

Diverticulitis in Older Adults: A Review of Etiology, Diagnosis, and Management

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ABSTRACT

Background: Diverticulitis accounts for over 300,000 hospitalizations annually in the United States and its incidence increases with age. Among older adults, diverticulitis is the fourth leading cause for emergency surgery. Older adults with multimorbidity and geriatric syndromes are often excluded from clinical studies, leaving a gap in the evidence needed to guide management. Here, we provide a clinically oriented review of the diagnosis and management of older adults with diverticulitis through the lens of age-friendly care.

Methods and Results: We reviewed the literature describing the epidemiology, diagnosis, management, and prevention of diverticulitis in older adults. Due to age-related physiologic changes, the presence of geriatric syndromes, and multimorbidity, older adults with diverticulitis often present with atypical symptoms, variable laboratory findings, and are at higher risk for complications than younger patients. Guidelines support a more aggressive approach to diagnosis in this population, with lower threshold for obtaining diagnostic imaging. Antibiotics remain a mainstay of treatment for uncomplicated disease, and surgical management should be focused on severity of disease and the balance between the likelihood of improving quality of life and risks and burden of treatment.

Conclusions: Diverticulitis is a common disease that has a unique presentation among older individuals with limited evidence to guide management. Diagnosis and treatment should focus on what matters most to the patient, providing the most meaningful outcome possible within the context of multimorbidity, patient goals, symptom burden, and anticipated treatment outcomes.

1 | Introduction

Sigmoid or left-sided diverticulosis (hereafter termed "diverticulosis") refers the presence of false diverticula of the colon. Diverticulosis affects 60% of the U.S. population by age 60 [1]. Most individuals with diverticulosis are asymptomatic, however, 10%–25% develop symptoms ranging from minor abdominal pain and changes in bowel habits to severe pain, sepsis, or diverticular bleeding [2, 3]. This review will focus specifically on diverticulitis, defined as inflammation centered on the

diverticular orifices. The majority (85%) of individuals with diverticulitis develop uncomplicated disease while the remaining 15% experience disease complicated by abscess, fistula, obstruction, or perforation [4, 5].

Among gastrointestinal diagnoses, diverticulitis is the sixth most common cause of hospital admissions and 11th most common cause of non-malignant deaths in the United States [6]. The overall incidence of diverticulitis is increasing, driven in part by the aging population in the United States

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Summary

- · Key points
- o Diverticulitis is a disease of aging.
- Older adults with diverticulitis present with atypical symptoms, variable laboratory findings, and are at higher risk for complications compared to their younger counterparts.
- Diverticulitis treatment in older adults should focus on what matters most to the patient, providing the most meaningful outcome possible within the context of patient goals, symptom burden, and anticipated treatment outcomes.
- Why does this paper matter?
- Diverticulitis is a common, age-related condition that can lead to significant morbidity and mortality. Here, we provide a clinical review of the diagnosis and treatment of diverticulitis in older adults through the lens of age-friendly care.

[3]. Diverticulitis increases with age, as does the number of diverticulitis related Emergency Department visits [7]. Diverticulitis is the fourth most common cause for emergency surgery in older adults [8, 9]. Older adults with diverticulitis are at higher risk of in-hospital mortality and complications of diverticulitis and resulting surgical treatments than younger patients [8, 10].

Treatment strategies for diverticulitis include observation, medical management, elective surgery, and emergency surgery. Treatment decisions for older adults require weighing symptom severity, impact on quality of life, and risks associated with intervention and non-intervention. The data supporting optimal management of older adults is sparse and the variable presentation and differing outcomes among older adults support a nuanced approach to diagnosis and management. Recent European multi-society guidelines for the care of older adults with diverticulitis establish a foundation for unique considerations in this population [11]. Relevant literature was identified via pub med and embase. Articles were selected based on review of their abstracts, which indicated that they were original articles or practice guidelines relevant to diagnosis or management of diverticulitis in older adults or age-related outcomes related to diverticulitis. This review aims to provide clinically relevant context and recommendations for the diagnosis and treatment of diverticulitis in older adults.

