Diverticulitis

As mentioned, diverticulitis is felt to develop from inflammation of a diverticulum [82], likely due to fecalith obstruction of the diverticular sac, which leads to low-grade inflammation and obstruction [83]. It is the most common complication of diverticulosis occurring in about 4% of those with diverticulosis [24•]. Diverticulitis can occur in either an acute or chronic process and is categorized as either uncomplicated or complicated. As mentioned previously, complicated diverticulitis presents with abscesses, fistulas, stenosis, obstruction, or perforation (Fig. 1) [83]. The decision-making process in the management algorithm of complicated diverticulitis includes consideration for hospitalization and antibiotic initiation. American Society for Colon and Rectal Surgery (ASCRS) has made several recommendations on this issue. They recommend hospitalization admission and initiation of intravenous antibiotics and IV hydration in patients who do not tolerate oral intake and have relevant comorbidities, and those who do not have adequate home support [84•]. Furthermore, immunosuppressed patients, patients with chronic kidney disease, and those with collagen vascular disease also have a higher risk of recurrent complicated diverticulitis; and therefore, special consideration for use of antibiotics and operative

intervention should be taken in these patient populations [84•, 85]. Lidor et al. evaluated a large cohort of patients with a mean age of 77.8 years and found that in the inpatient setting, only about 14% of the elderly presenting with diverticulitis underwent surgery and that the majority of elderly patients (82.5%) did not have any further recurrences of their disease [86]. Moreover, in the outpatient setting and even in patients 80 years of age or older, even fewer had recurrence of diverticulitis and required surgical intervention [86]. These findings are further supported by the fact that older patients undergoing elective surgery for diverticulitis have an increased risk of mortality, intestinal diversion, and 30-day readmission [87].

Hemorrhage

Diverticular bleeding is one of the most common etiologies of acute lower gastrointestinal bleeding especially in the elderly [52••]. Diverticular bleeding spontaneously ceases in most cases with a recurrence rate of about 14–38% of cases [88, 89]. Most diverticular bleeding occurs in the left colon; however, about 50% of large-volume hemorrhagic episodes originate from the right colon [90, 91]. The pathogenesis of diverticular bleeding entails the rupture of an artery at the base of the diverticulum due to vessel wall injury [92]. The risk factors associated with first diverticular hemorrhage include advanced age, anticoagulation use, nonsteroidal anti-inflammatory drug (NSAID) use, right-sided diverticulosis, obesity, hypertension, and atherosclerosis [90, 93•, 94–96]. In the elderly population, Bokhari et al. showed that the success of diverticular hemorrhage treatment does not depend on the initial hemoglobin level, number of blood transfusions, or a history of previous diverticular bleeding [97]. Given the common use, avoidance of NSAIDs is arguably the most important intervention in elderly patients after an episode of diverticular hemorrhage.

Surgical Management in the Elderly

Conventionally, surgical interventions were recommended after the second attack of acute diverticulitis as it was thought that patients with recurrent episodes of diverticulitis have more severe episodes and therefore likely to require more emergent surgical resection [84•, 98]. However, there is a shift in this paradigm as well. The AGA guidelines and the ASCRS guidelines both now suggest an individualized approach (and later interventions) to the surgical management of patients with acute uncomplicated diverticulitis [24•, 84•]. This paradigm shift was in part due to several studies showing a lower risk of recurrent diverticulitis and complications. Recurrence rate of diverticulitis in acute diverticulitis is about 13–23% [99–101]. A decision analysis by Salem et al. suggests that in both younger and older patients, performing colectomy after the fourth episode of diverticulitis resulted in fewer deaths and fewer colectomies and was more cost effective [102]. This data, along with those showing that the risk of recurrent diverticulitis persists even after colectomy at a rate of about 2.6–10.4% [103–107] and that the risk of mortality and colostomy with elective colectomy is as high as 2.3–11.4% [108], further supports the AGA guideline's recommendation to individualize the approach to surgical management [24•].