The John A. Hartford Foundation and the Institute for Healthcare Improvement comprehensive guide for Age-Friendly Health Systems encourages emphasis on four elements of care for older adults: What Matters, Medication, Mentation, and Mobility [12]. This framework can be applied to diverticulitis care in this population. Here, we place emphasis on "what matters" when considering the best approach to diagnosing and managing diverticulitis in older patients. Understanding what is important to the patient and how diverticulitis and its treatment may impact the patient's life goals can be a powerful guide for management. In some cases, deviating from the management strategies advocated for younger healthier patients may be best for an older adult with diverticulitis.

2 | Pathophysiology, Risk Factors, and Primary Prevention

The pathophysiology of diverticulosis and subsequent progression to diverticulitis is poorly understood. Age-related changes in the colonic wall, including decreased colonic motility and increased collagen deposition, may play a role in the development of diverticulosis [13]. There are also contributions from genetics, diet, lifestyle, and medications that affect the neuromusculature and microbiome, ultimately leading to inflammation and diverticulitis [13].

There are several well-established risk factors for diverticulitis, including smoking, obesity, red meat intake, and NSAID/ aspirin use [14-16]. One study demonstrated a dose-dependent association between number of cigarettes smoked per day and incidence of diverticulitis and its complications. Another study found red meat consumption was associated with an increased risk of diverticulitis, whereas poultry and fish were associated with decreased risk [16]. Overweight and obesity are risk factors for diverticulitis and its complications, whereas physical activity and weight loss are protective [15]. Additionally, regular use of aspirin or NSAIDs is associated with an increased risk of diverticulitis and diverticular bleeding [17]. Because older individuals are more likely to have indications for daily aspirin use or have a higher number of total pack year smoking history, many of these risk factors are particularly relevant for older adults. Counseling for prevention of diverticulitis is aligned with general recommendations for a healthy lifestyle, including regular physical activity, weight management, diet high in fiber that limits red meat intake, abstinence from smoking, and avoidance of NSAIDs. Reviewing patient medications and omitting unnecessary NSAIDs or aspirin may help mitigate risk. After an individual has recovered from an index episode of diverticulitis, there are no known means of effective secondary prevention with exception of surgery, which will be discussed in detail later.

3 | Diagnosis

Patients with diverticulitis typically present with abdominal pain, change in bowel habits, nausea, and low-grade fevers. Diagnosis and management hinges upon distinguishing uncomplicated from complicated disease. Acute uncomplicated diverticulitis is defined as isolated colonic inflammation in the setting of diverticulosis. Complicated diverticulitis encompasses a spectrum of disease from microperforation (localized specks of extraluminal air) to free perforation with stool throughout the abdomen (feculent peritonitis). Abscess, stricture, and fistula are also considered complicated disease. Patients with complicated diverticulitis may present with more severe systemic symptoms, peritonitis, obstruction (secondary to strictures), or symptomatic fistulae (pneumaturia, urosepsis, feculent vaginal discharge), although these findings may be more subtle in older adults as discussed below. Complicated diverticulitis is diagnosed based on symptoms and cross-sectional CT imaging (Figure 1).

Accurate and timely diagnosis of diverticulitis in older adults can be challenging due to age-related physiologic changes, multimorbidity, and atypical clinical presentations [18]. Symptoms such as abdominal pain, fever, altered bowel

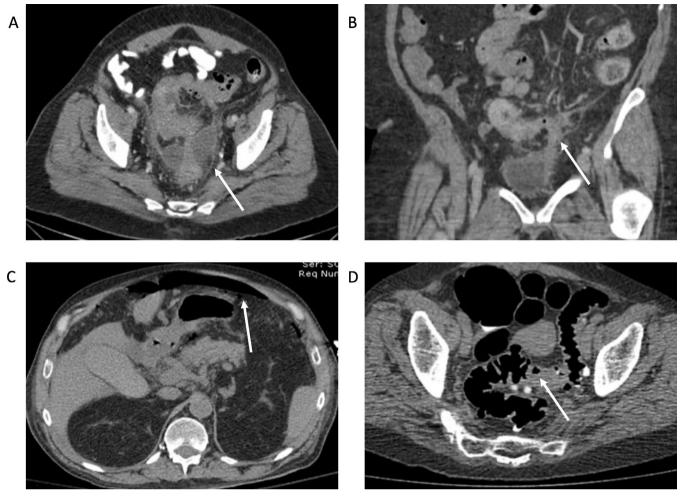


FIGURE 1 | Example CT images of various presentations of complicated diverticulitis. (A) Diverticular abscess. (B) Colovesical fistula. (C) Free air secondary to perforation. (D) Sigmoid stricture.