The notion of earlier elective surgery in younger patients has historically been more accepted as several studies show that younger patients experience more virulent forms of diverticulitis with a 5-fold increased risk of complications [109–112]. In fact, a population-based study demonstrated that younger patients < 50 years were more likely to have a recurrence of diverticulitis than older patients and younger patients were also more likely to have recurrent hospitalizations with emergent colectomy/colostomy placement [100]. However, recurrence of diverticulitis even in young patients only occurred in a minority of patients, and even in those, only about 7% ever required emergency colectomy/colostomy [100]. Therefore, even though the time to surgery in the elderly is unclear, the above data show that even with higher virulence in the young, expectant medical management in both the young and old is the best strategy for most patients at this time.

Considerations in the Elderly

In evaluating diverticulosis and its association with colonic symptoms, Jarbrink-Sehgal et al. found in a population-based study in 2016 that patients with diverticulosis are more likely to report symptoms of loose stools with urgency, frequency, and passage of mucus. In addition, diverticulosis with associated abdominal pain and diarrhea-predominant IBS was more commonly seen in patients older than 60 years [6].

Although the role of antibiotics in the treatment of diverticulitis has become more individualized, Peery et al. recommend that uncomplicated diverticulitis should still be treated with antibiotics in patients who are immunosuppressed, pregnant, septic, and with significant comorbid disease [45•]. As comorbidities increase in the elderly, strong consideration should be given to the elderly when it comes to the use of antibiotics.

In terms of medication reconciliation in the elderly, it is important to consider which medications increase the risk of diverticular disease and which are protective. For example, NSAIDs commonly used in the elderly are linked to an increased risk of diverticulitis and bleeding and therefore should be avoided if possible [93•]. Conversely, calcium channel blockers (CCB) and statins may be somewhat protective in patients with diverticular disease [113].

Elderly patients are at an increased risk of ischemic colitis, which often presents with symptoms of abdominal pain and hematochezia [10, 114]. Since this same population is also at a

higher risk of developing diverticular bleeding, there should be a high index of suspicion so that patients are diagnosed and managed appropriately. Of note, diverticular bleeding usually presents with painless hematochezia [10]. Lastly, elderly patients with atherosclerosis are at a higher risk of developing diverticular bleeding as compared with patients without atherosclerosis [10].

Conclusion

Diverticulosis is the most common incidental finding on colonoscopy with a prevalence that increases progressively with age. As such, it is expected that the elderly experience complications associated with diverticulosis more frequently and more severely, and therefore a high index of suspicion and great care should be taken into account when taking care of this vulnerable population.

Compliance with Ethical Standards

Conflict of Interest Neil Stollman has consulted for AlfaSigma and Aries Pharmaceuticals.

Mona Rezapour declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad hoc practice parameters committee of the American College of Gastroenterology. Am J Gastroenterol. 1999;94:3110–21.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. Gastroenterology. 2009;136:741–54.
3.•• Peery AF, Crockett SD, Murphy CC, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology. 2019;156:254–72 **Updated report of the financial and economic burden of diverticular disease**.
4. Boynton W, Floch M. New strategies for the management of diverticular disease: insights for the clinician. Therapeut Adv Gastroenterol. 2013;6(3):205–13.
5. Peery AF, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012;142:266–72.
6. Jarbrink-Sehgal ME, Andreasson A, Talley NJ, et al. Symptomatic diverticulosis is characterized by loose stools. Clin Gastroenterol Hepatol. 2016;14:1763–70.e1.
7. Strate LL, Modi R, Cohen E, Spiegel BMR. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012;107:1486–93.
8. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clin Gastroenterol Hepatol. 2013;11:1609–13.
9. Ambrosetti P, Chautems R, Soravia C, Peiris-Waser N, Terrier F. Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: a prospective study of 73 cases. Dis Colon Rectum. 2005;48:787–91.
10. Comparato G, Pilotto A, Franze A, et al. Diverticular disease in the elderly. Dig Dis. 2007;25:151–9.
11. Burkitt DP. Epidemiology of cancer of the colon and rectum. Cancer. 1971;28:3–13.
12. Burkitt DP. Cancer of the GI tract: colon, rectum, anus. Epidemiology and etiology. JAMA. 1975;231(5):517–8.
13. Peery AF, Sandler RS, Ahmen DJ, et al. Constipation and a low-fiber diet are not associated with diverticulosis. Clin Gastroenterol Hepatol. 2013;11:1622–7.
14. Jun S, Stollman N. Epidemiology of diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16(4):529–42.
15. Chan CC, Lo KKL, Chung ECH, et al. Colonic diverticulosis in Hong Kong: distribution patter and clinical significance. Clin Radiol. 1998;53(11):842–4.
16. Rajendra S, Ho JJ. Colonic diverticular disease in a multiracial Asian patient population has an ethnic predilection. Eur J Gastroenterol Hepatol. 2005;17:871–5.
17. Granlund J, Svensson T, Olen O, et al. The genetic influence on diverticular disease: a twin study. Aliment Pharmacol Ther. 2012;35:1103–7.
18.• Strate LL, Erichsen R, Baron JA, et al. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. Gastroenterology. 2013;144:736–742.e1 **One of the significant studies suggesting a familial and genetic basis to diverticular disease**.
19. Connelly TM, Berg AS, Hagerty JP, et al. The TNFSF15 gene single nucleotide polymorphism rs7848647 is associated with surgical diverticulitis. Ann Surg. 2014;259(6):1132–7.
20. Painter NS. The cause of diverticular disease of the colon, its symptoms and its complications: review and hypothesis. J R Coll Surg Edinb. 1985;30:118–22.
21. Aldoori WH, Giovannucci EL, Rockett HR, et al. A prospective study of dietary fiber types and symptomatic diverticular disease in men. J Nutr. 1998;128:714–9.
22. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. BMJ. 2011;343:d4131.
23. Crowe FL, Balkwill A, Cairns BJ, Appleby PN, Green J, Reeves GK, et al. Source of dietary fibre and diverticular disease incidence: a prospective study of UK women. Gut. 2014;63:1450–6.
24.• Stollman N, Smalley W, Hirano I, et al. American gastroenterological association institute guideline on the management of acute diverticulitis. Gastroenterology. 2015;149:1944–9 **The most recent AGA guidelines addressing several important considerations regarding management of acute diverticulitis**.
25. Barbara G, Scaioli E, Barbaro MR, Biagi E, Laghi L, Cremon C, et al. Gut microbiota, metabolome and immune signatures in patients with uncomplicated diverticular disease. Gut. 2017;66:1252–61.
26. Rajilic-Stojanovic M, Biagi E, Heilig HG, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. Gastoenterology. 2011;141:1792–801.