habits, and signs of systemic inflammation may be less pronounced, leading to underdiagnosis and delayed treatment. Patients 80 years and older with acute diverticulitis are less likely to experience abdominal pain and fever, and more likely to present with atypical symptoms, such as gastrointestinal bleeding, chest pain, syncope, or fatigue [18]. Older adults are also less likely to develop leukocytosis than their younger counterparts [19].

Diagnosing diverticulitis requires an approach that considers atypical presentations in older adults (Figure 2). The 2022 European multi-society guidelines on the diagnosis and treatment of diverticulitis in older adults provide recommendations for how to incorporate these differences into clinical practice [11]. They suggest avoiding diagnosis based solely on exam findings or laboratory results, as this may lead to underdiagnosis. Instead, cross-sectional CT imaging with IV contrast is suggested for all patients older than 65 years with suspected diverticulitis. Obtaining a CT scan in every patient over 65 with abdominal pain and suspected diverticulitis may not be feasible, and this may be omitted in select cases with mild local symptoms and reliable close clinical follow-up. However, patients with any systemic signs, including atypical symptoms such as fatigue, renal insufficiency, chest pain, or syncope

should be evaluated with CT imaging to rule out complicated disease that may require inpatient management or procedural intervention.

Case example part 1: A 78-year-old woman with atrial fibrillation on anticoagulation, prior stroke, obesity, COPD and one prior episode of diverticulitis presents to clinic with 3 days of left lower quadrant abdominal pain, loose stools, anorexia, and fatigue. Physical exam reveals tachycardia to 105 with an irregular rhythm, fever to 38°C, and focal left lower quadrant tenderness. Her white blood cell count is 13,000 and creatinine is 1.4. Other laboratory values are normal. Given her systemic symptoms such as anorexia and fatigue, in addition to her elevated creatinine, a CT scan is obtained which demonstrate acute uncomplicated diverticulitis.

4 | Non-Surgical Management

As with all cases of diverticulitis, optimal management in older adults depends on disease severity and is based on presence or absence of complicated features such as perforation, abscess, fistula, obstruction, or peritonitis.

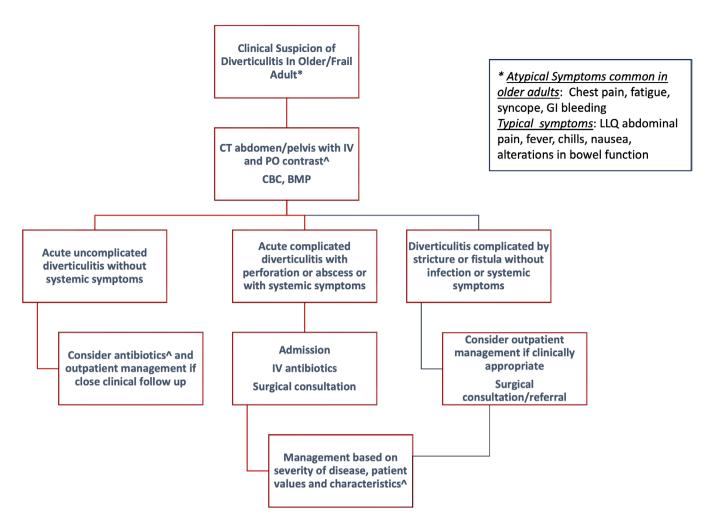


FIGURE 2 | Algorithm for diagnosis and management for diverticulitis in older and frail adults. ^indicates where algorithm may differ from standard of care for younger, heathier patients. LLQ, left lower quadrant.