27. Dicksved J, Halfvarson J, Rosenquist M, Järnerot G, Tysk C, Apajalahti J, et al. Molecular analysis of the gut microbiota of identical twins with Crohn's disease. ISME J. 2008;2:716–27.
28. Spiller R. How inflammation changes neuromuscular function and its relevance to symptoms of diverticular disease. J Clin Gastroenterol. 2006;40(Suppl 3):S117–20.
29. Humes DJ, Simpson J, Smith J, Sutton P, Zaitoun A, Bush D, et al. Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. Neurogastroenterol Motil. 2012;24:318–e163.
30. Horgan AF, McConnel EJ, Wolff BG, et al. Atypical diverticular disease: surgical results. Dis Colon Rectum. 2001;44:1315–8.
31. Bottner M, Wedel T. Abnormalities of neuromuscular anatomy in diverticular disease. Dig Dis. 2012;30:19–23.
32. Golder M, Burleigh DE, Belai A, Ghali L, Ashby D, Lunniss PJ, et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. Lancet. 2003;361:1945–51.
33. Peery AF, Keku TO, Addamo C, et al. Colonic diverticula are not associated with mucosal inflammation or chronic gastrointestinal symptoms. Clin Gastroenterol Hepatol. 2018;16:884–91 E1.
34. Bassotti G, Villanacci V, Bernardini N, Dore MP. Diverticular disease of the colon neuromuscular function abnormalities. J Clin Gastroenterol. 2016;50(Suppl 1):S6–8.
35. Dai L, King DW, Perera DS, Lubowski DZ, Burcher E, Liu L. Inverse expression of prostaglandin E_2-related enzymes highlights differences between diverticulitis and inflammatory bowel disease. Dig Dis Sci. 2015;60(5):1236–46.
36. Goldstein NS, Admad E. Histology of the mucosa in sigmoid colon specimens with diverticular disease: observations for the interpretation of sigmoid colonoscopic biopsy specimens. Am J Clin Pathol. 1997;107:438–44.
37. Tursi A, Elisei W. Role of inflammation in the pathogenesis of diverticular disease. Mediat Inflamm. 2019;14:1–7.
38. Rustom LBO, Sharara AI. The natural history of colonic diverticulosis: much ado about nothing? Inflamm Intes Dis. 2018;3:69–74.
39. Niikura R, Nagata N, Shimbo T, et al. Natural history of bleeding risk in colonic diverticulosis patients: a long-term colonoscopy-based cohort study. Aliment Pharmacol Ther. 2015;4:888–94.
40. Shayto R, Hanna K, Ziyade N, Chehab H, Chalhoub JM, Harb AH, et al. The natural history of incidental colonic diverticulosis on screening colonoscopy: a prospective cohort study. Gastroenterology. 2016;150:S308.
41. McConnel EJ, Tessier DJ, Wolff BG. Population-based incidence of complicated diverticular disease of the sigmoid colon based on gender and age. Dis Colon Rectum. 2003;46(8):1110–4.
42. Mosadeghi S, Bhuket T, Stollman N. Diverticular disease: evolving concepts in classification, presentation and management. Curr Opin Gastroenterol. 2015;31:50–5.
43.• Strate LL, Morris AM. Epidemiology, pathophysiology and treatment of diverticulitis. Gastroenterol. 2019;156:1282–98 **Most recent thorough review article with clinical assessment algorithm for diverticulitis**.
44. Narayan R, Floch MH. Microscopic colitis as part of the natural history of diverticular disease. Am J Gastroenterol. 2002;97(9):S112–3.
45.• Peery A, Stollman N. Antibiotics for acute uncomplicated diverticulitis: time for a paradigm change? Gastroenterology. 2015;149:1650–1 **Concise overview of the shift in antibiotic usage including use in immunocompromised population**.
46. Feuerstein JD, Falchuk KR. Diverticulosis and diverticulitis. Mayo Clin Proc. 2016;91(18):1094–104.
47. Halligan S, Saunders B. Imaging diverticular disease. Best Pract Res Clin Gastroenterol. 2002;16(4):595–610.
48. Adams JT. Therapeutic barium enema for massive diverticular bleeding. Arch Surg. 1970;101:457–60.
49. Miller RE, Skucas J, Violante MR, Shapiro ME. The effect of barium on blood in the gastrointestinal tract. Radiology. 1975;117:527–30.
50. Matsuura M, Inamori M, Nakajima A, Komiya Y, Inoh Y, Kawasima K, et al. Effectiveness of therapeutic barium enema for diverticular hemorrhage. World J Gastroenterol. 2015;21(18):5555–9.
51. Biondo S, Lopez Borao J, Millan M, Kreisler E, Jaurrieta E. Current status of the treatment of acute colonic diverticulitis: a systematic review. Color Dis. 2012;14(1):e1–e11.
52.•• Flor N, Maconi G, Cornalba G, Pickhardt PJ. The current role of radiologic and endoscopic imaging in the diagnosis and follow-up of colonic diverticular disease. AJR Am J Roentgenol. 2016;207(1):15–24 **A detailed paper outlining the role of various radiographic studies in the evaluation of diverticular disease**.
53. Lameris W, Van Randen A, Bipat S, et al. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. Eur Radiol. 2008;18:2498–511.
54. Liljegren G, Chabok A, Wickbom M, Smedh K, Nilsson K. Acute colonic diverticulitis: a systematic review of diagnostic accuracy. Color Dis. 2007;9:480–8.
55. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85–109.
56. Ambrosetti P. Acute left-sided colonic diverticulitis: clinical expressions, therapeutic insights, and role of computed tomography. Clin Exp Gastroenterol. 2016;9:249–57.
57. Mora Lopez L, Serra Pla S, Serra-Aracil X, Ballesteros E, Navarro S. Application of a modified Neff classification to patients with uncomplicated diverticulitis. Color Dis. 2013;15:1442–7.
58. Buckley O, Geoghegan T, O'Riordain DS, et al. Computed tomography in the imaging of colonic diverticulitis. Clin Radiol. 2004;59(11):977–83.
59. Sharma PV, Eglinton T, Hider P, Frizelle F. Systematic review and meta-analysis of the role of routine colonic evaluation after radiologically confirmed acute diverticulitis. Ann Surg. 2014;259:263–72.
60. Daniels I, Unlu C, de Wijkerslooth TR, et al. Yield of colonoscopy after recent CT-proven uncomplicated acute diverticulitis: a comparative cohort study. Surg Endosc. 2015;29:2605–13.
61. Lau KC, Spilsbury K, Faroque Y, et al. Is colonoscopy still mandatory after a CT diagnosis of left-sided diverticulitis: can colorectal cancer be confidently excluded? Dis Colon Rectum. 2011;54:1265–70.
62. Cuomo R, Barbara G, Pace F, Annese V, Bassotti G, Binda GA, et al. Italian consensus conference for colonic diverticulosis and diverticular disease. United European Gastroenterol J. 2014;2:413–42.
63. Lahat A, Yanai H, Menachem Y, Avidan B, Bar-Meir S. The feasibility and risk of early colonoscopy in acute diverticulitis: a prospective controlled study. Endoscopy. 2007;39:521–4.
64. Jensen DM, Machicado GA. Diagnosis and treatment of severe hematochezia: the role of urgent colonoscopy after purge. Gastroenterology. 1988;95:1569–74.
65. Hizawa K, Miura N, Matsumoto T, Iida M. Colonic diverticular bleeding: precise localization and successful management by a combination of CT angiography and interventional radiology. Abdom Imaging. 2009;34:777–9.
66. Loffroy R. Multidetector CT angiography for the detection of colonic diverticular bleeding: when, how, and why? Dig Dis Sci. 2013;58:1822–4.
67. Nagata N, Niikura R, Aoki T, Moriyasu S, Sakurai T, Shimbo T, et al. Role of urgent contrast-enhanced multidetector computed tomography for acute lower gastrointestinal bleeding in patients undergoing early colonoscopy. J Gastroenterol. 2015;50:1162–72.