5 | Uncomplicated Diverticulitis

Little data exists to support optimal medical management of diverticulitis in older or frail adults. Historically, management of acute uncomplicated diverticulitis involved inpatient admission with intravenous antibiotics and bowel rest. Following several large randomized controlled trials of younger patients (mean age ~57) with few, if any comorbidities, outpatient management with omission of antibiotics has become the recommendation for young patients with mild uncomplicated diverticulitis [20-24]. However, this treatment strategy has not been evaluated in older or frail adults. As such, the American Gastroenterological Association (AGA) and American Society of Colon and Rectal Surgeons (ASCRS) guidelines recommend selected use of antibiotics in cases of uncomplicated diverticulitis in patients who are frail or have significant comorbidities [25, 26]. Close clinical follow-up is essential in older adults, and antibiotics and/or inpatient observation should be considered in older, frail patients with systemic symptoms, fever, leukocytosis, multiple comorbidities, or unreliable follow-up.

6 | Complicated Diverticulitis

Complicated diverticulitis encompasses a wide spectrum, and management is based on disease severity, symptoms, and individual patient factors. Localized microperforation without diffuse free air or peritonitis can generally be managed conservatively with inpatient admission for IV antibiotics and symptom management [27]. Small abscesses can be treated with antibiotics, but percutaneous drainage is recommended for abscesses greater than ~4cm [26, 28]. Management of diverticular strictures can include colonoscopic dilation, stenting, or surgery depending on symptom severity, patient goals, and comorbidities [29, 30]. Inflammation from diverticulitis can also cause fistula between the colon and small bowel, bladder, uterus, vagina, or skin. Fistulae can be managed surgically and are usually managed in the elective setting [26].

In general, all patients with complicated diverticulitis should be referred to a surgeon, if surgery aligns with their goals of care (Figure 2). While some manifestations of complicated diverticulitis, such as perforation with peritonitis warrant emergent surgical intervention, others may be managed non operatively. Thus, surgical decision making should consider not only the patient's clinical presentation but also their broader clinical context, comorbidities, functional status, and goals of care.

7 | Interval Colonoscopy

The recommendation for interval colonoscopy after an episode of diverticulitis depends on imaging characteristics, time since the last colonoscopy, and patient goals. Current data supports

omission of interval colonoscopy in patients with uncomplicated diverticulitis if there are no high risk features by CT imaging such as mass or significant lymphadenopathy [31-34]. According to a 2019 meta-analysis, prevalence of colorectal cancer (CRC) following uncomplicated diverticulitis is low (pooled risk 0.5%, CI 0.2-1.2) and comparable to asymptomatic controls [32]. However, overall risk of CRC increases with age, and two studies identified age as an independent risk factor for advanced adenomas or CRC on interval colonoscopy [35, 36]. For patients with complicated diverticulitis, the risk of an underlying CRC is higher (ranging from 2%-11%), and according to the ASCRS guidelines, interval colonoscopy should be performed in all patients if a recent colonoscopy has not been performed [26, 37]. Based on this evidence, for older adults in whom treatment of CRC is aligned with goals of care, interval colonoscopy should be considered 6-8 weeks following an episode of complicated or uncomplicated diverticulitis. Interval colonoscopy can likely be safely omitted in patients who have had a colonoscopy within the past 3 years.

Case example part 2: The patient lives at home alone, is mostly independent but has help from her daughter who comes to visit her twice per week to help with grocery shopping. She enjoys walking her dog, but lately has been having more difficulty going farther than a block. She has fallen at home twice in the past year. She follows regularly with her primary care provider with whom she has close and reliable follow up. The patient strongly wishes to avoid hospitalization and wants to stay at home. Her daughter can check on her twice per day. Given the patient's mild systemic symptoms, family support, uncomplicated disease and close and reliable follow-up, she is managed in the outpatient setting. A 7-day course of oral antibiotics is prescribed due to her systemic symptoms, age, and multiple comorbidities. One month later she is feeling much better. She had a colonoscopy 2 years ago with one small polyp removed, so an interval colonoscopy is not recommended. She asks if it is likely she will have another episode in the future.

8 | Recurrence and Secondary Prevention

Risk of recurrence after an initial diverticulitis episode managed medically ranges between 11% and 36% [13, 38, 39]. Recurrence risk increases with each episode, with an estimated risk of 20%–55% after a second recurrence [3, 40]. Identifying strategies to prevent recurrent diverticulitis is an active area of investigation. Studies of medications such as mesalamine, rifaximin, and probiotics have had disappointing results [41–43]. The only strategy shown to reduce risk of recurrent diverticulitis is surgical resection of the affected colon. Three randomized trials comparing elective surgery to medical management demonstrated that diverticulitis 5 year recurrence risk after surgery is ~4%–10% compared to ~30%–60% with medical management [39, 44, 45]. Observational studies have demonstrated similar recurrence rates [46–48].