68. Laing CJ, Tobias T, Rsenblum DI, et al. Acute gastrointestinal bleeding: emerging role of multi detector CT angiography and review of current imaging techniques. RadioGraphics. 2007;27: 1055–70.
69. Jacobs DO. Clinical practice: diverticulitis. N Engl J Med. 2007;357:2057–66.
70. Chabok A, Pahlam L, Hjern F, AVOD study group, et al. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. Br J Surg. 2012;99:532–9.
71. Westwood DA, Eglinton TW. Antibiotics may not improve short-term or long-term outcomes in acute uncomplicated diverticulitis. Evid Based Med. 2013;18:32–3.
72. Isacson D, Andreasson K, Nikberg M, Smedh K, Chabok A. No antibiotics in acute uncomplicated diverticulitis: does it work? Scand J Gastroenterol. 2014;49:1441–6.
73. Daniels I, Unlu C, de Korte N, et al. Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis. Br J Surg. 2017;104: 52–61.
74. Annibale B, Carabotti M, Cuomo R. Italian guidelines. J Clin Gastroenterol. 2016;50(Suppl 1):S44–6.
75. Tursi A, Brandimarte G, Elisei W, Picchio M, Forti G, Pianese G, et al. Randomised clinical trial: mesalazine and/or probiotics in maintaining remission of symptomatic uncomplicated diverticular disease. A double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther. 2013;38:741–51.
76. Raskin JB, Kamm MA, Jamal MM, Márquez J, Melzer E, Schoen RE, et al. Mesalamine did not prevent recurrent diverticulitis in phase 3 controlled trials. Gastroenterology. 2014;147:793–802.
77. Khan MA, Ali B, Lee WM, Howden CW. Mesalamine does not help prevent recurrent acute colonic diverticulitis: meta-analysis of randomized, placebo-controlled trials. Am J Gastroenterol. 2016;111:579–81.
78. Papi C, Ciaco A, Koch M, Capurso L. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon: a multicenter double-blind placebo-controlled trial. Aliment Pharmacol Ther. 1995;9:33–9.
79. Latella G, Pimpo MT, Sottili S, Zippi M, Viscido A, Chiaramonte M, et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disease of the colon. Int J Color Dis. 2003;18:55–62.
80. Bianchi M, Festa V, Moretti A, Ciaco A, Mangone M, Tornatore V, et al. Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. Aliment Pharmacol Ther. 2011;33:902–10.
81. Lahner E, Bellisario C, Hassan C, et al. Probiotics in the treatment of diverticular disease: a systematic review. J Gastrointestin Liver Dis. 2016;25:79–86.
82. Rezapour M, Ali S, Stollman N. Diverticular disease: an update on pathogenesis and management. Gut Liver. 2018;12(2):125–32.
83. Bhucket TP, Stollman NH. Diverticular disease of the colon. In: Feldman M, Friedman LS, Brandt IJ, editors. Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management, vol. 2. 10th ed. Philadelphia: Elsevier; 2014. p. 1–15.
84.• Feingold D, Steele SR, Lee S, et al. Practice parameters for the treatment of sigmoid diverticulitis. Dis Colon Rectum. 2014;57: 284–94 **The American Society for Colon and Rectal Surgery recommendations on hospitalization, antibiotic use, and necessity of colonoscopy after an episode of diverticulitis**.
85. Klarenbleek BR, Samuels M, van der Wall MA, et al. Indications for elective sigmoid resection in diverticular disease. Ann Surg. 2010;251:670–4.
86. Lidor AO, Segal JB, Wu AW, Yu Q, Feinberg R, Schneider EB. Older patients with diverticulitis have low recurrence rates and rarely need surgery. Surgery. 2011;150:146–53.
87. Lidor AO, Schneider E, Segal J, Yu Q, Feinberg R, Wu AW. Elective surgery for diverticulitis is associated with high risk of intestinal diversion and hospital readmission in older adults. J Gastrointest Surg. 2010;14:1867–73.
88. Jensen DM, Machicado GA, Jutabha R, Kovacs TOG. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med. 2000;342:78–82.
89. McGuire HH. Bleeding colonic diverticula: a reappraisal of natural history and management. Ann Surg. 1994;220:653–6.