Age may play a role in risk of diverticulitis recurrence. A population-based study of 8606 patients with diverticulitis demonstrated a strong association between increasing age at index episode and recurrence [49]. In this study, for every 10 years of increased age at

the index episode, risk of recurrence nearly doubled [49]. Another study using Medicare claims data found a negative association between increasing age and risk of recurrence when considering only patients older than age 65. A single institution prospective study of 686 inpatients with diverticulitis found no difference in recurrence when comparing three age groups (<45 years, 46–70 years and >70 years) [50]. Due to different patient populations and statistical methods, the association between age and recurrence is not yet clear. Factors that contribute to the interplay between age and recurrence warrant further investigation.

Case example part 3: This patient goes on to have three additional episodes of uncomplicated diverticulitis over the next year, two of which require inpatient hospitalization due to symptom severity. She now has been experiencing chronic, mild left lower quadrant discomfort for months. She experiences more fatigue and has trouble walking her dog and difficulty leaving the house to spend time with her grand-children. She is worried about another unexpected hospitalization and feels frustrated by her persistent symptoms. She asks if there is anything she can do to find relief.

9 | Elective Surgery for Diverticulitis

Although some patients present with severe diverticulitis requiring emergency surgery, most surgery for diverticulitis occurs in the elective setting. Surgery is considered in patients with recurrent uncomplicated diverticulitis, smoldering symptoms, and complications of diverticulitis such as abscess, fistula, or stricture. Patients with these manifestations of diverticulitis can be referred for a surgical consultation, but primary care providers and geriatricians play an essential role in helping patients navigate the ultimate decision of whether to undergo surgery.

For recurrent uncomplicated diverticulitis, AGA and ASCRS guidelines suggest disease severity, patient preferences and individualized risks and benefits be factored into surgical treatment decisions [25, 26]. For patients with complicated diverticulitis involving mild stricture or fistula, emergent operations are rarely indicated, but elective surgery can improve quality of life by reducing pain and other associated symptoms. Therefore, surgical referral is appropriate for patients with complicated diverticulitis, smoldering symptoms, and recurrent uncomplicated diverticulitis.

There is growing emphasis on the importance of patient-reported outcomes in surgical decision-making for diverticulitis. Two randomized trials of surgery versus observation for patients with recurrent uncomplicated or smoldering diverticulitis demonstrated that surgery was associated with improved overall and bowel-related quality of life [44, 51]. However, average age of participants was 55 and patients > 75 years old or with multiple medical comorbidities were excluded. The applicability of these data to older adults, who face greater risk with surgical and non-surgical treatment, is unclear. While there is evidence in younger patients that elective surgery for diverticulitis improves quality of life, there is a paucity of data regarding patient-reported outcomes among older adults.

Quality of life improvements after surgery for diverticulitis in older adults may be limited due to elevated perioperative risk and prolonged post-operative recovery. Surgery leads to more significant deleterious impacts on older patient's mobility and mentation than in their younger counterparts. Following elective resection, older adults have higher risk of stoma formation, discharge to nursing facility, post-operative delirium, and mortality compared to younger patients (Figure 3) [10, 52, 53]. In an evaluation of Medicare beneficiaries with diverticulitis who underwent elective surgical management, 41% of patients over 85 years old were discharged to a skilled nursing facility compared to 4.1% of patients aged 65–69 [10]. This same study found a strong relationship between age and mortality and showed that patients over 85 years old had 12 times greater odds of in-hospital mortality compared with younger patients [10]. Older patients should understand these risks prior to pursuing surgery for diverticulitis. The American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator is one tool that considers age, comorbidities, and procedure to help provide patient-specific perioperative risk calculations [54]. This can help guide individualized discussions. However, results must be interpreted thoughtfully, as factors not included in the calculation may significantly influence the risk of a complication or death. Regardless of which tools clinicians use to center these discussions, significant perioperative risks associated with age and geriatric syndromes should be discussed with patients.

Patients who feel engaged in treatment decisions for diverticulitis are more satisfied with their outcome. About one in three patients with diverticulitis experiences regret about the treatment they receive [55]. Regardless of disease severity or treatment

type, regret is more common among patients who report that they did not experience shared decision making and those who did not feel informed, supported, or effective in the treatment decision-making process [55]. Investing time in understanding what matters to each patient and helping them fully conceptualize risks and burdens of treatment is essential when considering elective surgical treatment of diverticulitis in older adults.

Focusing conversations on the patient's goals for an operation, setting expectations for what surgery can accomplish (e.g., decreasing pain of smoldering disease, treating symptoms of fistula or stricture, or preventing recurrence), and providing concrete illustrations of possible outcomes helps guide patients' decisions. For example, a frail patient with an asymptomatic stricture diagnosed on colonoscopy will not feel better as a result of surgery, and observation should be considered [56]. However, a patient with a colovesical fistula leading to chronic infections, persistent pain, fatigue, weight loss, and a decline in their functional status may stand to benefit greatly from an operation. Once goals for surgery have been established, risks and burdens of surgery inform whether the goal is valuable from the patient's perspective [57]. Risks and burdens include expected things such as postoperative pain and weakness, as well as potential for a permanent stoma or complications that can dramatically impact recovery and impact independence and cognition [57]. Framing decisions about treatment in this way can support clinicians, patients, and families as they deliberate whether surgery is the best treatment strategy.

Ultimately, the decision to move forward with surgery should take into consideration multiple factors, including risk and severity of possible recurrence, impact of diverticulitis episodes on

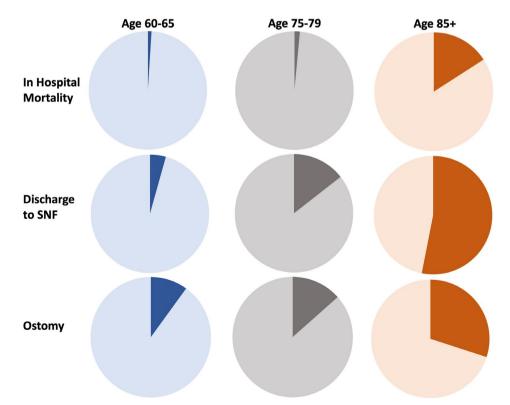


FIGURE 3 | Rates of mortality, disposition to skilled facilities, and ostomy creation following elective surgery for diverticulitis in older adults, by age. Data derived from Lidor et al. [10]. SNF, skilled nursing facility.

a patient's daily life and function, and risks associated with an elective procedure (Figure 4). Although a severe diverticulitis recurrence may be life threatening, understanding what matters to each patient and whether the anticipated outcomes of surgery align with their goals should primarily drive the decision.

10 | Emergency Surgery for Diverticulitis in Older Adults

Older adults are at greater risk for severe diverticulitis requiring emergency surgery, and those undergoing emergency surgery have a greater risk of postoperative morbidity and mortality compared to younger patients [58, 59]. In general, advanced age and frailty are predictors for worse outcomes following emergency abdominal surgery [8, 60]. One national retrospective

cohort study demonstrated that patients aged 65–79 years had 4-fold greater odds of death following emergency surgery for diverticulitis than younger patients, and this effect increases to 10-fold greater odds for individuals over 80 years old [61].

Emergency surgical treatment for older adults usually consists of resection of the sigmoid colon with end colostomy (Hartmann's procedure) with potential for colostomy reversal in a major subsequent surgery for those who are surgical candidates. However, colostomy reversal is uncommon in older adults given higher rates of comorbid conditions, preoperative fecal incontinence, and significant morbidity associated with a second operation [62–64]. Although there is now support for primary anastomosis with or without proximal diversion (ileostomy) in highly selected patients, this strategy is rarely used in older or frail adults [65, 66]. First, ileostomies (as opposed to colostomies)



FIGURE 4 | Factors that contribute to the decision to pursue surgical resection or continue observation in an older adult with diverticulitis. Essential considerations include the severity of disease, patient surgical risk, and desired and acceptable outcomes.