90. Gilshtein H, Kluger Y, Khoury A, Issa N, Khoury W. Massive and recurrent diverticular hemorrhage, risk factors and treatment. Int J Surg. 2016;33:136–9.
91. Lewis M. Bleeding colonic diverticula. J Clin Gastroenterol. 2008;42:1156–8.
92. Meyers MA, Alonso DR, Gray GF, Baer JW. Pathogenesis of bleeding colonic diverticulosis. Gastroenterology. 1976;71:577–83.
93.• Strate LL, Liu YL, Huang ES, et al. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. Gastroenterology 2011; 140: 1427–1433. **This is one of the seminal papers outlining the risk of NSAIDs in diverticulitis and diverticular bleeding.**
94. Strate LL, Liu YL, Aldoori WH, Syngal S, Giovannucci EL. Obesity increases the risks of diverticulitis and diverticular bleeding. Gastroenterology. 2009;136:115–22 **e1**.
95. Yamada A, Sugimoto T, Kondo S, Ohta M, Watabe H, Maeda S, et al. Assessment of the risk factors for colonic diverticular hemorrhage. Dis Colon Rectum. 2008;51:116–20.
96. Okamoto T, Watabe H, Yamada A, et al. The association between arteriosclerosis related diseases and diverticular bleeding. Int J Colorectal Dis 2012;27(9):1161–6.
97. Bokhari M, Am V, Ure T, Longo WE. Diverticular hemorrhage in the elderly—is it well tolerated? Dis Colon Rectum. 1996;39(2): 191–5.
98. Parks TG. Natural history of diverticular disease of the colon: a review of 521 cases. Br Med J. 1969;4(5684):639–42.
99. Broderick-Villa G, Burchette RJ, Collins JC, Abbas MA, Haigh PI. Hospitalization for acute diverticulitis does not mandate routine elective colectomy. Arch Surg. 2005;140:576–81.
100. Anaya DA, Flum DR. Risk of emergency colectomy and colostomy in patient with diverticular disease. Arch Surg. 2005;140:681–5.
101. Eglinton T, Nguyen T, Raniga S, Dixon L, Dobbs B, Frizelle FA. Patterns of recurrence in patients with acute diverticulitis. Br J Surg. 2010;97:952–7.
102. Salem L, Veenstra DL, Sullivan SD, Flum DR. The timing of elective colectomy in diverticulitis: a decision analysis. J Am Coll Surg. 2004;199:904–12.
103. Wolff BG, Ready RL, McCarty RL, et al. Influence of sigmoid resection on progression of diverticular disease of the colon. Dis Colon Rectum. 1984;27:645–7.
104. Farmakis N, Tudor RG, Keighley MR. The 5-year natural history of complicated diverticular disease. Br J Surg. 1994;81:733–5.
105. Moreaux J, Vons C. Elective resection for diverticular disease of the sigmoid colon. Br J Surg. 1990;77:1036–8.
106. Benn PL, Wolff BG, Ilstrup DM. Level of anastomosis and recurrent colonic diverticulitis. Am J Surg. 1986;151:269–71.
107. Thorn M, Graf W, Stefansson T, Pahlman L. Clinical and functional results after elective colonic resection in 75 consecutive patients with diverticular disease. Am J Surg. 2002;183:7–11.
108. Netri G, Verbo A, Coco C, et al. The role of surgical treatment in colon diverticulitis: indications and results. Ann Ital Chir. 2000;71:209–14.
109. Chodak GW, Rangel DM, Passaro E Jr. Colonic diverticulitis in patients under age 40: need for earlier diagnosis. Am J Surg. 1981;141:699–702.

110. Ambrosetti P, Robert J, Witzig JA, Mirescu D, de Gautard R, Borst F, et al. Prognostic factors from computed tomography in acute left colonic diverticulitis. Br J Surg. 1992;79:117–9.
111. Eusebio EB, Eisenberg MM. Natural history of diverticular disease of the colon in young patients. Am J Surg. 1973;125:308–11.
112. Schauer PR, Ramos R, Chiatas AA, Sirinek KR. Virulent diverticular disease in young obese men. Am J Surg. 1992;164(5):443–6.
113. Morris CR, Harvey IM, Stebbings WSL, Speakman CT, Kennedy HJ, Hart AR. Do calcium channel blockers and antimuscurinics protect against perforated colonic diverticular disease? A case control study. Gut. 2003;52(12):1734–7.
114. Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis and management of colonic ischemia. Am J Gastroenterol. 2015;110:18–44.