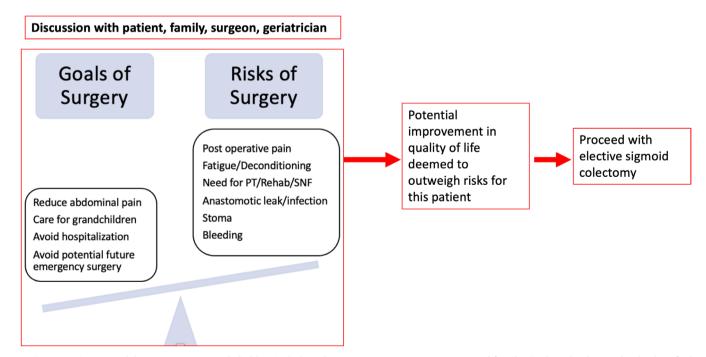


FIGURE 5 | Surgical discussion among stakeholders including the surgeon, geriatrician, patient, and family. Goals and risks are clearly identified and the patient and family have an opportunity to determine if the risks of surgery are acceptable, and the goals and possible outcomes of surgery are worth the risks. In this case, the patient and her family determined the benefits outweigh the risks and chose to proceed with surgery.

are associated with dehydration, kidney injury, and electrolyte derangements which may be poorly tolerated in older adults. Second, older adults have higher mortality risk when anastomotic leaks occur [8, 67]. Therefore, older and frail adults undergoing emergency surgery for diverticulitis usually undergo traditional Hartmann's procedure with a permanent colostomy [10, 59]. Deliberation of treatment options in the emergency setting should include a thorough understanding of the patient's goals, and clinicians should strive to provide patients with a realistic understanding of not only general risks and benefits of an operation, but likely outcomes specific to the individual.

Case example part 4: The patient is referred to a surgeon to discuss elective colectomy (Figure 5). They explore what she hopes to gain from surgery, including reduction in fatigue and abdominal pain that limits her ability to walk her dog and spend time with her grandchildren, as well as avoiding future hospitalizations. The patient feels apprehensive about surgery and the possibility of needing skilled nursing during recovery, but her symptoms have been getting worse and are limiting her ability to do the things that matter most to her. The patient and surgeon discuss expectations for postoperative recovery. This includes incisional pain, which usually resolves over weeks, fatigue, low appetite, weakness which can last for months, and changes in bowel habits which can be permanent. Unexpected complications may include bleeding, clotting or anastomotic leak, which can range from a problem treated with antibiotics to the need for an emergency operation and stoma creation (potentially permanent). In the case of a major problem after surgery, she may need to go to an inpatient rehabilitation center or nursing facility. After careful consideration, the patient, her family, geriatrician, and surgeon determine that the goal of feeling better is plausible, valuable, and worth the burdens and risks of surgery. Prior to surgery the patient and her family take time to discuss her advance care directives and document her wishes in the case of complications. Plans are made for an elective sigmoid colectomy.

Her immediate post operative course is complicated by a staple-line bleed after restarting her anticoagulation. This requires a blood transfusion, an endoscopic procedure, and additional 4days in the hospital. However, she recovers well and discharges home with home physical therapy. Three months later her symptoms have resolved, her energy levels have improved and she has returned to her baseline level of function.

11 | Conclusion

The prevalence of diverticulitis increases with age. Diverticulitis in older adults poses unique challenges due to atypical presentation and differences in the risk benefit profile of treatment strategies. Further research in this population is required to help define optimal medical management strategies (safety of omitting antibiotics), quality of life outcomes with and without surgical intervention, and the impacts of age on recurrence. Based on available data, CT imaging should be considered in any patient over 65 suspected of having diverticulitis and presenting with systemic signs or atypical symptoms such as fatigue, syncope, and/or acute kidney injury. Antibiotics should be considered for older or frail patients who present with systemic symptoms, and

patients with complicated, recurrent, or smoldering diverticulitis should be referred to a surgeon if surgery is within their goals of care. Overall, diverticulitis treatment should center on what matters most to the patient and provide the most meaningful outcome possible within the context of the patient's goals, symptoms, and likely treatment outcomes.

Author Contributions

J.H. preformed literature review, prepared and edited the manuscript. M.S. critically reviewed the manuscript. J.C. designed the study, preformed literature review, and critically revised the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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